The Assessment of Gene Patents Granted in Medical Biotechnology Area in the EU and the US: A Law and Economics Approach

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List of Abbreviations

AIA	(Leahy- Smith) America Invents Act of September 12, 2011.
Art.	Article
AUD	Australian Dollar
BIA	UK Bio Industry Association
B-IF	Beta – interferon
BRCA, BRCA1, BRCA2	Breast Cancer susceptibility genes
CAFTA	Central American Free Trade Agreement
CARIFORUM	Caribbean Forum -Economic Partnership Agreement between the Caribbean States
CBD	Convention on Biological Diversity
cDNA	complementary DNA
CETA	EU - Canada Comprehensive Economic and Trade Agreement
CHO	Chinese hamster ovary
CJEU	Court of Justice of the European Union
CRISPR	Clustered regularly interspaced short palindromic repeats
CRISPR-Cas	CRISPR-associated (proteins and genes)
DNA	Deoxyribonucleic acid
DOE	US Department of Energy
ECJ	European Court of Justice
EEA	European Economic Area
EMA	European Medicines Agency
EMEA	European Agency for the Evaluation of Medicinal Products
EP	European Parliament
EPC	European Patent Convention
EPO	European Patent Office
EST	Expressed sequence tags
EU Biotech Directive	Directive 98/44/EC on the legal protection of biotechnological inventions

EU GMO Directive	Directive 2015/412 amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory
EU	European Union
EUR	Euro
EUREKA	European R&D funding and coordination network
FDA	US Food and Drug Administration
gDNA	genomic DNA
GI	Genetics Institute
GM	Genetically modified
GMO	Genetically modified organisms
GSK	GlaxoSmithKline plc.
hESC	Human embryonic stem cell
HGP	Human Genome Project
HGS	Human Genome Sciences Inc.
HIV / AIDS	Human immunodeficiency virus / Acquired immunodeficiency syndrome
Human EPO	Human Erythropoietin
ICT	Information and communications technology
IP	Intellectual property
IPO	Initial public offering
IPR	Intellectual property rights
ISDS	Investor-State Dispute Settlement
ITC	US International Trade Commission
J-IF	Human fibroblast beta interferon
MPEP	USPTO Manual of patent examining procedure
mRNA	messenger RNA
NBER	National Bureau of Economic Research
Neutrokine-α	(human protein) Neutrokine-alpha
NHS	UK National Health Service
NIH	US National Institutes of Health

NPE	Non-practicing entities
OECD	Organisation for Economic Cooperation and Development
OJ	Official Journal
PTAB	USPTO Patent Trial and Appeal Board
PVPA	US Plant Variety Protection Act
R&D	Research & Development
SME	Small and medium-sized enterprises
SPC	Supplementary protection certificates
TBT	WTO Technical Barriers to Trade Agreement
T-cells	Thymus cells
TFEU	Treaty on the Functioning of the European Union
TNF	Tumor Necrosis Factor
TRIPS	WTO Agreement on Trade-Related Aspects of Intellectual Property Rights
UC Berkeley	University of California, Berkeley
UK	United Kingdom
UN	United Nations
UP	Unified Patents
UPC	Unified Patent Court
US	United States (of America)
USC	US Code
USD	US Dollar
USPTO	United States Patent and Trademark Office
VC	Venture Capital
VUS	Variant of unknown significants
WIPO	World Intellectual Property Organization
WTO	World Trade Organization

Summary

This dissertation is a law and economics analysis of gene patents in the EU and the US. Although the chosen area is the medical biotechnology applications, some patent related case law examples from agricultural biotechnology, as well as other sectors such as software and business methods were also given since their effects on medical biotechnology deem important. The terms gene patents and biotech patents were used interchangeably.

The law and economics analysis enables us to understand why particular rules exist and whether they relate to efficient outcomes in increasing social welfare. Social welfare is evaluated by welfare losses due to monopoly situations granted by patent protection, plus inefficient patent races and blocking patents versus the gains by means of increased innovation, better treatment, and diagnostics opportunities for patients with improved access to health care and unambiguous rules for the innovators, businesses and the society.

In this regard, the economic theory of patents, analysis of legal systems and some specific case law examples were given. There is a dedicated chapter on case law in Chapter 4, some examples were nevertheless given in Chapter 3 on analysis of legal systems, as case law and statutory law are indispensable parts of any legal system. Some of the earlier case law examples were mentioned to show the evolvement of the patent system. Furthermore, some recent legal disputes were also reflected; one-on-one comparisons for the EU and the US were possible for certain legal disputes such as the Myriad Genetics case, patenting of CRISPR methods, human embryonic stem cells, Onco-mouse and so on. Sometimes the exact quotations from court decisions and the wording of the rules and regulations were mentioned in order to facilitate the reader's understanding.

Legal and administrative developments till April 2020 have been reflected and publicly available data could be integrated.

In economic theory of patents incentives for innovation and dissemination of information versus alternative protection /reward methods, anticommons problems were discussed. It is indeed seen that patents and trade secrets can be both utilized by the same

company such as the Myriad Genetics. Although the R&D in this sector started with public funds in the earlier stage, the private investments have taken over at a fast pace.

The earlier case law examples refer to setting the boundaries of patentability requirements and strengthening them for gene patents. Although the patentability criteria are similar in both jurisdictions, the wording of law such as utility requirement in the US vs industrial application in the EU differs in setting the scope of assessment. Besides in the EU the ordre public and morality considerations have always set the agenda in the discussions, which are also codified in law both in EU Biotech Directive and in European Patent Convention. As a result, the examinations by European Patent Office (EPO) are done with more scrutiny, and the patents granted are narrower in scope. The number of applications per examiner is also almost the double for US Patents and Trademark Office (USPTO) compared to EPO and giving the examiners more time yields higher quality patents and saves costs in terms of litigation and other transaction costs. As a result of all of these some very broad gene patents have been granted in the US, which would not be possible in the EU.

For some innovators this may be desirable though. The patenting and the commercialization of products are much faster in the US. As result biotech start-ups receive five times more private funding than their European counterparts and since 2012 of out of three European companies file for Initial Public Offering directly in the US. Indeed, the US Supreme Court held as early as in 1966 in Brenner v. Manson case that a patent system must be related to the world of commerce rather than to the realm of philosophy. Nevertheless, there is a trend of increased judicial review of issued patents in the US and the latest court cases also refer to “patent-eligibility” of subject matter. Hence, there seems to be some harmonisation between the EU and the US.

Although the (interpretation of the) different patent laws create different ex-ante and ex-post incentives, the case law has generally evolved efficiently to address some inefficiencies such as anticommons and to clarify the ambiguous rules. Some businesses have also evolved to share their patent information freely for research purposes such as at the CRISPR dispute. However decreased patient access to diagnostics and treatment has been a focal issue. In both jurisdictions the number of patent applications and the granted gene patents increase, but this does not immediately mean increased innovation. Some patenting is done in order to have a strategic bargaining position. The problem with

patent trolls and non-practicing entities (the ones which assert patent rights with litigation without practicing the invention) is especially acute in the US, but further research is necessary to determine their impact in gene patents.

In the EU, the patenting system is rather fragmented due to European and national patent systems and once the Unified Patent Court is established and unified patents are applicable, this issue will be dealt to certain extent. However, the new system will not be flawless, and there are still some uncertainties regarding the national enforcement in the EU member states.

Due to the fragmented EU patent system the full "European" setting could not be illustrated. Besides lack of litigation and other data both in the EU and in the US necessities further research in the area such as interviews with field professionals, court case and patent office analytics and quantitative research in costs and benefits. We need to measure whether after ground-breaking decisions from courts, or after certain legal amendments claim rejections from patent offices or at the courts significantly differ; how this affects the claim drafting for new applications; how many gene patents have been invalidated so far; what is the real cost of gene patents in terms of enforcement and litigation; what is the real private and social return for the patents, as well as the commercial products; how effective have gene patents been in inducing innovation; whether patent term differentiation and other R&D and tax incentives could be an option; what is the real cost of increased / decreased patient access to new therapeutic and diagnostic products. Then we may develop a clearer insight and be able to make appropriate suggestions for policy and legal amendments.

1. INTRODUCTION

1.1 Background, Motivation and Research Question

The motivation beyond this dissertation is to make a comparative study of the similar patent laws with different patenting outcomes in the EU and the US and analyze the patents given in medical biotechnology[1] from law and economics point of view. The research question to be investigated is whether the increased number of patents granted in this area are really encouraging the innovation, as well as whether they are being capable of increasing the social welfare.

Innovations belong to the group of goods and services referred to as public goods, which may be regarded as non- rivalrous: i.e., consumption of them by one person does not prevent other persons from consuming. Once new knowledge is published, anyone can enjoy this knowledge and can use this information for his own further research. Other persons can even be stimulated to come up with ideas of even bigger commercial values. As Stieglitz (1999) states there may be costs associated with the transmission of such knowledge, however this does not affect the public good nature of knowledge itself. There may be private providers who pay such costs and the good itself remains free of charge. The marginal cost of profiting from knowledge remains zero.[2]The legal rights conferred by intellectual property rights (IPR) enable the protection of an invention / creation for a certain period of time. Hence the legal framework with IPR brings exclusivity to the public good "innovation", however the ability to exclude non-payers is difficult for non-tangible goods. The non-tangible nature of IPR poses challenges compared with tangible property such as land in creating right balances for their creation and precise level of

[1] Medical biotechnology refers to use of biological material to develop pharmaceutical and diagnostics products for the prevention and treatment of diseases. The rapid growth in recent years in the medical processes and products using numerous biotech techniques have already transformed the healthcare sector allowing for quick diagnostics by gene screening, mass production of new drugs and vaccines, advancements in individualized drugs, as well as treating some genetic diseases that were previously deemed chronic or even fatal. A more detailed description and an overview on various applications of medical biotechnology are given in Chapter 3.1 Some Basics on Biotechnology

[2] STIGLITZ, J. (1999). Knowledge as a Global Public Good in I. Kaul, K. Grunberg & M. Stern (Eds.) *Global Public Goods, International Cooperation in the 21st. Century*. Oxford University Press pp. 308-325. See also CALLON, M. (1994). Is science a public good?. *Science, Technology & Human Values*, Volume 19. No. 4. pp. 395-424 where he challenges the argument that governments should invest in scientific knowledge, because of its intrinsic characteristics that makes its transformation into a complete commodity impossible and hence the market failure should be corrected by the direct investment or incentive scheme of government. He defines science as a source of variety and flexibility that causes new states of the world to proliferate and that is the very reason why the governments should invest in scientific knowledge.

exclusion limited not only in time, but also in scope. Patents exclude the non-payers and grant exclusive rights to right holders to engage in the making, using and marketing / sale of the invention and recoup the commercial benefits. In the US Constitution the IPR grants are seen as means to promote the progress of science and useful arts.[3]On the other hand, as suggested by Landes and Posner (2003) the term "public good" may be misleading referring to goods produced by the government. There are public goods such as national defense that cannot be excluded from non-payers. However intellectual property goods can be exclusive when the condition to access to them depends on payment, hence such goods do not need to be provided by the government.[4]

Patent law makes the use of the knowledge exclusive to the inventor. In order to enjoy these exclusive rights, third parties need to pay royalties to the inventor. By this way the problems associated with the underproduction of a knowledge would be solved that would come along with the non-exclusivity of the knowledge. However, the society might then underuse the patented activity, because of the monopoly rights granted to the inventor, and the monopoly price and output stemming thereof. In order to overcome this issue, the patent law grants the exclusive rights for a certain period of time and when the time passes, the knowledge is at public domain so that the marginal cost of using the knowledge becomes zero. Another way of overcoming the issue is the restriction of the scope by not granting a very broad protection. If the legislators want to make a compromise between the dynamic efficiency gains i.e. giving the necessary incentives to innovate and static efficiency losses i.e. dissemination of the knowledge and making use of the knowledge, a balance needs to be found regarding the length and the scope of the patent protection. Applying this logic to inventions in medical biotechnology is complex. Dynamic efficiency gains require the broadest scope and the longest term of protection. Static efficiency considerations require the patients to have access to testing, treatment and medicinal opportunities, but the deadweight loss of monopoly cannot be avoided. Since the length of patent protection is fixed in many jurisdictions, only the scope of

[3] The clause referred as "Patent and Copyright Clause" in the US Constitution in Article I, Section 8, Clause 8, grants the US Congress the power "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries." Based on this clause the Congress enacts legislation covering patent and copyright protection.

[4] LANDES W. M., POSNER, R.A. (2003). *The Economic Structure of Intellectual Property Law*, Harvard University Press Cambridge/Mass. p. 14

protection can be affected by (the interpretation of) the law.

If the innovators fear that other persons will consume their product for free, there is a danger that the innovation will fall below the level, which is socially optimal. In such a case, innovators will direct their efforts to those areas, where they can better recoup the costs of their innovations. As a result of this level of innovative activities, which are below the socially optimal level and innovators engaging in more profitable activities, which are not necessarily socially optimal ones; society at large will suffer.[5] In an important quantitative study on social and private returns of industrial innovations it was concluded that social rate of return (55%) from the innovations was much higher than the private rate of return (25%) to the innovating firm, itself.[6] More recent studies also point to similar results. Bresnahan's (1986), and Trajtenberg's (1990) studies also conclude that investment done for commercial research generated new output.[7] Similarly Lichtenberg (1992) found that private- funded research and development (R&D) investment has significant effect on productivity and the social rate of return from such investment is seven times as large as the return to investment in equipment and structure, whereas the social marginal product of government-funded research capital is much lower than that of private research capital. However, this finding does not necessarily imply that government funding does not contribute to social welfare. A substantial fraction of government spending on R&D is done on intangible goods such as defense and health and is not perfectly valued at national accounts data.[8] If we apply this finding to medical biotechnology it may be argued that if the private return on R&D investment is less than expected, firms may have less incentive to invest in basic research, which then becomes a publicly provided good and should be supported by the government instead.

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[5] KITCH E. (1977). The Nature and the Function of the Patent System. *Journal of Law and Economics.* Volume 20, pp 265-290 p. 265. See also EISENBERG, R., S. (1989). Patents and the Progress of Science: Exclusive Rights and Experimental Use. *University of Chicago Law Review*. Volume 56, pp. 1017-86 for a discussion of exclusive rights promoting research, and GALLINI, N. and SCOTCHMER S. (2001). Intellectual Property: When Is It the Best Incentive System?. *UC Berkeley Working Paper* No: E01-303 for a review of optimal design issues for IP especially in the case of cumulative innovation.

[6] MANSFIELD E. et al. (1977). Social and Private Rates of Return from Industrial Innovations. *The Quarterly Journal of Economics*. Volume 91. No. 2. pp. 221-240.

[7] BRESNAHAN, T. (1986). Measuring the Spillovers from Technical Advance: Mainframe Computers in Financial Services. *American Economic Review*. Volume 76. Issue 4. pp. 742-755, TRAJTENBERG, M. (1990). *Economic Analysis of Product Innovation*. Cambridge: Harvard University Press.

[8] LICHTENBERG, F. R. (1992). R&D Investment and International Productivity Differences. *NBER* Working Paper No. 4161.

Although intellectual property rights will typically create higher private returns on innovation, there are also higher costs of innovation associated with IPR. Especially in case of patent protection, costs related to prior art searching, patent filing, appeals to a patent rejection can reach significant amounts.[9] The knowledge generated in upstream research and its role in developing downstream products are also further factors that can increase the costs. If downstream product development is dependent on upstream research, which is dominated by earlier filed patents that are especially owned by multiple patent holders, the research environment can be very complicated. Hence, increased costs of sequential innovation can decrease innovative activity. Indeed, in their experimental analysis, Brüggemann et al.(2016) find that IPR enforced by license fees result in less sophisticated innovations and significantly reduce welfare by 20 to 30%.[10] Besides, according to Davidson and Potts (2016) failure to take into account social costs can also result in distorted and overstated public policies for innovative activity. The economic effect of intellectual property is not only higher consumer prices, but also centralization of industry structure and the loss of dynamic adaptive benefits that accrue from decentralization.[11] The social costs that accrue due to centralization of social control of

[9] In addition to fees charged by Patent Offices for filing, the patent attorneys also charge several fees for drafting patent files. To have an idea see for instance flat rates of a law firm in the US that focuses on start-up companies' applications starting at $ 570 up to $ 16K+ depending on the complexity of the drafting http://www.icaplaw.com/sites/default/files/ICLG%20Fee%20Schedule%20Patent.pdf. last visit 30.04.2020

An interesting court decision was given by the District Court of Düsseldorf (Landgericht Düsseldorf) on 15.01.2015 (Ref: 4b O 21/14). In this case a mandate was given to a patent attorney for the preparation and defence of a patent application, where no flat rate or hourly fee agreement was made between the parties. At the end of the application the invoice prepared by the attorney was not paid and the District Court reviewed the appropriateness of attorney fees according to Section 315 of the German Civil Code (BGB). The Court decided that an increase of 355% in flat fees compared to the fee schedule of patent attorneys from the year 1968 is appropriate given the general income and cost development over the years and acknowledged standard rates of € 90.74 for the review and forwarding of an examination report, € 54.46 for monitoring the deadline and an application for renewal, € 9.98 writing fee per page, € 54.46 for the payment of an annual fee, € 453.76 for a hearing at the German Patent and Trademark Office and several copying-costs ranging between €7.80 and €37,85. The Court also awarded an hourly fee, within a range of €200-€600 for IPRs, calculation of which would depend on the cost structure of individual law firms depending on their location whether they are in major cities with high rental and staff costs or in low-priced rural areas. The Court also emphasized that these fees are not dependent on the success of the attorney in getting the patent granted.

[10] BRÜGGEMANN J. et al. (2016). Intellectual Property Rights hinder sequential innovation. Experimental evidence. *Research Policy.* Volume 45. Issue 10. pp. 2054-2068. The authors designed an experimental Scrabble-like word – creation task, which involved use of scarce resources (letters) over a known vast space (words) fallowing sequentiality by allowing only three-letter words to be created and for such creations, subjects can license for a fee.

[11] DAVIDSON S. & POTTS J. (2016). The Social Costs of Innovation Policy. Economic Affairs, Volume 36. Issue 3. pp 282-293 at p.286.

innovation can be summarized preferential treatment of favoured firms / sectors, government selection of industry, risk-averse investment and fewer radically new discoveries.[12]

In order to generate a reasonable return on investment in R&D, patents have an impact on the incentives to invent and are expected to increase the amount of innovation. The patent system has been an essential factor to foster innovation in many technologies including medical biotechnology, particularly in the development of pharmaceuticals and diagnostic testing. Patents may also have negative effects on innovation when the results of patenting are patent races, obstructing upstream research by blocking patents, increased transaction costs in the case of licensing agreements and litigation costs. Lemley (2008) notes that especially in IT-industries, but also in some gene therapy industries, evidence suggests that the companies simply ignore the patents and do not seem to be deterred from making products due to litigation threats. When their research leads to an invention, they sometimes even don't conduct a search for prior patents before applying to US Patent and Trademark Office (USPTO). They rather wait and see if any patent holder makes a claim for the infringement of the new product with the existing patent. Even if these companies receive the first cease and desist letter from the previous patent holder, they ignore it knowing that the patent litigation is expensive and some of these warnings never result in a lawsuit. The situation is different in the pharmaceutical industries, which identify all the prior patents covering a drug, since the entry into market is strictly regulated by the Food and Drug Administration (FDA). If a generic drug company plans to enter the market, it must inform the patent holder. Even after the approval is given by the FDA to the drug company, the patent holder may still sue and receive an automatic preliminary injunction till the outcome of the patent litigation is announced. And in the pharmaceutical context, patent holders essentially almost always sue, when there is an infringement. Since the market entry is regulated and the scope of the patent, i.e., chemical structure of the drug, is clearer than in information technologies, where it is disputed what constitutes the patent, pharmaceutical companies respect the exclusivity coming with the patents and always make a prior search on the existing patents. As a result, there are rarely any generic drugs on the market before the patents

[12] Ibid pp. 288-289.

covering the drug have expired.[13]

There is also a secondary aim of the patent system in promoting the dissemination of information. Technical information that would otherwise be kept secret is made available to the public by means of a patent. Eisenberg (1989) noted that promoting scientific progress by means of patent laws can be seen as counterintuitive by the research community, which thinks that the science advances most rapidly when free access to new discoveries is possible. Although it is expected that industrial research scientists in the applied research sphere would keep their discoveries secret or patent them and academic research scientists in the basic research sphere would publish their discoveries without the fear of infringement liability, the distinction between the two spheres is difficult to maintain, especially in the biomedical sciences.[14]

Biotechnological inventions are playing an even more important role in the field of diagnostics and therapeutics today. The subject matter of the inventions in medical biotechnology is often biological material. The processes involving isolation and reproduction of these materials are expected to challenge medical diagnostics, treatments, and development of pharmaceuticals. The speed of the increase of the biotechnological methods in generating tools to be used in scientific and profitable commercial projects has resulted in a huge financial and intellectual investment by both private and public researchers. The research in biotechnology is a long lasting and expensive investment, hence there must be certain means to make it for the investor possible to recover his investment costs and to encourage him in further investment. Patent protection with the right scope may make this possible.[15] Thus, one can easily imagine that many of the investments in the field of biotechnology would not have been made if there were no patent protection. On the other hand, the fact that medical biotechnology sector gains the benefits from the patent system does not imply that the patent system in this area is working perfectly and that no further improvements shall be made. There is evidence about the commercial success of patent protection, however the social benefits of the patent system and whether the existing legal and administrative system yields the best

[13] LEMLEY, M. A. (2008). Ignoring Patents. *Michigan State Law Review*. Volume 19. Issue 1. pp. 19-34.

[14] See Eisenberg at supra note 5.

[15] The optimal duration and the optimal breadth are vital elements of the patent system, as will be explained in Chapter 2.2.

benefits for the society at large is legally and economically a more difficult task to prove. For instance, in 1990s the USPTO had stated that no new body of patent law is necessary for biotechnological inventions, provided that all requirements for patentability are met by patent applicants. The then Director of Biotechnology Examination of USPTO was comparing biotechnology to polymer chemistry industry some 40 years back, in its emerging technology state, where people had argued that granting too broad generic claims on basic polymers would devastate the industry and no such thing occurred. [16] However, we can see after 30 years of biotechnological innovation and patenting that there is evidence of too broad biotechnology patents impeding innovation due to monopolized research areas, stacking patents, patent trolls and so on. Patent trolls have been estimated to cost USD 29 billion to firms in 2011, where 59% of the defendants were SMEs. The figure does not only cover litigation costs, but also non-litigated settlements, however, does not include non-direct costs such as delays in new products, loss of market share, diversion of resources, etc.[17] Failure to account for social costs of innovation policies makes public support for such policies both distorted and overstated.[18]

The numbers of biotechnology patent applications and grants have boomed in recent years. 55% of the granted biotechnology patents at European Patent Office (EPO) in 2015 have been for medical and pharmaceutical products. [19]

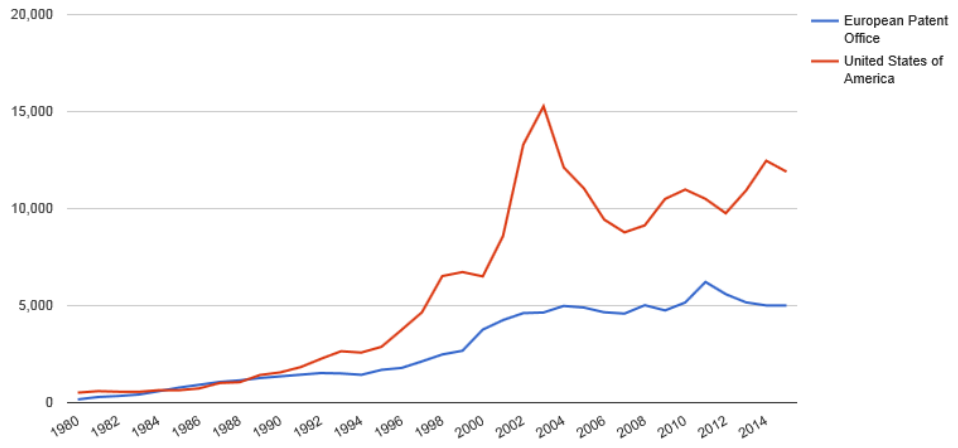
[16]. See former Director of Biotechnology Examination of USPTO, DOLL J.J. (1998). The Patenting of DNA. *Science*. Volume 280, Issue 1, pp.689-690.

[17] BESSEN, J.E. & MEURER, M. J. (2014). The Direct Costs from NPE Disputes. *Cornell Law Review*. Volume 99, Issue 2, pp 387-424. NPE (non-practicing entities) are the parties that strategically hold patent rights not with the aim of practicing the patented invention, but in order to assert these rights against infringers mostly by litigation or licenses. Patent troll is also an NPE, but in a more demeaning manner; the term is used for those ones which refuse to license and/or use infringement claims at courts to make profit and hence have no contribution to innovation, on the contrary they stifle innovation.

[18] See Davidson & Potts at supra note 11

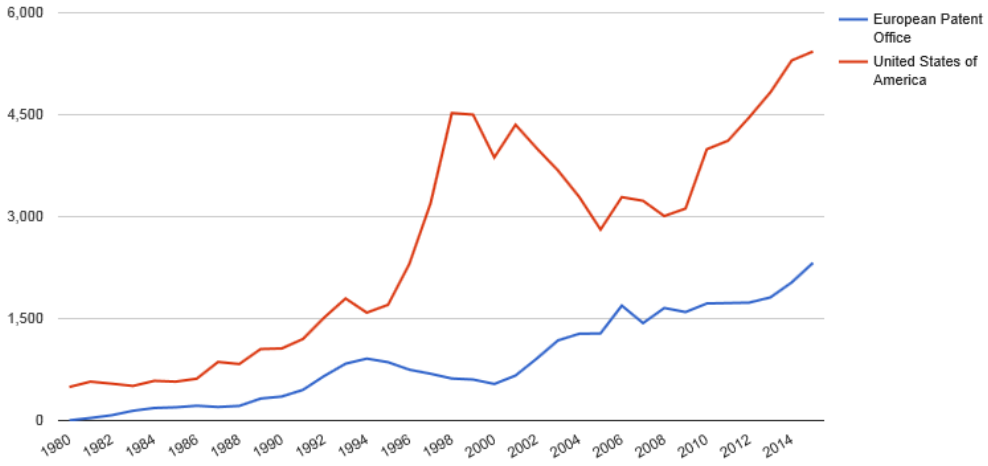
[19]https://www.epo.org/news-issues/in-focus/biotechnology-patents.html last visit 30.04.2020.

Chart 1: Biotechnology patent publications 1980-2015



Source: WIPO Statistics Database – Total count by filing office

Chart 2: Biotechnology patent grants 1980-2015



Source: WIPO Statistics Database – Total count by filing office

The above charts also point to the fact that almost 1/3 of the biotechnology patent applications is actually granted patent protection. This ratio is ½ or higher in other sectors[20], which may indicate the thorough review by patent examiners at both EPO and USPTO in biotechnology applications, as well as legal uncertainties.

Gene patents on biotechnological inventions are given for the isolated gene sequences or the chemical composition of the specific gene sequence. DNA sequencing means the process of determining the exact order of chemical blocks (nucleotide bases – adenine, guanine, cytosine, and thymine). The claims for patent protection can also be made for the naturally occurring sequences in their isolated and purified form. Today with the use of highly advanced sequencing machines and techniques, it is not a much of a challenging task to analyze genetic information. The question is whether we can view the DNA and other genetic material as any other chemical composition that is granted patent protection. The proliferation in the number of patents granted in medical biotechnology shows that the gene patents are granted according to the usual patentability requirements of the current patent laws. However, many court cases also indicate that the

[20] Own observation from WIPO Statistics database

biotechnological patent grants have indeed been very controversial and there are oppositions.

The underlying aim of having a socially optimal innovative legal framework demands an optimal level of IPR protection that is balancing all relevant interests and this approach is also reflected into sustainable development concepts of recently concluded / negotiated trade agreements.

As Ashford and Hall (2019) point out trade is accepted as a major driver of growth. However, economic rationalism and pursuit of free market conditions that eliminate / reduce barriers to competition and trade might construct the problem of unsustainable development through the lens of inadequate property rights. Economic rationalists would argue that if property rights were reassembled in a more appropriate manner, environmental resources would be "treated as inputs to the social machine," resulting in more sustainable forms of development. Hence, free market conditions may also mean elimination of restrictive health, safety, labor and environmental regulations that hamper trade and the solution to the problem is balancing the role of government with costs and benefits of the market.[21]

The introduction of more stringent standards (designed to facilitate dramatic and/or possibly to disrupt technological change) is likely to increase production costs and might encourage industries to relocate to countries with more lenient standards.[22] What we see in recently concluded / negotiated trade agreements of EU with third countries and/or trade blocks is that both the sustainable development objective and the IPR protection are integrated for a balanced policy goal where the IPR protection is not the end goal but a tool to achieve the goal of sustainable development.[23]

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[21]ASHFORD, N. A. & HALL R. P. (2019). *Technology, Globalization, and Sustainable Development, Transforming the Industrial State*, Revised Edition. Routledge, New York, pp 638-640.

[22] Ibid pp. 641-642. Although the authors argue from the point of view of environmental standards, the same line of argumentation holds for any innovation-driven strategy and how the governments should design industrial policies on one hand enabling cooperation and competition, and on the other hand increasing the welfare of industries and regions.

[23] See for instance on IPR Article 131(2) of the Economic Partnership Agreement between the Caribbean States (CARIFORUM) and the EC, OJ L 289, 30.10.2008 sets the Context stating "(parties) recognize that the protection and enforcement of intellectual property plays a key role in fostering creativity, innovation and competitiveness, and are determined to ensure increasing levels of protection appropriate to their levels of development." The significance about "levels of protection appropriate to their levels of development" in this text is that it recognizes the fact that the IPR protection must be "adapted to the needs and realities

The aim of this dissertation is to analyze the patenting of medical biotechnological inventions in the EU and the US from law and economics point of view in order to assess whether current patent laws are efficient for a new technology such as biotechnology, or whether there is a case for changes to patents law to be made. A good and efficient patent law by giving a temporary monopoly power to the inventor should support the incentives to innovate and promote the dissemination of information. In this way the static efficiency loss to consumers due to monopoly pricing and output is meant to be more than offset by dynamic efficiency gains of increased innovation. An inefficient law can on the other hand not reach these purposes and may for instance result in suboptimal level of innovation and/or litigation.

There is immense literature on the issue, but empirical findings are relatively less available. Throughout this dissertation not only theoretical aspects of the existing patent system will be discussed from a law and economic point of view but also empirical evidence about the impacts of patenting on research and development will be given by case law examples. These cases show us that patenting of a new technology such as biotechnology has not only resulted in the usual patent controversies such as monopolies, restriction of competition, hindering of research, patent thickets and trolls, restrictions in licensing terms and patent pools, but also new questions have been raised during the patenting of biological substances such as limits of patentable subject matter, ethical concerns, breadth of claims and its effect on complementary and subsequent research, access to medical care for patients, delays in treatment methods, collaborations between the public and private sector, legal uncertainties for the inventors, who want to patent in both the EU and the US, and also legal uncertainties within the EU, in different member states due to national jurisdictions.

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of individual countries". Whereas the IPR chapter in the EU-Singapore FTA, starts with the objectives in Chapter 10.2 of the Agreement such as "facilitating the production and commercialization of innovative and creative products and the provision of services between the Parties; and increasing the benefits from trade and investment through the adequate and effective level of protection of intellectual property rights and the provision of measures for the effective enforcement of such rights". Given the fact that Singapore is a more industrialized state than those ones in the Caribbean, this distinction should not be unexpected. Indeed, formal incorporation of IPR protection into trade agreements came with the Agreement on trade related aspects of intellectual property rights agreement TRIPS. Before TRIPS countries could exclude certain sectors and products from IPR protection. TRIPS set minimum standards for such protection and also brings Most Favored Nation (MFN) treatment to IPR relations among signatory parties so that nationals, products, services of different countries cannot be treated differently over IPR protection. If a country is given a preferential treatment by a WTO Member state, this treatment is extended to nationals all other WTO members. More information on TRIPS will be given in Chapter 3.2

Patenting of genes are not regarded as appropriate or inappropriate in its essence throughout this dissertation. We cannot think of gene patents as isolated forms of innovation. The innovation in medical biotechnology is an accumulated form by follow-on research. Follow-on research can be hindered in medical biotechnology because ex-ante negotiations are difficult due to transactions costs related to licensing practices, where several licenses are required from different parties. The question that is analyzed from law and economics point of view is whether the increase in gene patents also mean increased innovation and we are reaching at socially desirable situations, or whether the increase in applications and patents just point out to a strategic move to induce non-practicing entities, receive royalties, grow the firm value and profits.

1.2 Methodology

In analyzing the patenting of medical biotechnological inventions by law and economics approach the main aim is to see whether the patent laws of the EU and the US are efficient for a relatively new technology as explained in Chapter 1.1. The efficiency theory from law and economics point of view necessitates maximizing the social welfare, efficiency as such requires highest level of utility for the members of the society.[24] Hence taking individual persons into account, designing law to maximize efficiency would also be a good way of maximizing happiness.[25] As a result, in doing this analysis by taking into account dynamic and static efficiency issues, some sub-aims of the dissertation also emerge such as the impact of different patent systems on innovation, on consumer welfare by means of access of patients to medical diagnostics and treatments. Indeed, some empirical studies based on data from Gallup World Poll suggest that countries (not only developed, but also transition and less-developed ones) with generous public spending and welfare state policies report higher levels of life satisfaction[26] and out-of-pocket health spending significantly reduces people's well-being.[27] As a result, patient access

[24] SCHÄFER, H-B and OTT, C. (2004), *The Economic Analysis of Civil Law*, Edward Elgar Publishing, Cheltenham, UK.

[25] FRIEDMAN, D. (2000), *Law's Order*, Princeton University Press, Princeton, USA. p.24.

[26] O'CONNOR, K.J. (2017). Happiness and Welfare State Policy Around the World, *Review of Behavioral Economics*, Volume 4, No:4, pp-397-420.

[27] BOARINI, R. et al (2013). Can Governments Boost People's Sense of Well-Being? The Impact of

issues to diagnostics and treatment are an integral part of the discussion in this dissertation, since the social welfare in biotech patents is evaluated both by increased (incentives for) innovation, ease of performing R&D for the innovators as well as ease of commercializing the end-products / processes and by patients' access issues at reasonable costs and decreased illnesses or treated illnesses that were deemed incurable before the emergence of novel technologies.

One of the questions to be answered in this dissertation is then whether different patent systems (EU and US) have positive or negative impacts on social welfare by means of increased innovation and dissemination of information. Costs and benefits of different patent laws need to be examined from law and economics point of view with regards to dynamic and static efficiency; incentives to innovate, dissemination of information, monopoly situation and patent race. At the end it will be concluded whether the current patent laws are efficient for biotechnology or whether biotechnology needs to receive special treatment in intellectual property law. Indeed, it is observed especially in case law that although the statutory law and the patentability requirements may create inefficiencies, some of these inefficiencies are resolved by court cases.

Consequently, with regards to the problem statement above, the aim of the dissertation is to study the impact of different patent systems for medical biotechnology inventions on innovation and social welfare, the costs of monopoly situations and patent race and the possible solutions such as reward system and licensing or patent activities by public universities, where taxpayers bear the cost of investment and solving the monopoly problem. By making this analysis from a law and economics perspective, the dissertation aims to show why particular legal rules exist in different patent systems and which rules should exist, i.e., positive and normative analysis.

These analyses are primarily a discussion of the economics of patent protection and patenting requirements in the different legal systems (EU and US), related jurisprudence with some examples from the case law.

With this discussion of the economics of patent protection comes the trade-off

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Selected Labour Market and Health Policies on Life Satisfaction, *Social Indicators Research*, Volume 114, Issue 1, pp. 105-120.

between incentives to innovate and the costs for the society, especially the increased costs for the consumers also in terms of access to health care and the R&D costs of the inventors. In doing this static and dynamic efficiency gains and losses will also be taken into consideration. The losses in static efficiency by means of increased costs for the consumers due to monopoly situation should be met by the gains in dynamic efficiency by increased innovative activity. The main goal of patent protection is to increase the incentives to innovate, however such protection can also hinder innovation, especially secondary innovation mainly due to blocking patents. The economic significance of patents also depends on their scope and duration. So, it is aimed to analyze whether the current patent laws in the EU and the US for biotechnological inventions are efficient according to the economic theory of patents.

Though the methodology takes a deeper look at the law and economics approach such as the law and the application of law from incentives point of view, comparative and doctrinal legal research methods were also applied throughout the dissertation. In doing so the primary and secondary sources of law relevant for biotechnology patents were introduced with their evolution and some suggestions were made for the directions they should develop into based on their descriptive analysis and significance. As such, a comparative legal research is also part of the methodology, since different legal rules in patenting of biotechnological inventions in different legal systems of the US and the EU are discussed with slight reference to the rest of the world such as Australia, Canada, China, Central America and the Republic of South Africa. Especially in analyzing the legal differences between the EU and US systems, social, political, cultural, and historical backgrounds of the two legal systems were also discussed, as these have helped to shape the patenting of biotechnological inventions to a great extent.

1.3 Structure of the Dissertation

The first chapter of the dissertation explains the background as well as the motivation of the dissertation. The dissertation aims to investigate the impact that gene patenting in medical biotechnology products have on innovation and consumer welfare both from law and economics point of view; dynamic and static efficiency issues are explored in the EU and the US. The goal of the study is not to say one patenting system

is better than the other, but to investigate whether the current legal treatments of gene patents in both systems are optimal and whether there is a scope for change and if yes on what basis this change should rely on.

The second chapter gives an overview on the patents from an economic point of view. Scope of patent protection, theories on incentives to invent and to disclose, prospect theory as well as property and liability rules with regards to medical biotechnology patents are discussed.

The third chapter is the positive analysis of the legal systems in the EU and the US with respect to patentability criteria of genes confronted with the findings of the economic theory as discussed in Chapter 2.

The fourth chapter gives examples from the current practice in the EU and the US via case law. Different patenting approaches are discussed.

The fifth chapter is the economic assessment of the legal differences between the EU and the US on having innovation versus having access to information and for the consumers having access to health care and for the innovators and businesses the legal certainty provided by the systems.

The final chapter concludes the dissertation.

2. ECONOMIC THEORY OF PATENTS

The economic rationale of patents is to give the inventors a temporary monopoly power in order to encourage invention. The net social benefit of a patent is the difference between the welfare of the society due to the innovation and the costs related to the invention, i.e., private costs of the inventor due to R&D and the cost to the consumers due to monopoly pricing. There are also other costs associated with over-investment due to patent races and accruing additional costs for sequential innovators and rent seeking.[28]

An interesting study claims that patent protection is not always necessary for investments to be made. With patent protection, R&D competition leads to a symmetric equilibrium where firms over-invest in marginal innovation but under-invest in difficult innovation and calls for public authorities to intervene to promote specific research in certain sectors.[29]

In a study of the causal effect of removing patent rights by court invalidation on subsequent research related to the focal patent, (by exploiting random allocation of judges at the U.S. Court of Appeals for the Federal Circuit to control for endogeneity of patent invalidation) it was seen that patent invalidation leads to a 50% increase in subsequent citations to the focal patent on average (beginning two years after the court decision), with heterogeneous impact and depending on characteristics of the bargaining environment. Patent rights block downstream innovation and invalidations have a significant impact in computers, electronics, and medical instruments (including biotechnology), but not in drugs, chemicals, or mechanical technologies. This effect is found to be entirely driven by invalidation of patents owned by large patentees that

[28] Boldrine and Levine define rent-seeking as keeping the competitive advantage by turning the innovation into a monopoly, either through various forms of legal exclusion, or by making it very hard for competitors to imitate and reproduce the good. By quoting Adam Smith they point out to the fact that a monopoly granted to an individual or a company has the same effect of a trade secret. Hence monopolistic and trade secret activities are referred as public and private rent-seeking. Their results are mixed as public rent-seeking does not necessarily imply reduced private rent-seeking or increased welfare. They state that an optimal patent policy is the one treating different goods, different industries, and different markets differently. See BOLDRIN M. & LEVINE D. K. (2004). Rent-seeking and innovation. *Journal of Monetary Economics.* Volume 51. Issue 1. pp.127-160.

[29] LAFAY, T. & MAXIMIN C. (2015). How R&D Competition Affects Investment Choices. *Managerial and Decision Economics*. Volume 38. Issue 2. pp 109-124.

triggers more follow-on innovation by small firms.[30]

Buchak (2016) argues that when there are many investors relative to investment opportunities, and investors have sufficient bargaining power, they would quickly fund uncertain projects without making a through due diligence due to fear of missing out and this gives rise to bubble-like high-quantity, high-valuation investment behavior with many funded projects failing.[31] Designing the optimal patent law with regards to biotechnological inventions is a difficult task that should compromise the various economic theories.

Below an overview of some economic aspects is given.

2.1 Some Basics on Patents as Property Rights from an Economic Point of View

In order to determine whether it is socially beneficial to grant patent protection to a new invention, we need to analyze the costs and benefits of patent protection. The benefits of excluding third parties from production, distribution, or commercial use of the patented subject matter plus the benefits of having increased amount of innovation should exceed the costs of enforcing the patent protection, and also the social costs of granting monopolistic rights. If not, the inventor may consider alternative protection methods such as trade secrets, which are less costly than patenting. In addition to the usual costs in terms

[30] GALASSO, A. & SCHANKERMAN M. (2015). Patents and Cumulative Innovation: Causal Evidence from the Courts, *The Quarterly Journal of Economics*, Volume 130, Issue 1, pp 317–369 at p. 320-321.

[31] BUCHAK, G. (2016). Overinvestment and the Fear of Missing Out. *University of Chicago research paper* available at https://pdfs.semanticscholar.org/5861/526cd9eee4a0a78f2481fc6dc89d04f8ad80.pdf last visit 30.04.2020. The author further states that the fear of missing out drives claimants to forgo information-producing activities that are efficient but time-consuming because they risk losing out on the claim altogether. The option to invest only after learning is a valuable real option, but that option belongs in the commons. Starting with HARDIN (1968. *Science.* Volume 162. Issue 3859. pp. 1243-1248) analysis of Tragedy of the Commons, he finds similarities with the claim jumping model of California Gold Rush for natural resource extraction. His project model is not based on mining activities for natural resources, but on innovating industry with potentially profitable ideas and in his analysis, he finds severe claim jumping, i.e., illegal possession of or the attempts to seize those claims that legally belong to another party. He also shows that the financial structure of an innovating industry is also important even if intellectual property rights exist.

of fees to be paid, patent application and registration procedures are lengthy, which may add additional up-front costs to the innovators and businesses if they want to commercialize the product.

The legal concept of property is a bundle of rights over resources that the owner is free to exercise and whose exercise is protected from interference by others, hence property creates a zone of privacy in which owners can exercise their will without being answerable to others.[32] Innovation is an important element for economic growth.[33] The dissemination of information versus protection of the inventor's rights has been a controversial issue. It needs to be analyzed which incentive problems may arise in a world without patent protection and what alternative protection methods may be applicable so that the socially optimal level of wealth may be reached with the least economic costs.[34]

A patent is a set of exclusive rights given to the inventor for a limited period of time as a counterpart for making the information available to the public. This is a right to exclude others from making, using, offering for sale, or selling or importing the invention throughout geographical coverage of the patent. The word "patent" is the short form of the "letters patent" and it derives from the Latin "litterae patentes" meaning an open letter, i.e., some kind of a government notice for the grant of an exclusive right for making

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[32] COOTER R.& ULEN T. (2016). *Law and Economics,* 6th Ed. Addison Wesley Educational Publishers Inc. p. 73.

[33] The relationship between economic growth and innovation has been studied well in the literature and it is accepted that technological innovation has been a major drive in output growth of industrialized countries. See for instance SCHUMPETER, J. A. (1934). The Theory of Economic Development: An Inquiry into Profits, Capital, Credit, Interest, and the Business Cycle. *University of Illinois at Urbana-Champaign's Academy for Entrepreneurial Leadership Historical Research Reference in Entrepreneurship*. Available at SSRN: http://ssrn.com/abstract=1496199 last visit 30.04.2020 MANSFIELD E. (1972). Contribution of R&D to Economic Growth in the United States. *Science* 4 February 1972: Vol. 175 no. 4021 pp. 477-486; RIVERA-BATIZ L. A. & ROMERP. M.(1990), Economic Integration and Endogenous Growth, *NBER Working Paper* No. 3528; AGHION, P. & HOWITT P. (1992). A Model of Growth through Creative Destruction. *Econometrica.* Volume 60, pp. 323-51. And for the last but not least SOLOW, R. M. (1957). Technical Change and the Aggregate Production Function. Review of Economics and Statistics. Volume 39. Issue 3. pp 312-320. According to his model the US economic growth during 1909-1949 resulted mainly from technical advancements, i.e., innovation and not much by factor inputs of labor and capital.

[34] EGER, T. (2006). Patentrecht – Fluch oder Segen? Einige Anmerkungen zu einem ewig jungen Thema aus ökonomischer Sicht, in: H. G. Nutzinger (Hg.): *Wissenschaftsethik – Ethik in den Wissenschaften?*, Marburg: Metropolis pp. 79 – 110.

something open for the public eye. The first grants of exclusive rights were merely associated with medieval guild system in Europe.[35] Especially monarchs of Middle Ages gave out royal grants not necessarily to inventors, but to their favorites in order to create commercial monopolies. It was through such monopolies that some cities and associations thereof such as the Hanseatic League strengthened their situation and rose to great power.[36] For the continental Europe it is generally accepted that patenting started in Italy, in the Republic of Venice. As early as 1332 the Republic of Venice had a special privilege fund, from which payments to inventors were made. Such financial aids were early means of promoting new arts and science. To give such a privilege the notion of "utility" was the main requirement. Disclosure of the "invention" took place by the actual use, instead of written specifications. Novelty and inventive step were investigated merely in an incidental way. It was by the patent law of 1474 that required a new invention.[37]

In England, the first patent in today's sense was a 20-year monopoly right given in 1449 to John of Utyman in a process of manufacturing of colored glass. However this was an isolated grant and no similar grants occurred until the middle of the 16th century.[38] In 1552 Henry Smyth received again a 20 year monopoly right for production of a Normandy glass.[39] However monopoly patents were merely regarded as political patronage and royal prerogative rather than legal rights.[40] With the adaption of "Section 6 of the Statute of Monopolies" in 1623, the English monarchs started granting

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[35] MOSSOFF, A. (2001). Rethinking the Development of Patents: An Intellectual History. 1550-1800. *Hastings Law Journal*. Volume 52. pp. 1255-1322.

[36] FEDERICO, P. J. (1929). Origin and Early History of Patents. *Journal of the Patent Office Society*. Volume 11. pp.292-305 at p. 292.

[37] PRAGER, F. D. (1944). A History of Intellectual Property from 1545 to 1787 *Journal of Patent Office Society*. Volume 26. pp 711 – 760 at p: 711-716. For English translation of the Venetian Statute on Industrial Brevets, Venice (1474) see Primary Sources on Copyright (1450- 1900). In L. Bently, & M. Kretschmer (Eds.*)*. *www.copyrighthistory.org* – last visit 30.04.2020.

[38] BOEHM, K. & SILBERSTONE, A. (1967). *The British Patent System Volume 1. Administration*, Cambridge, UK, Cambridge University Press, p. 14.

[39] See Mossoff supra note 35 p. 1260.

[40] See Mossoff supra note 35 p. 1267.

monopolies only to inventions.[41] Mossoff (2001) argues that the Statute of Monopolies represents the first definitive step toward the shift away from royal prerogative and privileges to legal rights.[42] He states that the development of patent law between 1600 and 1800 involved a fundamental change from "viewing a patent as a contract between the crown and the patentee" to "viewing it as a 'social contract' between the patentee and society".[43]

During the Industrial Revolution, the number of patents granted increased particularly in England; the number of patents sealed increased from 1,811 during the period 1750-1800 to 11,416 during the period 1801-1850.[44] Consequently some other countries started to adapt their legal system as well. The first patent law was introduced in 1790 in the US[45]; over 17,000 patents were granted in the period 1790 -1850.[46]

At the same time nineteenth century Europe witnessed controversies and criticisms on granting of special privileges and monopolies. Especially between 1850 and 1875 the discussion was about not only a reform but a total abolishment of the patent system.[47] The opponents of the patent system argued that patents were similar to tariffs; restricting free trade and competition and that the inventors should receive alternative rewards such as payments from government or private industry.[48] These arguments were more

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[41] See Mossoff supra note 35 p. 1272- 1273.

[42] See Mossoff supra note 35 p. 1272.

[43] See Mossoff supra note 35 p. 1257-1258 - quoting the article of WALTERSCHEID, E.C. (1995). The Early Evolution of the United States Patent Law: Antecedents (Part 3). *Journal of Patent and Trademark Office Society.* Volume 77. pp. 771-793.

[44] DUTTON, H. I. (1984). *The patent system and inventive activity during the Industrial Revolution*. Manchester University Press, p. 2, Table 1. English Patents sealed 1750-1851.

[45] PRAGER, F. D. (1961). Historic Background and Foundation of American Patent Law. *American Journal of Legal History*, Volume 5, pp.309- 325 at p. 320.

[46] Own calculations from the table of annual US patent activity since 1790, available at http://www.uspto.gov/web/offices/ac/ido/oeip/taf/h_counts.htm, last visit 30.04.2020. Starting in 1930 we see the first plant patent applications at USPTO some of which have been granted patent protection in 1931.

[47] MACHLUP F. & PENROSE. E. (1950). The Patent Controversy in the Nineteenth Century. *Journal of Economic History*. Volume 10, Issue 1, pp. 1-29.

[48] See Machlup & Penrose supra note 47 pp 3-9.

significant in some countries, than in others. For instance, in Holland the patent system was abolished as a result of these debates in 1869 and could only be enacted again in 1912.[49]

The proponents of the patent system regarded patent protection as a natural right and private property of own ideas, an instrument of a duty of the society to secure an inventor a fair share of his work, enabling him to live by his work, as well as a way of assuring society's interest in having industrial progress at the least possible costs, where inventions and their exploitation were deemed essential to secure industrial progress and the most effective way of achieving this progress.[50]

Similar arguments as in the 19th century are debated in favor of and as opposed to patent protection today. Yet today patents are one of the key legal tools along with first mover advantages and trade secrecy to assure protection of intellectual property. In some industries innovators can prefer first mover advantage and secrecy over patents due to high costs of patenting or with the belief that early entry into market with correct branding will yield substantial rent. In a survey given to 1478 research labs in the US manufacturing sector, over 50 % of the respondents stated that first mover advantage (lead time) and secrecy are the two most effective mechanisms for product innovations except pharmaceutical and medical instruments industries, whereas 34.8% responded that patents are effective. In process innovations trade secrecy is seen as the most effective mechanism by over 50% of the respondents, followed by complementary manufacturing (43%), lead time (38.4%) and patents (23.3%). The preference of secrecy in process innovations to product innovations is not regarded surprising to the authors, as processes are less subject to public scrutiny and can be kept secret more easily. The effectiveness of patents is less for process innovations compared to product innovations, which is also not surprising, as patent infringements are more difficult to detect for process than product innovation given that the former is less public.

[49] See Machlup & Penrose supra note 47 pp 5-6.

[50] See Machlup & Penrose supra note 47 pp 8- 10.

One of the most striking outcomes of the survey is that patenting firms in product industries claim to be patenting in order to prevent copying, but also in order to block rivals to strengthen their positions in cross-licensing negotiations, and to prevent lawsuits. Although most firms in product industries consider first mover advantages, secrecy and the exploitation of complementary capabilities as the most effective means of protecting their inventions, instead of patents, the study suggests that patent portfolio races in these industries may show excessive patenting, which is undesirable from a social welfare perspective and which raises the cost of innovation unduly.[51]

However, if there is a bias to use trade secrecy rather than patenting, this may move the innovative activity from innovations that cannot be kept secret easily to those ones that can be.[52] Evidence from 19th century world fairs show that countries without patent protection had similar rates of innovation compared to countries with patent system, however they were specialized in industries that were easy to keep secret.[53]

If we analyze the situation from a law and economics point of view, in case an innovation can be kept secret for a period of N years, and the patent system grants protection for a period of T years, the innovator shall patent if $N \leq T$ when the additional marginal costs of extending the patent is smaller than the additional marginal benefit of having the patent. In most patent systems patent protection is granted for a period of 20 years starting from the filing date of application.[54] Both in the EU and in the US, it is possible to receive an extension of the patent term under specific conditions.[55] This

[51] COHEN, W.M., NELSON, R.R. & WALSH, J.P. (2000). Protecting Their Intellectual Assets: Appropriability Conditions and Why U.S. Manufacturing Firms (or Not). *NBER Working Paper* 7552.

[52] MOSER, P. (2004). Determinants of Innovation - Evidence from 19th. Century World Fairs. *The Journal of Economic History*, Volume 64, Issue 2, pp. 548-552.

[53] See Moser supra note 52 also MOSER, P. (2005). How do Patent Laws Influence Innovation - Evidence from 19th Century World Fairs. *The American Economic Review*, Volume. 95, pp. 1214-1236.

[54] Article 33 of World Trade Organization's TRIPS (Trade Related Aspects of Intellectual Property Rights) Agreement reads as follows: The term of protection available shall not end before the expiration of a period of twenty years counted from the filing date. Also, Article 63 of the EPC (European Patent Convention) reads as follows: "The term of the European patent shall be 20 years from the date of filing of the application". Similarly, for the US 35 USC§ 154 reads as: "Subject to the payment of fees under this title, such grant shall be for a term beginning on the date on which the patent issues and ending 20 years from the date on which the application for the patent was filed in the United States."

[55] For the US case, see US 35 USC § 154, where USPTO (United States Patents and Trademark Office)

limited monopoly power for the inventor makes it possible to recoup the costs invested in research and development (R&D). Hence the first aim of the patent system is to give incentives for inventors to recover their sunk costs, to invest more in R&D and to create innovative products and methods.[56]

The second aim of the patent law is to promote dissemination of information. Information that would otherwise be kept secret is directed to public domain with the help of the patent. This is a very important characteristic of the patent system. Without patents inventors could only utilize trade secrets to protect their inventions. This could result in repetitions of existing inventions and would slow down the process of developing further inventions.[57]

Since the subject matter of a patent is an invention, the claims can be on "products", on "processes" (methods of making or using something) or on "products by process" (products in terms of the method or means used to create that product). A product patent allows a monopoly right to the patentee on the final product apart from the processes used to manufacture it. A process patent allows monopoly right to the patentee in a specific process; however, it does not exclude others from using different methods or processes in order to obtain the same product. A product by process patent allows the patentee monopoly rights on the product obtained through the exact process of preparation as described in the claim. As Merges and Nelson (1990) point out, product patents allow a broader scope of protection than process patents, that's why they are more favorable for inventors. Hence the inventors usually seek and obtain product patents.[58] The broader the

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guarantees the extension of the patent term, if delays happen due to the failure of USPTO or by the time consumed by a Federal Court during the examination of the patent application. US 35 USC § 156 allows the extension of a patent if the product has been subject to a regulatory review period before its commercial marketing or use. This is especially the case for products, which primarily use recombinant DNA technology. In the EU it is possible to obtain an extension of the patent term for pharmaceutical products by means of a supplementary protection certificate (SPC) for a maximum of 5 years after the expiry of the original patent term. The rationale of the SPCs is also to compensate the time elapse between the filing of a patent application and regulatory authorization for the marketing of the product. The SPCs for medicinal products are granted under Regulation 469/2009/EC.

[56] See Kitch supra note 5 pp.276-280.

[57] See SHAVELL, S. (2004). *Foundations of Economic Analysis of Law*, Harvard University Press p.145.

[58] MERGES R. P and NELSON R. R. (1990). On the Complex Economics of Patent Scope. *Columbia Law*

scope of a patent, the larger will be the number of competing products and processes that will cause an infringement.[59] In a patent application the applicant describes in the first part the invention and in the second part he presents the set of claims. Thus, the products and processes that the inventor claims to be the scope of the invention are presented in the second part. However, the scope of the patent is determined by the patent offices and the courts.[60] It is up to the patent office examiners to review a patent application and approve the grant of protection for the specified claims and courts may further determine the scope especially in cases of infringement. The scope of a patent determines the economic significance of the patent[61] and determining the appropriate scope matters in terms of economic efficiency in a world where the Coase theorem with zero transaction costs for bargaining and licensing would not apply.[62]

In biotechnology legitimacy of product patents is often disputed. Researchers in medical biotechnology use microorganism such as bacteria and yeast, or biological substances such as enzymes and other means or processes to produce purified and isolated versions of naturally occurring biological substances. The process, by which the purified version of the naturally occurring product is created, is specified in the claim of the application. But in some cases, even a novel process can be found to be infringing an existing product patent.[63] Hence the patent offices and the courts must be very careful in assigning product patents on genetic material, as this initial allocation of property rights would affect the efficient progress of science and technology in medical biotechnology.

Trade secrets may be utilized as alternative means of protecting biotechnological knowledge. Unlike patent protection, which has a limited term of protection, trade secrets

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Review, Volume 90, No: 4, pp. 839 – 916 at pp 851-852.

[59] Ibid p. 839.

[60] Ibid p. 840.

[61] Ibid p.841.

[62] See Cooter & Ulen supra note 32 at pp. 120-122, for a review of the realistic assumption that transaction costs impede bargaining.

[63] See Merges & Nelson supra note 58 at p. 851, footnote 52. For the analysis of the Coasian world with zero transaction costs see COASE, R.H. (1960). The Problem of Social Cost. *Journal of Law and Economics*, Volume 3, pp 1-44.

bring the benefit of not being in the public domain at all. However, in the age of biotechnology where there are numerous developments, publications and movement of research staff from one institution to the other, it is very difficult to keep methods and techniques secret.[64]

The first patent for a biotechnological invention is regarded to be initiated by Diamond v. Chakrabarty case in the US.[65] After several discussions, which will be examined in Chapter 4.2 of the dissertation, the Supreme Court of the US ruled that a live human-made micro-organism is a patentable subject matter.

Accordingly, the first challenge with the patenting of biotechnological inventions is the notion of patenting living creatures and the dispute over man-made versus naturally occurring forms of existence. The discussion on invention versus discovery will be presented for both the EU and US patent systems throughout the dissertation.

Another controversial issue with the patent system is the notion of efficiency. In addition to the philosophical discussion on "natural rights" of inventors; much discussion and economic analysis is currently on patents' ability to improve economic welfare by encouraging technical progress.[66] The static efficiency loss due to monopoly situation in patent system is expected to be offset by means of dynamic efficiency gains of increased innovation. Consequently, the second challenge with the biotechnological patents is the continuous blend of various biological sciences in applications, hence the proliferation of upstream research patents and the slowdown in downstream product development, i.e., innovation.[67] So it needs to be analyzed, whether the patents in medical biotechnology

[64] See Microbix Biosystems, Inc. v. Biowhittaker, Inc. 184 F. Supp. 2d 434 (D. Md. 2000) where the plaintiff sought damages for violation of "Illinois Trade Secrets Act" due to movement of scientists.

[65] Case 447 US 303 (1980).

[66] See for instance WALLERSTEIN, M.B, MOGEE, M.E. & SCHOEN, R.A. (1993), *Global Dimensions of Intellectual Property Rights in Science and Technology*, First edition, National Research Council, Washington, p.20, DERCLAYE, E. (2012). Eudemonic intellectual property: patents and related rights as engines of happiness, peace, and sustainability, *Vanderbilt Journal of Entertainment and Technology Law*, Volume 14, Issue 3, pp.495-543. HUANG, C-Y. & YANG, Y. (2017), The Growth and Welfare Analysis of Patent and Monetary Policies in a Schumpeterian Economy, *International Review of Economics & Finance*, Volume 52, pp 409-426.

[67] The expressions "upstream" and "downstream" indicate the place of the institutions in the R&D field.

really give incentives to innovate, or whether other forms of protection should be favored. For instance, the case of monopoly prices in medical biotechnology results in problems of access to pharmaceuticals especially in developing countries.[68]

2.2 Scope of patent protection

2.2.1 An overview

Generating incentives to innovate may encourage innovative activity, however, a patent system with less innovative activity but more disseminated knowledge may be more beneficial than a system with more innovative activity but less disseminated knowledge. The important issue is whether the patent system generates a balance between creating knowledge and disseminating knowledge. In creating this balance, the scope of the patent protection is very significant. It is the key element to address the R&D and monopoly trade-off. By scope the focus is on the breadth and length of patents.

Patent breadth is an important tool of patent protection. The patent application consists of the description of the invention and a list of claims. The claims are not valid, if they are not fully described and enabled. Thus, the breadth of a patent is very much related to the non-obviousness and enablement requirements of the patent law. Breadth

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Upstream institutions produce raw data and enable downstream institutions to use these data and develop therapeutic, diagnostic and other materials. See RAI, A.K., (2001), Fostering Cumulative Innovation in the Biopharmaceutical Industry: The Role of Patents and Antitrust, *Berkeley Technology Law Journal*, Vol. 16 Issue 9 pp 813-853.

[68] A report of World Health Organization's (WHO) Commission on Intellectual Property Rights, Innovation and Public Health (CIPIH) reveals problems arising from intellectual property rights and access to drugs in developing countries and suggests some open solutions; "Public health, innovation and intellectual property rights" World Health Organization, 2006, available at http://www.who.int/intellectualproperty/documents/thereport/ENPublicHealthReport.pdf, last visit 30.04.2020. Also see UNCTAD, 2011 report Using Intellectual Property Rights to Stimulate Pharmaceutical Production in Developing Countries, http://unctad.org/en/Docs/diaepcb2009d19_en.pdf last visit 30.04.2020

'T HOEN, E. (2016). *Private patents and public health, changing intellectual property rules for access to medicines*, Health Action International, the Netherlands pp 2-11.

MITCHELL, A. D. & VOON, T. (2009). Patents and Public Health in the WTO, FTAs and Beyond: Tension and Conflict in International Law, *Journal of World Trade,* Volume 43, Issue 3, pp. 571-601.

refers to the scope that the patent covers in which another inventor can build an invention upon the existing patent without infringing the original invention. In patent disputes the courts first need to decide on the legally accepted breadth as granted by the Patent Office, then need to determine whether or not an infringement takes place. If a new patent claim is very similar to the previously granted one, the courts may see an infringement case and narrow the breadth. Hence in many cases it is acknowledged by the court how broad or narrow a claim can be and which claims shall be excluded from the patent. So, the breadth will be determined by setting the scope of protection in order to enable someone skilled in the art to make use of the patented invention. The higher the number of claims that are being protected in a patent, or the more widely their specifics are formulated, the broader will be the scope of protection and more difficult for the competitors to invent around. If there is a lack of enablement or a lack of written description with very broad patent scope, there is a problem with the very essence of the patent that the inventor must disclose information to the public on how to make / use the patented invention. A recent court case demonstrates this problem where the Federal Circuit affirmed the district court's decision invalidating the claims of two patents of antibodies for failing to meet the written description requirement.[69] The breadth of the patent depends on the number of claims that are protected, thereby defining the range of similar inventions that are also protected.[70] In a patent with a high number of claims the value of the patent also increases, but also the

[69] 759 F.3d 1285 (2014) AbbVie Deutschland GmbH & Co. v. Janssen Biotech, Inc., The Company AbbVie owned two patents on antibodies that bind to human interleukin 12 (IL-12). The patent owner Abbvie sued company Janssen for infringement and Jannsen and Centoor Biologics LLC started an interference action seeking district court's review of the patents. Their argument was that AbbVie did not disclose enough specification, hence could not have possessed such an invention to claim such a broad genus of antibodies. It was stated by the Federal Circuit that AbbVie's application shared the same written description, and both claimed priority from a provisional application filed in 1999, claiming what the antibody is capable of doing rather than specifically defining the invention. These two patents claimed the entire genus antibodies that bind IL-12. Furthermore, AbbVie provided about 300 antibodies having a range of IL-12 binding affinities with very similar characteristics to each other (such as sharing a 90% or more amino acid sequence similarity and over 200 of those antibodies were generated by site-directed mutagenesis of Y61 and thus differ from Y61 by only one amino acid and sharing a 99.5% sequence similarity in the variable regions). These examples did not cover the broad scope defined by the claims put into application of the patents. Hence the Federal Circuit ruled that AbbVie's claims lacked adequate written description affirming the district court judgement. Patents were invalidated.

[70] See LANJOUW, J. & SCHANKERMAN, M. (1999). The Quality of Ideas: Measuring Innovation with Multiple Indicators, *NBER Working Paper No. 734.* Number of claims is regarded as one of the measures of patent breadth, which is also an indication of greater potential profitability.

likelihood of being litigated.[71] It was also shown for privately held biotechnology firms that the breadth of patent scope significantly affects valuations of the firms where one standard deviation increase in average patent scope suggests a 21% increase in the value of the firm.[72]

In terms of incentive effects, the expected value of patents is very important for the inventor's patent application. The larger the breadth of a patent, the greater is the profit of the inventor and the incentive to invent. However broad patents increase the monopoly power of the inventor and the deadweight loss, hence decrease the consumer welfare. Patent scope policies differing across product groups and increasing the patent profit for the inventor with the least social cost should be the preferred optimal policy. If the demand for the product is elastic, then the non-consumption of the patented product may occur, or the demand may shift to unpatented lower-priced varieties of the products sold by the competitors. In such a case a narrow patent scope to ensure low prices should be the preferred policy. If the consumers have similar demand for a (biotechnological) drug with alternative formulations of different side effects, then a broad but a short-lived patent may be preferred.[73]

It was shown that there is a higher probability of grant and a shorter examination process with narrower claims at publication than with broader claims also that the examination process narrows the scope of patent claims in terms of both claim length and claim count, and that the changes are more significant when the duration of examination process is longer.[74] In his Prospect Theory, Kitch (1977) states that patent system should grant broad patents in the early development phase of inventions to serve as a prospect

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[71] Ibid p. 18.

[72] LERNER, J. (1994). The Importance of Patent Scope: an empirical analysis. *RAND Journal of Economics*, Volume 25, No 2, pp 319 – 333.

[73] KLEMPERER; P. (1990). How broad should the scope of patent protection be? *RAND Journal of Economics*, Volume 21 No.1, pp 113-130. at p. 127

[74] MARCO, A.C., SARNOFF, J. D. & DE GRAZIA, C. (2016). Patent Claims and Patent Scope. *USPTO Economic Working Paper No:2016-04* available at SSRN: https://ssrn.com/abstract=2825317 last visit 30.04.2020.

function.[75]

Patent length determines the term during which the inventor will keep his monopoly power. Hence it is expected that the longer the expected valuable use of the patent is, the longer should be its duration. This would efficiently induce innovators to invest more into R&D.

Optimal length and breadth of a patent are related to achieve socially desirable ends. Increasing the length and breadth of a patent can both increase the incentives to invent and the problem of monopoly pricing. Moreover, an increased breadth also brings the problem of patent infringements and oppositions. Other way around if there are too many oppositions and infringing claims, this may also mean that the first patent has been too broad. Gilbert and Shapiro (1990) showed that a narrow patent with infinite duration is more preferable to a broad patent with short duration due to the reason that the increase of the deadweight loss is higher with increased breadth than with length.[76]

In practice the term of patents is limited to 20 years in Europe and the US. European Patent Convention and TRIPS provide 20 years of protection starting from actual filing date. In the US the patent term was also changed to 20 years for utility patents starting as of June 8, 1995 filing date to comply with TRIPS. Before this date, the patent term was 20 years from filing date or 17 years from issue date. This meant intentionally delayed publication and issue by the applicants for longer protection and resulted in the so-called "submarine patents". Before 2000 the patent applications were not published in the US till the patent was granted. For strategic reasons inventors kept their applications pending at the USPTO for a long period of time till further scientific, technological or industrial developments have taken place in the market, which would require a license from the first inventors. The patents then emerged like a submarine coming on surface, where the first inventors could claim priority to their initial applications.

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[75] See Kitch supra note 5 pp.267,276-277.

[76] GILBERT R. & SHAPIRO C. (1990). Optimal Patent Length and Breadth, *The RAND Journal of Economics*, Volume 21, pp. 106-112.

The submarine patents were especially problematic in industries with rapid innovation and caused significant costs on firms doing independent research. Among the famous submarine patent holders there were persons holding nearly 500 patents and several hundreds of other applications that have been pending at USPTO for 20 years or more. Abolition of this system was regarded as a major benefit by many, who regarded that 17 -year term was at the expense of the public.[77] However, the biotechnology industry had opposed the new law which brought 20 years of protection after the filing date. The industry argued that USPTO's processing of applications was very slow and biotechnological applications can take more than 3 years to process.[78] Changing the patent term to 20 years from the filing date on would mean shortening of the life of a patent, and effective life of a patent indeed begins for biopharmaceutical products after the FDA approval. Yet, an empirical study carried on as early as 1994 showed that the new law gives the patentees more protection than the old law in many industries with general, electrical, and chemical patents. For the biotechnology industry the results were not fully conclusive due to the small sample size but hinted to less protection.[79]

On the other hand, a fixed patent term of 20 years is found to be distorting cancer R&D investments due to the time lag between the invention and commercialization of the product. Effective patent terms can be different for different stages of commercialization. Patent protection is granted at the time of invention, and commercialization takes place at a later stage. Drug companies choose not to continue with R&D, if they think that the remaining patent life is not sufficient to make clinical trials, get an approval and put the drug onto the market. The estimation of the R&D distortion is found to be USD 89 billion per year, taking also into account social value of patients' life-years lost.[80]

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[77] See Lemley at infra note 79 pp 377-379.

[78] See the Biotech Trade Association BIO position available at https://archive.bio.org/advocacy/letters/bios-testimony-patent-reform-maximize-innovation-biotechnology-industry last visit 30.04.2020, also Lemley at infra note 79 at p. 376.

[79] LEMLEY, M. A. (1994). An Empirical Study of the Twenty-Year Patent Term, *AIPLA Quarterly Journal*, Volume 22, Numbers 3&4, pp. 369-424.

[80] BUDISH, E. B., ROIN, B. N. & WILLIAMS, H. L. (2013). Do Fixed Patent Terms Distort Innovation?: Evidence from Cancer Clinical Trials. *Chicago Booth Research Paper* No. 13-79.

A possible extension of the patent length up to 25 years exclusively for pharmaceutical patents is in discussion and even enforced in some jurisdictions. For instance, in the EU supplementary protection certificates (SPC) add up to 5 years of additional protection. In Australia pharmaceutical substance claims can be extended up to 5 years so that effective patent term can be 15 years provided that the patent protection shall not exceed 25 years.[81] China's draft 4th. patent law amendment also envisages a patent term extension of 5 years for innovative drugs to compensate for the delays in approval processes provided that the total effective term of the patent shall not exceed 14 years.[82] On the other hand, these extensions in patent duration result in delays for the generic medications to enter the market. A balance needs to be made between the incentives for drug innovators to offset for the losses they encounter due to reduced effective patent term and the access to medicines at lower prices. Australia acknowledged the problem of rising costs for the government subsidy program that is used to offer affordable medicines to citizens. This problem was addressed to some extend by a brand substitution policy to encourage the use of generic drugs allowing the pharmacists to give the patients generic medicines unless otherwise stated on their prescriptions. However, a 2016 report from the Australian Productivity Commission found these patent term extensions to be unwarranted and expensive, resulting in an estimated AUD$ 244 million per year to consumers, generic competitors, and the Government.[83]

An international extension of the patent length under TRIPS is very unlikely, for the twenty- year term was accepted after long negotiations. Lester and Zhu (2019) report that several countries had argued for flexible patent durations determined by their national interests and had even proposed leaving out the pharmaceutical sector from patent protection. In the negotiating texts patent duration was to be left to national legislation to be determined till the final text with twenty-years of protection and being applicable to

[81] SADICK, A. (2019). The dispute of the patent term extension in Australia. *Journal of Intellectual Property Law & Practice*, Volume 14, Issue 9, pp 699–715. This amendment to the Patent Act came into force in as early as 1998 and the extension does not cover method claims.

[82] See EPO update from 08.01.2019 China: Draft Amendments to Patent Law released for comment available at https://www.epo.org/searching-for-patents/helpful-resources/asian/asia-updates/2019/20190108.html last visit 10.04.2020.

[83] See Sadick at supra note 81 pp. 707-708.

all industries was agreed by all countries as developing countries were persuaded that stronger IP protection would facilitate their access to international markets.[84]

2.2.2 Implications for medical biotechnology

The length of the patent protection is pre-determined with some possible extensions, as described in Chapter 2.2.1. The breadth of a patent is determined by the claims that are put forward during the application. Patent examiners may find a claim too broad and reject it or grant the patent protection to a narrower claim. There are undoubtedly different incentive effects resulting from broad and narrow patents.[85] Expected value of the patent is an important determinant of patent application. In medical biotechnology although some research is basic, most of the research can be regarded as sequential, that is invention in one area is correlated with similar research carried out by various researchers. For simplicity let's assume that there are 2 research activities, one for the upstream research on a particular gene fragment and the other one is the downstream product development, say in diagnostics or treatment. If only one of the research team, the one that invents first is granted patent protection for both inventions, i.e., under a broad patent protection, it would be "winner takes all" kind of protection and it would stimulate fast duplicative research. However, if both research teams are given separate patent protection, i.e., a narrow patent protection, this would stimulate slow complementary research. Broad patents encourage basic research with no immediate commercial value; narrow patents encourage applied research, hence product development. [86]

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[84] LESTER, S. & ZHU, H. (2019). Rethinking the Length of Patent Terms. *American University International Law Review*, Volume 34, Issue 4, pp 787-806 at pp 794-800. The authors citing many economists argue that a flexible patent term across sectors may be beneficial, but these arguments are mostly in favour of shortening the patent term except for the pharmaceutical and the biotech sector, and even in these two sectors this duration is found to be long and to have less incentive effects for invention, but more on litigation – driven patent holders to assert their rights.

[85] Cooter & Ulen at supra note 32 pp.120-122.

[86] Ibid p. 120

In order to find out the most efficient breadth of patents, one should have a look at the social value of investment in basic and applied research. If the net social benefit of investment in basic research is greater than the net social benefit of investment in applied research, then a broad patent protection should be favored. On the other hand, if the reverse case holds, then a narrow patent protection should be favored.[87] Bessen and Maskin (2000) demonstrated that if two firms make invention, but only one of them gets the patent, this gets at the idea that patents have *breadth* (emphasis added), and so a patent-holder can hold up the implementation of other firms' discoveries that are similar, but not identical, to his own.[88] In this case, the patent holder becomes a monopolist in the market, but consumers are assumed to be better off compared to the absence of innovation. The net social benefit produced by one firm applying the innovation is larger than the case where no firm applies the innovation, but the net social benefit is less than the case where both firms apply the innovation.

According to the US legislation in dispute cases courts decide on the breadth of patent protection by applying doctrine of equivalents. In reality regarding the breadth, a patent infringement would occur if one or more of the claims of the patent are included in the new (accused) product or process.[89] Doctrine of equivalents allows a determination of an infringement, even though there is not literally 100% matching scope in the claims of the accused product. If there is considerable equivalence to the claimed invention, the accused party can be held liable for patent infringement.

In fact, commercial applications and pioneering inventions are seen as joint products of fundamental research and if researchers, who do fundamental research receive only the sale value of the pioneering invention but not the sale value of the commercial

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[87] Ibid.

[88] BESSEN, J. & MASKIN E. (2000). Sequential Innovation, Patents and Imitation. *MIT Working Paper* no 11/99 at p.6.

[89] In 946 F.2d 1534, 1538-39 (Fed. Cir. 1991) London v. Carson Pirie Scott & Co., "Although designing or inventing around patents to make new inventions is encouraged, piracy is not. Thus, where an infringer, instead of inventing around a patent by making a substantial change, merely makes an insubstantial change, essentially misappropriating or even "stealing" the patented invention, infringement may lie under the "doctrine of equivalents"."

application, there will not be enough fundamental research.[90] For instance the Supreme Court of the United Stated used doctrine of equivalents extensively for a century to protect pioneer patents against infringement.[91] According to the doctrine of equivalents an infringing party may be held liable even if the infringing claim does not fall within the whole scope of the first patent, but there is nevertheless an equivalence between the claim and the patented invention. The Supreme Court was using in the earliest infringement cases dating back to the 19th century, a specific approach to decide whether there was a patent infringement under doctrine of equivalents in such a way that the invention was classified as either pioneer or an improvement in relation to its prior art. The doctrine was applied broadly to protect pioneer inventions and narrowly to protect improvement inventions. Starting in the 20th century the Supreme Court put the primary reliance on the file history and specification and the discussion of pioneer status was secondary. Hence a non-pioneer patent could also be granted patent protection under the doctrine of equivalents if the invention was proven to be innovative and the patentee's own words as recorded in file history do not limit the claims.[92]

To solve this incentive problem mentioned above, Cooter and Ulen (2016) suggest it would be ideal to merge fundamental research and commercial product development in one single firm. The incentive problem could also be solved in case of separate firms, if transaction costs were zero and Coase theorem would apply where the breadth of patents would not matter in terms of economic efficiency as long as the firms can bargain with each other without costs and can make efficient contracts.[93] If pioneering inventions have little stand-alone value, they should be given a broad patent protection. If they have large stand-alone value, then the patent protection should be narrow. However, when courts apply doctrine of equivalents, it is noted that sometimes just the opposite of the result is

[90] Cooter & Ulen at supra note 32 p. 121.

[91] STEINHAUER, E. (1992). Using the Doctrine of Equivalents to Provide Broad Protection for Pioneer Patents: Limited Protection for Improvement Patents. *Pace Law Review*, Volume 12, Issue 2, pp.491-528.

[92] Ibid. pp 495- 503.

[93] Cooter & Ulen supra note 32 p. 121.

reached.[94] The Federal Circuit of the United States was criticized for being too pro-patent and applying doctrine of equivalents giving a broad protection to improvement patents rather than pioneer patents.[95]

As an example, a medical biotechnology firm requires an average investment value up to USD 500 million in the first 9 years after firm is founded and the R&D and clinical trial phase is completed with drug approval.[96] As suggested by Cooter and Ulen (2016) if Firm 1 invests this amount to do the pioneering invention without a commercial value, and Firm 2 is undertaking the development of the commercial application without necessarily investing this amount, there may be real incentive problems where there are transaction costs of bargaining. One solution can be reached where Firm 2 pays Firm 1 for the research Firm 1 has done where bargaining is possible without undue costs Alternatively dominant and dependent patents may be granted to Firm 1 and Firm 2 respectively which allow both firms to agree on a contract for the division of profits from the commercial value of the application product. In this regard dominant and subservient patents may be an alternative option to granting broad and narrow patents. But when there are high transaction costs, this solution of granting dominant and subservient patents, faces the similar incentive problems. A difference between the two solutions of payment for research versus granting of dominant / subsequent patents is especially important in the biotechnology sector with fast-evolving technologies where commercialization is necessary to bring products on the market. Without any transactions costs the parties would bargain freely and make efficient contracts without the breadth of the patent mattering too much. However, in the situation of granting of dominant and subservient patents timing of the contract is important in decision making process of the manufacturing of the application. It can be argued that this result is similar to a result reached under a narrow patent regime.[97] A broad patent regime stimulates fundamental

[94] Cooter & Ulen supra note 32 p. 122.

[95] See Steinhauer at supra note 91.

[96] Risk adjusted net present value. See STEWART, J.J., ALLISON P. N. & JOHNSON R.S. (2001). Putting a price on biotechnology. *Nature Biotechnology*, Volume 19, Issue 9, pp 813-817.

[97] Cooter & Ulen supra note 32 p. 122.

research and pioneering inventions whereas a narrow patent regime stimulates development and improvements. The two patents can block each-other if the broad patent on invention is dominating the narrow (subservient) patent on some improvement of the invention. In this case the holder of the subservient patent cannot use / practice the invention without a license from the dominant patent holder. It may also be the reverse case where the dominant patent holder will need a license from the subservient patent holder to use / practice the improved feature. Since transaction costs always exist, which solution of whether the firm doing the fundamental research will get a compensation from the other firm, or whether the legal system will grant dominant and subservient patents depends on the cost structures in the transactions, be in in the value of patents, or generally the cost to the society. The economic rationale of granting subservient patents would imply that such patents would bring improvements, cost-saving features and similar quality upgrades to the original patent and would encourage bargaining between the holders of dominant patent and subservient patent. However, the holder of dominant patent may use her hold-up right to maximize the profits from the improvement. If the dominant patent has the biggest value or the dominant and subservient patents have similar values, granting a subservient patent can be efficient. But if the biggest value comes from the subservient patent, and there is a hold-up problem from the dominant patent, the result is inefficient because the improvement may be delayed until the dominant patent expires, and /or due to high litigation costs and consumer prices. Hence as stated by Cooter and Ulen (2016) if the social value of the investment on fundamental research exceeds the social value of investment on developing applications, broad patents should be granted. If the reverse holds, then narrow patents should be granted.[98]

2.3 Incentives to Invent

2.3.1 An Overview of the Theory

One of the mostly agreed purposes of patents is to encourage inventions. Patents

[98] Ibid.

are especially essential for technologies and processes that can easily be reverse engineered. If others can easily copy a new product, producers of the new product will not be able to acquire a sufficient portion of the value of their innovation.[99] However patentable inventions are usually difficult to copy or reverse engineer if the patent protection is effectively enforced. That is why it can be argued that such an inventor will enjoy the benefits of a monopoly power, at least in the short run, even though there is no patent protection. As Eisenberg (1989) also states when the copying of inventions is possible and simple, then competitors can easily imitate the inventions, free riders would then decrease the price of the invention, hence the inventors could not recoup the costs they invested in the research and development phase. They would invest in those areas, where the recoup of the sunk costs is available.[100] To achieve the purpose of encouragement of invention, every patent law requires novelty, inventive step, disclosure, and utility /industrial application. By law and economics analysis it can be seen that the issue with the recouping of sunk costs is a controversial one. It needs to be carefully analyzed how the patent law addresses this issue. Granting a patent protection also has some negative consequences by means of increased prices, increased deadweight loss, losses related to the limited use of the invention, which is not granted to the public domain, hence cannot be accessed freely.

It is widely argued that the patent system distorts the research pattern. Pharmaceutical companies do not have enough incentives to develop drugs for the diseases that affect poor people, since the pricing of the drugs would then not be profitable. One of the proposed ideas to address this problem is establishing a guaranteed purchase fund, which would ensure the flow of money to those who develop the cures in the poorer parts of the world.[101]

The trade-off between promoting invention and losses from monopoly situation

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[99] ARROW, K. J. (1962). Economic Welfare and the Allocation of Resources for Invention, in *The Rate and Direction of Inventive Activity: Economic and Social Factors*, National Bureau of Economic Research, Princeton, Princeton University Press, pp 609-626.

[100] See Eisenberg supra note 5 pp.1024-1025.

[101] See Stieglitz & Greenwald infranote 216 at p. 484.

hence dynamic and static efficiency has been analyzed by many authors.[102] The consideration is that a monopolistic firm which sells its good at the monopoly price will make monopoly profits. Dixon and Greenhalgh (2002) and Shavell and Ypersele (2001) note that a monopolist holding a patent right may have fewer incentives to invest than in a competitive market. Because the monopoly profits may be less than the general consumer welfare. The consumers may be worse off with restricted output and increased price of the monopolist. Hence it can be argued that a rational monopolist will only invest in the amount of R&D, that will allow him to earn the monopolistic profits. This amount may be less than the socially optimal amount.[103] Deciding whether the losses for the society by monopoly output pricing is less than benefit to the society by increased innovation is the core of the economic analysis of the patent law.

An argument against this theory is that patents are not the only forms of rewards to create incentives to invent. There are other ones such as trade secrets or reward systems. The possible problem with trade secrets in biotechnological research was mentioned in Section 2.1 due to high movement of scientists among institutions. Having a look at the reward system might be worthwhile. Shavell and Van Ypersele (2001) argue that rewards paid by the government to the innovators on the basis of their sales would also create incentives to innovate without creating monopoly power and in their model the patent or the intellectual property right system do not possess a fundamental social advantage over the reward system.[104] So if the innovator chooses the reward, the overall social welfare is improved, since the deadweight loss from selling too little at the monopoly price is eliminated. The authors further state that the reward system is especially helpful in areas where the social losses due to intellectual property rights are likely to be high, where the

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[102] See NORDHAUS, W. (1969). *Invention, Growth and Welfare: A theoretical treatment of technological change*. Cambridge, MA: MIT Press, Also NORDHAUS, W. (1972). The optimal life of the patent: reply. *American Economic Review*, Volume 62, No 3 pp. 428-431. ORDOVER, J. A. (1991) Patent system for both Diffusion and Exclusion. *Journal of Economic Perspectives*, Volume 5, Number 1, pp 43-60, Kitch supra note 5 at pp. 266-267.

[103] DIXON, P. & GREENHALGH C. (2002). The Economics of Intellectual Property: A Review to Identify Themes for Future Research. *University of Oxford, Department of Economics Discussion Paper Series* No: 135. p.5. See Shavel and Ypersele at infra note 104.

[104] SHAVELL, S. & VAN YPERSELE T. (2001). Rewards versus intellectual property rights. *The Journal of Law and Economics*, Volume 44, No 2, pp. 525-547.

difference between price and production cost (after innovation) is large. Biotechnological medical products are sold at prices much above their marginal cost of production, as in the case of any other monopoly pricing issue. As soon as the patent on the product expires, the generic companies start producing and selling the product at prices much closer to marginal cost than the patented drug. In the U.S. generic drugs are available at prices that are between 30% and 80% lower than the originally patented product.[105] In a reward system these products may also be sold at lower prices and may be more widely used. It is expected that patents should be regarded as very important in industries where the R&D intensity is high. In a survey based study respondents from pharmaceutical industry state that in absence of patent protection 65% of the inventions would not have been introduced and 60% of the inventions would not have been developed.[106] However, data show that industries with less R&D intensity also regard patent protection as very important, and at least half of the patentable inventions are patented, since the benefits of patent protection in terms of royalties and as bargaining tools exceed its costs.[107] In a more recent study it is suggested that in most industries, patents are less favored than other protection means such as secrecy and first mover advantages.[108] Similarly, in her study Moser (2004) concluded that in countries without patent protection, inventors focused their innovative activity on sectors where other protection means were available.[109]

Certainly, these studies are not to suggest that patent protection does not bring any considerable returns. Patents have played an important role in creating specialized research activity in certain sectors such as chemicals, biotechnology, semiconductors, and scientific instruments.[110] In his duopoly model where investments in R&D and patents

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[105] BOLDRIN M. & LEVINE D.K. (2010). *Against Intellectual Monopoly*. Cambridge: Cambridge University Press, p. 241.

[106] MANSFIELD, E. (1986). Patents and Innovation: An Empirical Study. *Management Science*, Volume 32, No. 2 pp. 173-181, p.175, Table 1.

[107] Ibid pp. 175, 176.

[108] See Cohen et al. (2000) at supra note 51.

[109] See Moser at supra note 52.

[110] ARORA, A., FOSFURI, A. & GAMBARDELLA, A. (2001). *Markets for Technology: Economics of Innovation and Corporate Strategy*, Cambridge, MA: MIT Press. pp 5-8. They estimated the US market

are inputs in the production of firm rents, Hunt (2006) suggest that if patents are easy to obtain, and if firms are sufficiently active in their R&D activities and patenting, where there is sufficient overlap in firms' patented technologies, incremental reductions in the cost of obtaining patents result in less R&D. This does not imply the elimination of R&D investments, but rather less innovation than would otherwise occur.[111] In a more recent study of the US manufacturing sector, Aurora et al. (2008) estimated the effect of patenting on R&D with a model linking a firm's R&D effort with its decision to patent. Their finding is similar to that of Mansfield (1977). They conclude that patent protection has a positive effect on average on very few industries and varies across industries and firm size. Survey respondents with higher patent effectiveness scores are described by higher patent premium levels. Larger firms have higher patent premia, and this is consistent with the notion that larger firms have better access to legal and other resources which are important elements of patent enforcement. Respondents with more technological competitors have lower premia, significant positive effects can be shown only for the biotech and pharmaceutical industries. The industries such as biotech and pharmaceutical, where sophisticated IP strategies and a belief in the value of patents are the norm, will obtain higher returns to patenting – and therefore report higher patent effectiveness scores.[112]

The theory about recouping of sunk costs of innovation is one of the main economic theories in literature.[113] There are various sunk costs associated with the development of an invention. In addition to the R&D cost of developing the innovative idea, the inventors must undertake patent searches to be sure that there are no patent infringements and pay

for technology is around USD 36 billion and the global market USD 53 billion including licensing fees. pp. 29-32.

[111] HUNT, R.M. (2006). When do more patents reduce R&D? *American Economic Review*. Papers and Proceedings, Volume 96, Issue 2, pp. 87–91.

[112] ARORA A., CECCAGNOLI, M. & COHEN, W.M., (2008), R&D and the Patent Premium, *International Journal of Industrial Organization*, Volume 26, pp. 1153–1179 at pp1170-1172.

[113] BESSEN, J. and MASKIN E., (2000), Sequential Innovation, Patents and Imitation, *MIT Working Paper* no 11/99 state at p 6 "The standard economic rationale for patents is to protect potential innovators from imitation and thereby give them the incentive to incur the cost of innovation". See also Eisenberg at supra note 5.

considerable amounts of administrative and legal fees to apply for a patent. In cases of disputes, the amount of legal and court fees are even higher.[114] Murphy and Topel (2003) state that in 1995 the total spending in the US for biomedical research was about $25 billion, of which about 45% was funded by the federal government, 41% by the industry and 14 % by the academic research (not funded by the federal government).[115] In 2003 the biomedical research funding increased to $ 94.3 billion, of which 57 % was funded by the industry, 28% by National Institutes of Health (NIH) and 11% by other federal, state and other local government resources.[116] In 2010 the funding by the private industry reached $ 67.4 billion[117] and funding by the NIH was USD 31.2 billion. On average NIH invests USD 32.3 billion annually in medical research.[118] It can also be seen from the below table that the main sponsors of biomedical research have been the private industry and the NIH in the US.

[114] Using the tool available at http://rvg.pentos.ag the legal fee and court fee (excluding the patent attorney fee) is calculated to be a minimum of approximately 55.000 EUR for a patent worth of 5 million EUR in Germany. The losing party needs to pay the quadruple of this cost for his own legal advisor and patent attorney plus for the legal advisor and patent attorney of the opposite party. last visit 30.04.2020.

[115] MURPHY, K.M. & TOPEL R. (2003), The Economic Value of Medical Research, in *Measuring the Gains from Medical Research, An Economic Approach*, K. M. Murphy and R.H. Topel (Eds.) Chicago, the University of Chicago Press Books.

[116] MOSES III H. et al. (2005). Financial Anatomy of Biomedical Research. *The Journal of the American Medical Association*, Volume 294, No.11, pp 1333-1342, p. 1336, Table 1.

[117] See press release of PhRMA - the Pharmaceutical Research and Manufacturers of America from 16.03.2011 available at http://www.phrma.org/media/releases/rd-investment-us-biopharmaceutical-companies-reached-record-levels-2010, also factsheet from 14.09.2017 available at https://www.phrma.org/fact-sheet/america-s-biopharmaceutical-companies-randd-investments-at-an-all-time-high for 2016 figures of PhRMA member companies only reaching a total R&D figure of USD 65.5 billion (whereas the total industry figure by the entire US biopharmaceutical industry is estimated to be USD 90 billion in 2016). The members invested in 2017 USD 71.4 billion factsheet from 8 August 2018 available at https://catalyst.phrma.org/phrma-member-companies-rd-investments-hit-record-high-in-2017-71.4-billion-0. It is stated that member biopharmaceutical companies invest about USD 75 billion annually in R&D and have invested more than USD 600 billion since 2000. https://www.phrma.org/about last visit 30.04.2020.

[118] The figures are adapted from NIH official website – part on the budget https://www.nih.gov/about-nih/what-we-do/budget#note last visit 30.04.2020. The table is not adjusted for inflation.

Table 1 – Biomedical R&D investment in the US 1995-2010 (in billion USD)

Total	Academic	Industry	NIH	Year
25.1	3.5	10.2	11.4	**1995**
90.4	10.3	53.7	26.4	**2003**
98.6	NA	67.4	31.2	**2010**

Source: Calculations from NIH and National Science Foundation statistics and PhRMA – nominal results excluding foundations & charities' funding.

To give some more figures from the private sector, in 2015 some 369 companies in the EU made a total of EUR 30.6 billion R&D investment in pharmaceuticals and biotechnology sector, which is the biggest investment after automotive sector. This corresponds to an increase of 52% just in 10 years from 2006 with an R&D investment at EUR 20.16 billion.[119]

On the other hand, we also see that the biggest increase in the NIH budget came in the 2000s and jumped from USD 11.1 billion in 1990s to USD 26.30 billion on average. Since 2010 we see the budget remained flat around USD 30 billion and even declined in absolute terms in 2013 to USD 29 billion. The 2016 budget is the highest in the last decade at USD 32.31 billion.[120]

It can be seen that NIH was the biggest contributor in the beginning in 1995 in the early face of the sector. By the time the biggest contribution switched from the public funding to private sector. This can also be seen in the study of Dorsey et al. (2010).[121] For some private investment figures it may be mentioned that US private investment in pharma and biotech increased from EUR 29.6 billion in 2006 to EUR 44.28 billion in 2015 whereas the investment in the sector by their European counterparts increased by

[119] See 2016 EU Industrial R&D Investment Scoreboard at infra note 122 pp.15, 21.

[120] See infra note 126.

[121] DORSEY E. R. et al (2010) Funding of US Biomedical Research,2003-2008, *JAMA ..Journal of the American Medical Association,* Volume 303, Issue 2, pp 137-147.

almost 52% from EUR 20.16 billion in 2006 to EUR 30.6 billion in 2015.[122] This shows the continuous growth of the private R&D in the biotechnology and pharmaceutical sector.

As mentioned before, recouping of sunk costs in order to create incentives to invent is however a controversial issue. Because patents are actually not granted on the basis of costs that have incurred during the R&D or on the basis of those costs associated with further stages of innovative activity. Making the incurred costs the patent basis would be an inefficient solution. A patent application becomes important for the innovator if there is a high expected value from the protection. Especially for biotechnological innovations the scope of coverage plays an important role. If the innovator knows there is a certainty over sufficient protection and high value for her innovation, high sunk costs will be negligible. The requirements for patentability are much more diversified such as novelty, inventive step, utility/industrial application, disclosure as will be introduced in Chapter 3.

2.3.2 Basic research as a public good and applied research in medical biotechnology

The underlying reason to create incentives to invent is that if the inventor cannot recoup the costs of the R&D expenditures, socially desirable inventions either do not occur or occur at a delayed time and this may lead to under-investment in the research activity.[123] However, when considering this theory for medical biotechnology, it is better to distinguish between basic research and applied research.

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[122] The 2016 EU Industrial R&D Investment Scoreboard, European Commission - Joint Research Centre, available at https://ec.europa.eu/jrc/en/publication/eur-scientific-and-technical-research-reports/2016-eu-industrial-rd-investment-scoreboard last visit 30.04.2020 .It was even observed that companies operating in biotechnology increased their R&D by 23.8%, whereas traditional pharmaceutical companies increased it by only 7.2%. Worldwide pharmaceutical and biotechnology shows the highest one-year growth rate after software and computer services sector.

[123] Eisenberg supra note 5, p. 1025.

Basic research in medical biotechnology can be regarded as the explorative activity in areas such as genetic engineering and the analysis of the gene. Applied research aims at producing clinically effective biomedical diagnostic and therapeutic products by means of high risk, heavy cost investments.

There is strong evidence that publicly funded basic research has substantial direct and indirect economic benefits. It was shown that publicly funded basic research stimulates private R&D instead of being a substitute for it[124] also that companies which are located at close distance to universities have comparative advantage in terms of process innovation compared to those which are located further away.[125]

In the US alone National Institutes of Health (NIH), which is the primary government agency for biomedical research, had a total budget of USD 37.31 billion in 2018.[126] It was estimated that NIH spending in 2010 created USD 63.13 billion economic activity in the following year.[127] Similarly the US Department of Energy (DOE), which is the largest funder of basic research in physical sciences contributed together with the NIH to the Human Genome Project[128], which was carried out over a 13 year period during 1990-2003 to determine the complete sequencing of the 3 billion DNA bases, identify all human genes, and make them accessible for further biological studies.[129] It was estimated that the total investment of USD 3.8 billion for the Project has created in 2010 USD 67 billion economic impact and 310,000 jobs.[130] One of the most important impacts of the

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[124] NELSON, R. R. & ROSENBERG, N. (1993). Technical innovation and national systems, *in National innovation systems. A comparative analysis*, Nelson, R.R. (ed.) New York and Oxford: Oxford University Press, p. 341.

[125] MANSFIELD, E. & LEE J.Y. (1996). The modern university: contributor to industrial innovation and recipient of industrial R&D support. *Research Policy*, Volume 25 pp. 1047—1058.

[126] See http://nih.gov/about/almanac/appropriations/part2.htm last visit 30.04.2020.

[127] EHRLICH, E. (2011) An Economic Engine NIH Research, Employment, and the Future of the Medical Innovation Sector, report released by United for Medical Research, available at http://www.unitedformedicalresearch.com/wp-content/uploads/2012/07/UMR_Economic-Engine.pdf, last visit 30.04.2020.

[128] http://www.ornl.gov/sci/techresources/Human_Genome/project/whydoe.shtml last visit 30.04.2020.

[129] http://www.ornl.gov/sci/techresources/Human_Genome/faq/faqs1.shtml last visit 30.04.2020.

[130] Economic Impact of the Human Genome Project (May 2011) report prepared by Battelle Technology Partnership Practice, available at

project has been reducing costs and speeding up sequencing dramatically and the development of Genbank – a DNA sequence repository.[131]

The increase in the number of patents in basic research may be a consequence of the widening of the patentable subject matter, which will be discussed in Chapter 3.

Isolation and/or purifying processes for genes outside their natural environment are quite routine methods today.[132] It is difficult to determine whether the subject matter is not patentable being a discovery of sequences hence a product of nature or patentable being sequences of human interventions in nature through purified and isolated materials. Eisenberg (2002) argues that DNA sequences in naturally occurring forms are not patentable.[133] However, it is considered that the use of a technical process during this isolation and/or purification involves an inventive step, which is non-obvious to the persons having ordinary skills in that field. For instance, Utility Examination Guidelines of USPTO treats isolated and purified gene molecules as patent eligible. There are quite a number of patents that are granted for simply "purified" DNA molecules.[134] USPTO also grants patents on other purified biological molecules such as proteins, since it is assumed that purification of a biological molecule from its natural environment makes the claim eligible to grant patent protection.[135]

For the basic research, the argument that the investment would not take place without the prospect of a patent grant is questionable. There might be many researchers in the subject area, one/some of whom will be able to make the invention. Basic research,

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http://web.ornl.gov/sci/techresources/Human_Genome/publicat/BattelleReport2011.pdf last visit 30.04.2020. Cumulative impact during 1988-2010 is estimated to be around USD 796 billion economic output and 3.8 million job years.

[131] See supra note 129.

[132] See DEMAINE, L.J. & FELLMETH, A. X. (2003). Natural Substances and Patentable Inventions. *Science*, Volume 300, Issue 5624, pp. 1375-1376.

[133] EISENBERG, R. (2002). Molecules vs. Information: Should patents protect both? *Boston University Journal of Science and Technology Law*, Volume 8, Issue 1, pp. 190-202.

[134] US Patents No: 5,780,262; 6,262,247; 6,399,371; 6,448,042; 6,555,347

[135] US Patents No: 6,258,556 and 6,284,236

which is mainly done at public universities, aims the enhancement of general knowledge. It was found out that the private industry conducted during 1998-2012 less than 20% of the nation's basic research in the US.[136]

Implementing both basic and applied research is essential for the economic competitiveness of nations; that's why the National Science Foundation of the USA has started to fund Engineering Research Centers, which are interdisciplinary centers aiming collaboration between university scientists and the industry.[137] Similarly EU also supports "market oriented research" program EUREKA for applied research to promote the integration of science and industry.[138] The biggest EU Research and Innovation program Horizon 2020 also regards biotechnology as one of the key industries to fund investments needed for both improving the research base and transforming the knowledge into tangible industrial innovation.[139] Besides, empirical studies carried with EU, US and Japanese pharmaceutical companies indicate that those engaged in basic research are more likely to generate breakthrough inventions, not necessarily in the areas that was involved in basic research, but in other areas of the technology portfolio of the firm.[140]

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[136] DWORIN, K. (2015). The Changing Nature of U.S. Basic Research: Trends in Performance. *SSTI working paper* available at https://ssti.org/blog/changing-nature-us-basic-research-trends-performance last visit 30.04.2020.

[137] See http://www.nsf.gov/funding/pgm_summ.jsp?pims_id=5502&org=EEC for detailed information about the program; last visit 30.04.2020.

[138] See https://trimis.ec.europa.eu/programme/network-market-oriented-rd-network for specific program details; last visit 30.04.2020.

[139] The total budget of the Horizon 2020 program is EUR 80 billion over 2014-2020 period. For the next 7 years the European Commission has outlined and presented the Horizon Europe Program, where bioeconomy is again one of the clusters to be funded. See https://ec.europa.eu/info/horizon-europe-next-research-and-innovation-framework-programme_en The presentation from August 2019 is available at https://ec.europa.eu/info/files/horizon-europe-investing-shape-our-future_en last visit 30.04.2020.

[140] MALVA, A.D., KELCHTERMANS, S. & LETEN, B. et al. (2015). Basic science as a prescription for breakthrough inventions in the pharmaceutical industry. *Journal of Technology Transfer*, Volume 40, Issue 4, pp 670-695.

2.4 Incentives to Disclose and the Prospect Theory

2.4.1 An Overview of the Theory

The second function of patents is to disseminate the knowledge to the public domain.[141] They encourage disclosure of inventions that would otherwise be kept secret.[142] Besides, the public may discover new ways of using the invention that the patent holder has not thought of.[143] It is also argued that the disclosure function of the patents also cause positive externalities such as R&D spillovers[144], which are regarded as the major productivity growth[145] and found to have increased the social rate of return of R&D.[146] By doing so patents have a role in increasing the ex-post efficiency. In his comparative study of San Francisco and Los Angeles biotechnology industries, Casper (2013) found that if the university scientists are embedded within a regional economy where large and cohesive inventor networks exist, the number of granted patents is higher and the commercialization of science is easier.[147]

Public disclosure of new technologies and processes helps avoid duplicative research and the wasteful use of research and development efforts.[148] Hence more efficient investment in research may be assured. To achieve the purpose of public

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[141] See MAZZOLENI R. & NELSON R. R. (1998). The Benefits and Costs of Strong Patent Protection: A Contribution to the Current Debate. *Research Policy*, Volume 27, pp 274–284 at p 275.

[142] SCOTCHMER S. (1991). Standing on the Shoulders of Giants: Cumulative Research and the Patent Law, *Journal of Economic Perspectives*, pp 29- 41.

[143] See Landes & Posner at supra note 4 at p. 329.

[144] COHEN W.M. et al. (2002). R&D spillovers, patents and the incentives to innovate in Japan and the United States, *Research Policy*, Volume 31, pp 1349-1367 at p. 1350.

[145] GRILICHES Z. (1998). R&D and Productivity: The Econometric Evidence, in *Issues in Assessing the Contribution of Research and Development to Productivity Growth*, Chicago: University of Chicago Press, pp 17-45 at p. 19.

[146] The social rate of return from innovation (estimated coefficient on R&D intensity) is found to be 43% in a study done by using panel data for 12 OECD (Organisation for Economic Cooperation and Development) countries. See GRIFFITH, R. et al. (2004), Mapping the Two Faces of R&D: Productivity Growth in a Panel of OECD Industries. *Review of Economics and Statistics*, Volume 86, Issue 4, pp.883-895.

[147] CASPER, S. (2013). The spill-over theory reversed: The impact of regional economies on the commercialization of university science. *Research Policy*, Volume 42, pp.1013-1024.

[148] See Kitch supra note 5 p. 278.

disclosure, patent law should require full description of the invention, as this is the case both EU and US legislations which will be explained in Chapter 3 of the dissertation.

2.4.2 Implications for medical biotechnology

As discussed in Chapter 2.1, the costs of patent protection should fall behind the benefits of such protection. Otherwise, the inventor may consider alternative protection methods such as trade secrets. Trade secrets do not involve registration and enforcement costs as with patents, and they are also not limited in time. However, the level of protection with trade secrets is generally considered to be weaker than the protection granted by a patent. Trade secrets do not provide the exclusive right to exclude third parties from producing, distributing, and making commercial use of the subject matter. Third parties may be able to inspect the product, discover the secret and reverse engineer the product or once the trade secret becomes publicly available, anyone can benefit from it. Third parties my even patent the subject matter if they comply with the patentability requirements.

The function of patents in promoting disclosure of inventions that would otherwise be kept secret is sometimes of doubt.[149] Indeed a survey among R&D managers shows that in some industries such as the chemical industry, trade secrets are more profoundly used in order to protect the innovation.[150]

Calabresi and Melamed (1972) developed a framework to compare entitlements by property and liability rules. In this framework different legal areas of property and tort are discussed from a unifying perspective so that the correct setting of entitlements prevents the “might makes right” problem. Hence the fundamental thing that law does is deciding which conflicting parties shall prevail. The authors analyze the pollution

[149] See Eisenberg supra note 5 at pp.1028-1029.

[150] LEVIN R.C. et al. (1987). Appropriating the Returns from Industrial Research and Development, *Brookings Papers on Economic Activity,* No:3 pp. 783- 795.

problem through different criminal sanctions, but also through kind of protection to grant and different injunction and damage rulings. An entitlement protected by the property rule can be bought in a voluntary transaction where the buyer and the seller agree on the price. If the entitlement is protected by the liability rule, an initial decision needs to be made as regards to whom the entitlement shall be given to. The reasons for deciding to give the people the entitlement to pollute or to forbid pollution, to own property or to share it depend on economic efficiency, distributional preferences and other justice reasons.[151] Economic efficiency is assured where the society has knowledgeable choices between social benefits and social costs of obtaining or avoiding the entitlements.[152] Distributional preferences bring in the reallocation of wealth within the society and can be linked to dynamic efficiency concepts, but also to individualized preferences so as to who should be richer or poorer independent from equality and efficiency concerns.[153] The authors group remaining considerations for deciding of allocation of entitlements under other justice reasons. Admitting themselves that it is hard to know what content can be brought under this category, they say that criteria not fully enclosed under economic efficiency and distributional preferences or both can be described here.[154]

The article has become a fundamental one in law and economics theory, and it has recently been tested by a series of controlled experiments on liability and property rules using the US patent system as a model.[155] It is noted in this study that until 2006 the patent owners in an infringement case were entitled a permanent injunction as a general rule, as cited by the Federal Circuit. This has become the standard of the property rule. In 2006 in eBay v. MercExchange Case[156] the Supreme Court changed the Federal Circuit's

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[151] CALABRESI G. & MELAMED A. D. (1972). Property Rules, Liability Rules, and Inalienability: One View of the Cathedral. *Harvard Law Review*, Volume. 85, No. 6 pp. 1089-1128

[152] Ibid p. 1096.

[153] Ibid p. 1098.

[154] Ibid. p. 1105.

[155] TORRANCE, A. W. & TOMLINSON, B. (2011). Property Rules, Liability Rules, and Patents: One Experimental View of the Cathedral. *Yale Journal of Law & Technology*, Volume 14, pp. 138 - 161

[156] Ibid p. 141 Case 547 US 388, 394 (2006) The Supreme Court ruled that in case of an infringement an injunction shall not be automatically issued, but the Courts should still weigh the four factor test that is traditionally used to determine whether an injunction should occur; i.e., a "plaintiff must demonstrate: (1) that it has suffered an irreparable injury; (2) that remedies available at law, such as monetary damages, are

general rule in favor of injunctive relief – an entitlement by a property rule towards a liability rule quoting 35 USC §283 that:

> "…courts having jurisdiction of cases under (injunction) title may grant injunctions in accordance with the principles of equity to prevent the violation of any right secured by patent."

The Court further stated that:

> "…the decision whether to grant or deny injunctive relief rests within the equitable discretion of the district courts, and that such discretion must be exercised consistent with traditional principles of equity, in patent disputes no less than in other cases governed by such standards."

In their analysis Torrance and Tomlinson (2011) state that holders of an infringed patent are entitled to receive both injunctive relief and monetary damages; hence the Supreme Court's decision has shifted the entitlement protection from property to liability rule, where they quote a decline in granted injunctive relief decisions since the Decision on Ebay vs. MercExchange. In their experimental study the human subjects "play" four different property (injunction) and liability (damages) rules[157]on amounts of innovation, social utility and productivity. Hence the subjects were tested against conditions of "(1) strong injunctive relief, (2) strong damages, (3) both strong injunctive relief and strong damages, (4) neither injunctive relief nor damages".[158] Their data show that amounts in innovation, productivity and social utility vary across entitlements; they are the lowest in

inadequate to compensate for that injury; (3) that, considering the balance of hardships between the plaintiff and defendant, a remedy in equity is warranted; and (4) that the public interest would not be disserved by a permanent injunction."

[157] Rules 1-4 (in the Calabresi and Melamed article in supra note 151 applied to situations involving patent owners and patent infringers so that "Rule 1 (property rule) would hold patent owners the legal right to prevent others from practicing their patented inventions. It would be efficient for courts to apply this rule if the alleged infringer could avoid the cost of infringement more cheaply than the patent owner. Rule 3 (property rule) would provide infringers with the right to practice inventions covered by patents owned by others. It would be efficient for courts to apply this rule when the patent owner could avoid the cost of infringement more cheaply than the infringer. Rule 2 (liability rule) would hold patent owners the legal right to collect monetary damages from patent infringers. Rule 4 (liability rule) would hold patent infringers the legal right to collect monetary damages from patent owners in return for not infringing patents". See Torrance and Tomlinson supra note 155 pp. 146-147.

[158] Ibid p. 148.

patent systems where remedies for infringement included both injunctive relief and damages, higher where the remedy was only injunctive relief ad even higher where the remedy was only damage, and the highest where no remedy for infringement was available.[159]

Patent systems favoring property or liability rules may lead to different efficiency outcomes. If a system is emphasizing liability rule over the property rule, the patent owners may be expected to perform differently, also to act differently in licensing negotiations, as well as to interact differently with patent infringers. Epstein (1997) argues they may value and price their innovation at a different (presumably lower) rate, than at a strong property rule system, where the courts can determine the damage remedies. The proponents of strong property rights argue that the ex-ante incentives are better for innovation. Property rule gives one person the sole and absolute power over the use and disposition of a given thing and he can hold out for as much as he can before he pleases to sell that thing. By limiting the owner's protection to a liability rule that hold-out power is lost and the owner receives some right to compensation instead for the thing that has been taken away from him against his will.[160]

In terms of ex-ante incentives, it may be argued that when there is a possibility of injunction, the patent owners can have better terms of deal in licensing negotiations. The choice between the injunction and damage compensation is not an easy one. The tradeoff between the two is that if injunctive relief is given, the patent owner will not be harmed by the infringement. However, in cases where infringing party has made investments as to the patented technology, Lemley and Shapiro (2007) state the patent owner may be over-rewarded with injunction due to the problem of patent hold-ups. It is shown that the possibility of patent hold-ups is high if the patented technology has a feature that gives little value to the infringing product. The holdup problems caused by the threat of

[159] Ibid. pp 153-157.

[160] EPSTEIN R. A., (1997). A Clear View of the Cathedral: The Dominance of Property Rules, *Yale Law Journal*, Volume 106 pp. 2091 -2120. Epstein argues that the if there needs to be a choice between property and liability rules, one should choose property rules in order to safeguard the "stability of possession and social expectations that are necessary for the growth of any complex social order".

injunctions are reduced, if courts regularly grant stays to permanent injunctions to give defendants time to redesign their products to avoid infringement when this is possible. However, if the product redesign to avoid infringement is costly, the possibility of patent hold-up is again high. The holdup problems are magnified when there is royalty stacking with multiple patents on a single product.[161]

It is obvious that liability and property rules create different ex-ante incentives. The ex-post incentives of both rules were also studied taking it for granted that where the parties bargain efficiently, the property and liability rules are equivalent.[162] Efficient bargaining implies minimization of transaction costs where a particular transaction is most inexpensively carried out by the parties in a market setting.[163] However, in the absence of bargaining between the victim and the injurer in order to control some harmful externalities, liability rules are superior to property rules even when there is limited information on the level of harm to be able to set the damage.[164]

As noted by Calabresi and Melamed (1972) and Torrance and Tomlinson (2011) under the property rule, the owner of a gene patent would hold the entitlement until he agrees to sell it at the value agreed by himself. He would have exclusive power to keep the entitlement and set the transfer value however an objective third party should assign the initial entitlement, which in this case would be the Patent Office. The value of the gene patents under a liability rule shall be determined by an objective third party, rather than the holder of the patent. In this case the patent holder cannot forbid the transfer of the patent, if the transfer conditions coincide with the objectively set value of the

[161] LEMLEY, M. & SHAPIRO C. (2007). Patent Holdup and Royalty Stacking. *Texas Law Review*, Volume 86, pp. 1991-2049.

[162] See Calabresi and Melamed at supra note 151.

[163] See Coase at supra note 63.

[164] KAPLOW L. & SHAVELL S. M. (1996). Property Rules versus Liability Rules: An Economic Analysis. *Harvard Law Review,* Volume 109, Issue 4, pp.713-790. The authors examine situations for externalities and "taking of things" where parties do and do not bargain with each other, and also where bargaining is not successfully concluded. They also developed arguments in favor of neither rules particularly when additional factors are considered such as possibility of bargaining and administrative costs. When other factors such as victim behavior and judgment-proof need to be considered, property rules may be desirable, even though liability rule has an advantage.

entitlements. Again, if a buyer is interested in the entitlement, even if this sale is against the wish of the patent owner, the owner must accept the damage compensation.[165] Property rules may be considered to be superior to liability rules when there is a few numbers of parties involved and when the transaction and bargaining costs are low. They definitely put the patent owner in a more favorable position during the ex-post negotiations over licensing agreements. In economic models where ex ante licensing is possible and the courts have perfect information, it was shown that a credible threat of infringement can increase patent owner's profits rather than decrease it for patents on research tools.[166]

Not only for research tools but also in cases where the infringer is expected to have high lawyer's fees and punitive damages, ex ante licensing may be possible to avoid litigation.

The gene patents involve complex sets of data and negotiating parties. Moreover, the increasing complexity of patent claims may result in poorly defined intellectual property rights, infringement and lawsuit cases stemming thereof. The gene patent trolls organized to buy patents for the purpose of claiming extracting fees and infringement may result in excessive litigation instead of making the patents useful IP tools to promote innovation. Under the property rule the gene patent owner would have the incentive to assert the patent later, especially if the downstream companies have made some

[165] See Calabresi and Melamed at supra note 151, Torrance and Tomlinson at supra note 155.

[166] SCHANKERMAN, M. and SCOTCHMER S. (2001), Damages and Injunctions in Protecting Intellectual Property, *RAND Journal of Economics,* Volume 32, pp 199-220. The authors compare infringement of patents on research tools based on unjust enrichment versus on lost profits (lost royalty). Research tools are normally licensed, so that unjust enrichment protects the patent-holder better than lost royalty in the case of patented research tools. The examples given for such tools are the "Cohen-Boyer patent on the technology for inserting foreign genetic material into bacteria, the Genentech patent on a technology for getting foreign genes to ''express,'' the PCR technology for replicating DNA in test tubes, gene guns, and recent suppression technologies that cause gene sequences to become inactive". Under the unjust-enrichment rule, the infringer must relinquish his unfairly -received gains, and is left with zero profits. The problem with the lost-profit (lost-royalty) rule is that the presumed license fee determines the damages and damages determine the maximum license fee that a licensee would pay so that "license fees and prospective damages are equal and self-reinforcing". They argue that "many license fees and damages may be consistent with the doctrine, but the prospective damages will not deter infringement. License fees that more than exhaust the available profit could not arise in equilibrium and therefore could not be ''lost royalty"". at p.200.

investments regarding the patented gene. The shift of the US patent system from a property to a liability rule may induce that more innovation, social utility and productivity gains will be generated under the new rule.

2.5 Patent race and Anticommons

A central topic in the property rights literature is to allocate property rights efficiently so that under-investment can be prevented.[167] On the other hand it may be argued that property rights create over-investment, i.e., patent race so that absence of property rights may be a best possible solution in this sense. Patent races can be avoided where parties can agree on a license.

Patent races occur, when various researchers compete for the same outcome of the innovation, because they believe that the winner will alone reap all the benefits of the innovation. For this to emerge one should omit the diffusion, spillover, and other scale effects that the patents have in terms of growth. However, it was also shown for OECD countries that increases in R&D level do not necessarily have growth effects.[168] Also in their study Bessen and Maskin (2000) show that in industries where the innovation is sequential and imitation is costless, innovators in a sequential patent race are better off without patent protection and the patent protection may reduce overall innovation and social welfare.[169]

There are other studies on multi-stage patent races, as well. Scotchmer and Green (1990) show that when patenting around is possible, it is favorable to patent interim

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[167] See MIRELES, M.S. (2004). An Examination of Patents, Licensing, Research Tools, and the Tragedy of the Anticommons in Biotechnology Innovation. *University of Michigan Journal of Law Reform*, Volume 38, pp.141-235, BURK, D. L. & LEMLEY, M. A. (2003), Policy Levers in Patent Law. *Virginia Law Review*, Volume 89, Issue 7, pp. 1575-1696, RESNIK, D. B. (2003), A Biotechnology Patent Pool: An Idea Whose Time Has Come?, *The Journal of Philosophy, Science & Law*, Volume 3, Issue 1, pp 1-22.

[168] JONES, C.I. (1995). Time Series Tests for Endogenous Growth Models. *The Quarterly Journal of Economics*, Volume 110, No.2, pp 495-525 at 520-521.

[169] Bessen & Maskin supra note 88 at pp. 4-11.

knowledge since it accelerates aggregate innovation by disclosure of inventions.[170] They also argue that a strong patent protection in a cumulative innovation process is favorable provided that sequential innovations are carried out by different firms.[171]

Heller (1998) first pointed out to the "tragedy of anticommons" phenomenon as opposite to the "tragedy of commons".[172] He states that "tragedy of commons arises when "multiple owners are each endowed with the privilege to use a given resource, and no one has the right to exclude another. When too many owners hold such privileges of use, the resource is prone to overuse."[173] Hence "a resource is prone to underuse in a tragedy of the anticommons when multiple owners each have a right to exclude others from a scare resource and no one has an effective privilege of use."[174]

In their very famous article Heller and Eisenberg (1998) argue that granting patents in the biomedical research may not work well. Given the increase in the number of private actors, who are doing and funding the research and the increase in the number of patents granted at the earlier stages of the research, blocking patents and high transaction costs, the innovation may be deterred.[175]

Indeed, Parisi et al. (2005) regard commons and anticommons problems symmetric; both are the consequence of a lack of conformity between use and exclusion rights. The anticommons problem is associated with asymmetric transaction costs and relates to neglected positive externalities, when fragmented owners of the property decide independent of each-other. If all owners can relate to complementary assets of property

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[170] SCOTCHMER, S. & GREEN J. (1990). Novelty and Disclosure in Patent Law. *The RAND Journal of Economics*, Volume 21, Issue 1 pp.131-146.

[171] GREEN, J. & SCOTCHMER, S. (1995). On the Division of Profits in Sequential Innovation. *The RAND Journal of Economics*, Volume 26 Issue 1 pp 20-33.

[172] HELLER, M. A. (1998). The Tragedy of the Anticommons: Property in the Transition from Marx to Markets. *Harvard Law Review* Volume 11, pp. 621 -688.

[173] Ibid at p. 624.

[174] HELLER, M. A. & EISENBERG R. S. (1998), Can Patents Deter Innovation? The Anticommons in Biomedical Research. *Science* Volume 280 pp. 698 -701.

[175] Ibid

and they could exert a positive externality on use rights. Commons and anticommons problems are not limited to situations of insufficient or excessive fragmentation of ownership, but also result from the dismemberment - and resulting non-conformity - between the internal entitlements of the property right. A single owner would face no strategic cost when deciding on how to divide his property, however multiple non-confirming co-owners face such transaction cost, as they attempt to rebundle independently owned property fragments.[176]

It may be argued that the patents on basic research may be licensed against a reasonable fee rate, which the industry or the public researchers are willing to pay. However, evidence shows that patenting of genes indeed results in patent race and deters public research and creates private monopolies, which possibly results in increased prices for the biomedical goods and services.[177]

Especially in the area of human genome there has been an era of patent race and extensive patenting. The international publicly funded Human Genome Project (HGP) cost USD 3 billion and was able to map the human genome by 2003 and consisted of members from universities and research institutes mainly from the US but also from various other countries.[178] Meanwhile private biotechnology companies, such as the US based Celera Genomics, Human Genome Sciences and Incyte had also entered the

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[176] PARISI F., DEPOORTER B. & SCHULZ N. (2005) Duality in Property: Commons and Anticommons. *International Review of Law and Economics*, Volume 25, No. 4. pp 1-30. Authors argue that both commons and anticommons problems "are the effect of a lack of conformity between use and exclusion rights, with a consequential misalignment of the private and social incentives of multiple owners in the use of a common resource. The misalignment is due to externalities not captured in the calculus of interests of the users (commons situations) and excluders (anticommons situations)" at p.25.

[177] See EISENBERG, R. (2000). Re-examining the role of patents in appropriating the value of DNA sequences. *Emory Law Journal*, Volume 49, Issue 3, pp. 783-800, GOLD, E.R et al. (2010). Are Patents Impeding Medical Care and Innovation? *PLoS Med*. Volume 7, Issue 1: available online at https://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000208http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1000208%20last%20visit%2025.09.2019 last visit 30.04.2020. Also GOLD E.R. & CARBONE J. (2010). Myriad Genetics: in the eye of the policy storm. *Genetics in Medicine*, Volume 12, Issue 4, available at doi: 10.1097/GIM.0b013e3181d72661 last visit 30.04.2020.

[178] Total cost during 1990-2003 including other scientific activities related to the project. See the official website of the Project for more information on budget and project partners http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml, last visit 30.04.2020.

sequencing race by using both public and their own data.[179] The budget of only Celera Genomics for the project amounted to USD 300 million.[180] The estimated worldwide cost for advancing the "draft" human genome sequence to the "finished" sequence was USD 150 million**,** where the NIH contributed roughly 50-60%.[181] This was the cost for generating the first human genome sequence by the HGP, the total US contribution to the HGP was around USD 2.7 billion. This figure is the total U.S. funding for several scientific activities under the HGP such as technology development, physical and genetic mapping, model organism genome mapping and sequencing, bioethics research, and program management.[182] This is a huge budget for a publicly funded project. Celera findings also rely on the data comparisons from the publicly available genome sequences; hence the Company generated a 14.8 billion base pair (bp)[183] DNA sequence in over 9 months at a much lower cost.[184]

The main objection from the public to the patenting of human genome sequences was that the data were basic scientific data, and as such not patentable. However the assertive patenting of Celera Genomics continued. By 1999 the company had filed preliminary patent applications for more than 6500 whole or partial human genes[185], and also refused to combine its data with the public genome database Genbank till 2005.[186] The discussions led the then UK Prime Minister Blair and US President Clinton make public statements that there should be free access to human genome information.[187]

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[179] "The Human Genome Sector and the Private Sector" available at https://web.ornl.gov/sci/techresources/Human_Genome/project/privatesector.shtml last visit 30.04.2020.

[180] HUANG, K. G. & MURRAY, F. E. (2010). Entrepreneurial Experiments in Science Policy: Analyzing the Human Genome Project. *Research Policy*, Volume 39, Issue 5, pp. 567-582.

[181] https://www.genome.gov/27565109/the-cost-of-sequencing-a-human-genome/ last visit 30.04.2020.

[182] Ibid

[183] The genome or individual genes are measured in base pair since the DNA is double-stranded.

[184] VENTER, J. C. et al. (2001) The sequence of the human genome. *Science.* Volume 291, Issue 5507, pp 1304–1351.

[185] "Human Gene Patents Defended", 27 October 1999, BBC, available at http://news.bbc.co.uk/2/hi/science/nature/487773.stm, last visit 30.04.2020.

[186] KAISER, J. (2005). Celera to end subscriptions and give data to public GenBank, *Science*, Volume 308, Issue 5723, pp 775-776.

[187] BUTLER, D. (2000). US/UK statement on genome data prompts debate on free access, *Nature*, Volume

Although the HGP was finished in 2003, results of the project are still used in scientific research today and will continue to do so for many years having a profound impact on biomedical research and medicines.

Anticommons may be a preferred regime when the non-use of the resource is aimed due to environmental concerns, such as preservation of natural resources. However, there are examples that broad-based patents on gene sequences and biomedical diagnostic have detrimental effects in genetic research and access to health care.[188] Indeed the legal systems may respond to this problem by limiting grant of extensive property rights by limiting the patent breadth and by developing unification systems in cases of extensive fragmentation of rights.

Bertacchini et al. (2009) argue that the introduction of semicommons regime where both common and private users coexist over the efficient use of a property may be an answer to this problem. The semicommons regime may solve the collective action problems with the introduction of anticommons arrangements and various owners may benefit from multiple use of the resource by scale economies. It would provide collective production under common ownership.[189] However the introduction of a semicommons regime requires a scattering of the resource to address strategic behavior. In gene patents fragmentation of the resource could be problematic and increase the complexity of strategic behavior. Although in theory patent owners could come together to make a deal, the cognitive biases exist that prevent such deals.[190] Heller (2008) states expanding the scope of ownership in gene patents by the regulatory bodies especially in the US has helped the boom of the medical biotechnology development. Private funding was poured

404, pp 324-325.

[188] See Gold et al, supra note 177, also EISENBERG R. (2001), The Shifting Functional Balance of Patents and Drug Regulation, *Health Affairs*, Volume 20, Issue 5 pp.119-135.

[189] BERTACCHINI E., DE MOT J. & DEPOORTER B. (2009). Never two without three: Commons, Anticommons and Semicommons, *Review of Law and Economics*, Volume 5, pp.163-176. The authors discuss that a rule of scattering allows agents to contract into an anticommons regime in order to create a mix of private and common use of land. Due to individual benefits from common use, the tension between common and private use would be solved.

[190] See Heller & Eisenberg supra note 174.

into basic research because of promised profits. Patents were meant to be leading to better testing of drugs and safer health care and better access to health care. Had the private companies come together to share the patents, they might have developed the drugs faster and increased their profits. However, privatization of biomedical research has led to patent thickets and the wish for individual profits maximization can obviate the development of life saving drugs such as Alzheimer.[191]

It is for instance criticized that existing patent laws also direct biomedical research to products that yield high profits rather than needs in developing countries. Although diseases such as malaria, pneumonia, diarrhea, and tuberculosis together account for 21% of the global disease burden, they receive 0.31% of all public and private funds devoted to health research.[192]

Another example to this situation would be the Myriad patenting. In 2001 Myriad Genetics of the US was granted a European patent for sequencing BRCA1 and BRCA2 genes, mutations of which are found to be related to breast cancer.[193] Refusing to license its patents, the company asserted that all samples for diagnostic genetic testing in Europe should be sent to Myriad. The paradoxical situation here is that the work of Myriad had actually relied on the previous work of Institute of Cancer Research of the UK, which is a publicly funded body, and which also owned separate patents on the gene and announced that publicly owned laboratories would be allowed to free use of the patent.[194] Meanwhile the Curie Institute in France had developed another diagnostic test for breast cancer not covered by Myriad patents. But the method included an analysis of the sequence patented by Myriad so using BRCA 1 and 2 sequences as an input would mean

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[191] HELLER, M. (2008). *The Gridlock Economy: How Too Much Ownership Wrecks Markets, Stops Innovation, and Costs Lives*, New York: Basic Books, pp.3-6. See also RIMMER M. (2003). Myriad Genetics: Patent Law and Gene Testing. *European Intellectual Property Review*, Volume 20, Issue 1, pp. 20-33.

[192] ORBINSKI, J. (2009). *An Imperfect Offering: Humanitarian Action for the 21st Century*, New York, Walker & Company.

[193] See Rimmer supra note 191.

[194] BENOWITZ, S., (2004), Although European Laboratories Welcome Free Use of BRCA2, Access Still in Question, *Journal of the National Cancer Institute*, Volume 96, Issue 7, pp. 506-507.

infringing Myriad patents.[195] A broad patent on genes deterred innovation in this regard. A researcher, who sought to develop a diagnostic test or a treatment method using BRCA sequences would have to pay royalty fees to all those who have patented different variations of the genes. In 2001 Curie Institute challenged Myriad at the European Patent Office, which will be explained in detail in Chapter 4.1.3.

The Myriad patents have raised concerns in the US, as well. In an initial lawsuit in 2010 the US District Court ruled that the isolated DNA molecules and the methods claimed to compare gene sequences in assessing cancer risk are not patentable subject matter.[196] This decision was appealed to the US Court of Appeals for the Federal Circuit, and the Court decided in 2011 that isolated DNA molecules do constitute patentable subject matter, hence reversed the decision of the lower court. Meanwhile the Supreme Court was working on a different case but remanded in this case the Myriad case and sent it back to the Federal Circuit in 2012. In the same year the Federal Circuit issued its second decision on Myriad case rejecting claims to methods of comparing gene sequences from patients against the sequences of its isolated molecules however claims on isolated DNA molecules were still regarded as patentable subject matter.[197]

In 2013, The Supreme Court held in Myriad Case that solely isolated gene sequences are not patentable, even if they are removed from the human body, but the man-made cDNA sequences, are eligible for patenting.[198] This decision is expected to

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[195] See Gold and Carbone supra note 177.

[196] 702 F. Supp. 2d 181 (S.D.N.Y. 2010).According to Senior Judge Robert W. Sweet claims directed to isolated DNA molecules were failing to be patent-eligible subject matter under 35 USC § 101, because "the claimed isolated DNA molecules were not "markedly different" from native DNA molecules as they exist in nature". Hence the analysis of the Judge depended on the products of nature doctrine. Marking different doctrine emerged from earlier cases including the decision on Chakrabarty and held that claims would be patent ineligible since genetic sequences were not marked differently from their native DNA sequence.

[197] 689 F.3d 1303 (Fed. Cir. 2012) AMP v. USPTO.

[198] See the Case 133 S. Ct. 2107, 2111 (2013), Association for Molecular Pathology v. Myriad Genetics, Inc. The Court examined 2 types of claims being isolated genomic DNA (gDNA) and an isolated complementary DNA (cDNA). gDNA is derived from chromosomal DNA whereas cDNA is derived from a RNA, (RNA is again a nucleic acid helping carry out DNA's blueprint guidelines. It transfers the genetic code necessary to create proteins). The Court concluded that isolated gDNA is not an eligible patent claim, but some isolated cDNA claims may be.

have a big impact on the medical biotechnology industry in terms of drafting of claims for patent eligible subject matter and investment decisions especially by changing the flow of secrecy and patents. Especially in case of personalized medicine raising the patent-eligibility threshold also means intensifying regulatory scrutiny of medical diagnostics. Although Myriad decision considers the anticommons tragedy associated with gene patenting, it may in also worsen the commons problem in medical research by creating increased uncertainty about the patentability of complex, data-driven discoveries, as a result of which private payoffs associated with cooperation would be altered and socially productive sharing regimes would be undermined.[199] It would not be right to assume that patentability restrictions applied to genes and diagnostics methods would result in a big number of donations to genetic commons; innovators would now have choices of giving them to public domain or protecting them by trade secrets and by other encryption and password methods.[200]

Hence although the Supreme Court has declared the isolated gDNA sequence to be an invalid patent claim, the economic impact of this decision can be felt when owners of genetic testing turn their patents into trade secrets. Being an exclusive test provider in BRCA1/2 genes for over two decades, Myriad held that just 3% of its test results were concluded with a diagnosis of variant of unknown significants (VUS), whereas its competitors in Europe had results up to 20%.[201] Thus patients can have their gene screening done in other laboratories now that Myriad's exclusivity has been terminated, but if these laboratories have no access to Myriad data, the interpretation of VUS results will be difficult, if not impossible.

Myriad's and University of Utah's patents have monopolized the US market for

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[199] LAAKMANN, A.B. (2015). The New Genomic Semicommons. *U.C. Irvine Law Review,* Volume 5, pp. 1001 – 1040.

[200] Ibid pp. 1013 – 1015 Myriad has invested in a huge database that could disclose which DNA changes could increase the breast cancer risk. However, the company has developed a policy of keeping this data as trade secrets, which has enabled Myriad to retain its dominant position in the market, although some of the patent claims were declared invalid by the Court. To secure its competitive advantage in the market the company has engaged in contracts with the US Health plans /insurance companies that have agreed to protect its trade secrets.

[201] Ibid p. 1015.

genetic testing in breast cancer for a while. The company was charging between 350 – 3150 USD for the BRCA test, and had successfully stopped many laboratories from performing the test if they did not have the required license.[202] The opponents of DNA sequence patents argued that academic research community was concerned, because R&D was impeded due to the fact that patent claims were significantly upstream within the R&D pipeline and the actual functions of these genes and their protein derivatives were unknown.[203] Besides, patient access was also hindered due to barriers in availability and pricing of the tests.[204] As it is obvious in Myriad case, holders of gene patents may accumulate data, but removal of patents may result in further problems in disclosure of information.

2.6 Concluding Remarks

If the gene is given a novel and inventive use, the patent protection seems to be regarded appropriate. Merely saying that genes should not be patentable does not create any consideration at the granting of patent protection. The US ruling looks extremely broadly interpreted when it says "anything under the sun made by man" is included as a patentable subject matter.[205] However this view has its limits and the patent offices ensure that there is a clear distinction between discovery, material with no industrial application and patentable subject matter.[206] Due to ethical considerations of gene patenting and the discussion on discovery versus invention, there was a call that human genome should be our common heritage.[207] It is true that especially in-silico analysis (computational

[202] ROBERTSON A.S. (2011). The Role of DNA Patents in Genetic Test Innovation and Access. *Northwestern Journal of Technology and Intellectual Property*, Volume 9, Issue 7, pp 377-399 at p. 384.

[203] Ibid p.383.

[204] Ibid p.385.

[205] Case 447 U. S. 303 (1980) Diamond V. Chakrabarty.

[206] For instance, in Case 333 U.S. 127 (1948) Funk Bros. Seed Co. v. Kalo Inoculant Co.: products of nature (certain mixed cultures of nitrogen-fixing bacteria) were seen as the discovery of a phenomenon of nature and were not patentable.

[207] STURGES, M. (1999). Who Should Hold Property Rights to the Human Genome? An Application of the Common Heritage of Humankind. *American University International Law Review,* Volume 13, No. 1

analysis enriched by powerful statistical and machine learning algorithms) of gene sequences facilitates the prediction of the functions of the genes. And these functions may be regarded as already existing properties of the genes, and not invented ones. However, the practice shows that purified and/or isolated nucleotide chemicals of genes are granted patent protection by the USPTO and EPO, as they are regarded as having met the patentability criteria and ethical and/or moral considerations have resulted in the amendments in the legislation in the EU.

Another idea to bring into discussion would be to change the term of patent for gene patents and decrease it. However, it is hard to see in detail how this would help.

The change of the patent term in the United States in 1995 has been very controversial.[208] Under the old regime the patent holders received 17 years of protection from the date the patent was issued, and it was possible for the patent holders to keep submarine patents, i.e., patents whose publication and issuance dates have intentionally been delayed for some years. The patent applications that have been filed at the USPTO were not published and remained secret till the date the protection was granted. Hence like a submarine they stayed out of sight and came out unexpectedly typically after the markets have long adapted the patented technology.

The adoption of the 20-year term was done to bring U.S. patent law into conformity with the World Trade Organization's Agreement on Trade-Related Aspects of Intellectual Property Rights (TRIPS) as agreed in the Uruguay Round and also due to a bilateral executive agreement between the US and Japan.[209] The patent term was extended from the date it was issued to the date it was filed at the USPTO until 20 years. Some inventors then complained that the new patent term would reduce patent protection because some applications spend several years in prosecution before the USPTO. Under the old law, delay in processing an application did not hurt the patentee, but under the new law, each

pp 219-261 at p.224.

[208] LERNER, J., (2000), 150 Years of Patent Protection *NBER Working Paper* No. 7478 available at http://www.nber.org/papers/w7478 last visit 30.04.2020.

[209] See Lemley at supra note 79 , p. 376 and BOP position paper at supra note 78.

day spent in prosecuting the patent would mean a day of protection lost.[210] Patent prosecution is especially difficult in industries with rapid changes such as biotechnology and delays in prosecution can cause uncertainty among the patentee's competitors and downstream companies using the technology. Indeed, the opposition to the patent term amendment came especially from the biotechnology industry stating that USPTO was very slow in processing the patent applications and it may take more than three years to process a biotechnological patent application.[211]

An early empirical study estimated that the new law would yield less protection days for biotechnology patents, although the study was inconclusive for these patents due to the small sample size.[212]

Some further studies indicated that patent continuation process was also bringing difficulties. It was shown that the average patent in 1996-98 issued from 1.50 applications, the average pharmaceutical patent issued from 2.27 applications, and the average biotechnology patent from 2.38 applications.[213] As also noted by Brougher (2014), patent applicants who were not contented with the way patent prosecution was headed to, especially in cases where the patent examiner accepted some of the claims but rejected others, could abandon the application and file a continuation. Or applicants can prosecute more than one patent to be issued and keep relevant continuation application with additional claims with the hope that there would be a broader breadth of protection. The applicants could file as many continuations as desired till the USPTO changed the rules in 2007 so that the continuation was limited to two applications for each type of invention disclosed in an original patent application. For further applications, the

[210] See Lemley at supra note 79 p. 371.

[211] Ibid p. 376

[212] Ibid pp. 406-408. The study was carried out with a small sample size of 25 biotechnology patents testing the hypothesis that on average patentees receive a longer term of protection under the old law than under the new law, and the hypothesis that no subgroup (subsector) is worse off on average under the new law than they were under the old law. The new law with an expected reduction of 20% of prosecution time was giving the biotechnology groups less days of protection.

[213] ALLISON J. R. & LEMLEY M. A. (2000). Who's Patenting What? An Empirical Exploration of Patent Prosecution. *Vanderbilt Law Review*, Volume 53, Issue 6, pp 2099-2174.

applicant needs to show "good cause" to be able to file additionally.[214] These changes were also opposed by the biotechnology sector, on the grounds that limiting the number of claims would increase the cost and uncertainty for the sector especially for the smaller companies.[215]

Hence decreasing the patent length would be a challenging task especially for biotechnological innovations. Another option discussed as an alternative to patents is the prize system. This system involves giving a prize to the innovator when their innovations meet certain objectives. The size of the prize can be determined according to the magnitude of the contribution. For instance, finding a new cure to a disease would deserve a big prize, whereas developing a new drug with slightly fewer side effects than the existing ones, but otherwise not more effective than the other ones would receive a smaller prize.[216]

According to Stiglitz and Greenwald (2014) the current patent system can be reviewed as a prize system because the innovators are granted the "prize" of certain monopoly rights. However, with the monopoly power come the incentives to restrict the use of knowledge. With an efficient prize system, the competitive market would give enough licenses to a large number of participants and ensure dissemination of information. The competitive markets would also drive down the prizes and extend the benefit sharing.[217]

There are certainly also counter arguments for the prize system. Spulber (2014) argues that the administrative costs of government control of invention, innovation, and technology diffusion would be much more than the market transaction costs. Governments cannot be expected to improve static and dynamic efficiencies of market

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[214] BROUGHER, J. T. (2014). *Intellectual Property and Health Technologies Balancing Innovation and the Public's Health*, New York, Springer pp. 13, 26.

[215] See the letter dated 02 May 2006 of BIO (Biotechnology Industry Organization) to USPTO on proposed changes, available at https://www.uspto.gov/sites/default/files/documents/fpp_continuation_bio.pdf last visit 30.04.2020.

[216] STIGLITZ J. E. & GREENWALD B. C. (2014). *Creating a Learning Society, A New Approach to Growth, Development, and Social Progress*, Columbia University Press, p. 270.

[217] Ibid p.271.

allocation of inventions. The administrative costs of governmental control of invention, innovation, and technology diffusion would be much more than the market transaction costs. Hence replacing market prices with government prizes would generate bigger deadweight welfare losses. The Bayh-Dole Act[218] in the US is shown as a "natural experiment" illustrating how markets diffuse innovations and governments do not. The Act enables universities, SMEs, and non-profit organizations to carry on research with government funding and to own patents for their inventions rather than transferring the intellectual property rights to the federal government. It is noted that in the first 25 years following the Act, university patent licensing generated 4,350 new products and 6,000 new firms.[219]

Indeed, we may say that if prize system had been superior to the patent system, we would have seen revolutionary innovations with commercially available pharmaceutical products or diagnostic methods. The flaw of the prize system in the development of pharmaceuticals is that, after say the gene compound is put under public domain by the government and several companies would start producing a drug using this gene compound, it would be difficult to determine who shall be held liable in case of a quality defect. But we see that patent system also creates flaws in development and use of pharmaceutical products. One concern is for instance the production of so-called "me-too" drugs, which are follow-on drugs that are to a large extent similar to well-known blockbuster drugs and can offer little incremental therapeutic value.[220] Another noted concern is that when a patent on an antibiotic expires, other companies can now freely sell the antibiotic, more of the antibiotic is produced and prices fall. This creates antibiotic resistance, and since the benefits of reducing current production go to other firms, pharmaceutical companies do not bother about future resistance.[221] As a result, the current

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[218] See infra note 337. A more detailed analysis of the Act is given in Chapter 4.2 Practice in the US.

[219] SPULBER, D. (2014). Prices versus prizes: Patents, public policy, and the market for inventions. *Northwestern Law & Economics Research Paper*, available at http://www.law.northwestern.edu/research-faculty/searlecenter/innovationeconomics/documents/Spulber_Prices_versus_Prizes.pdf last visit 30.04.2020. pp.15-17.

[220] HOLLIS, A. (2005). An Efficient Reward System for Pharmaceutical Innovation, research paper submitted to WHO available at https://www.who.int/intellectualproperty/news/Submission-Hollis6-Oct.pdf last visit 30.04.2020.

[221] HOROWITZ J.B. & MOEHRING H.B., (2004), How property rights and patents affect antibiotic

patent system creates a vicious circle in terms of antibiotic resistance. Even before the patent expiry, the patent system creates incentives to invest in development of new antibiotics that can fight new bacterial infections, which in return creates an incentive to excessive selling of antibiotics, increasing antibiotic resistance of bacteria. It would be considerable to reward drug innovators based on the social benefits of such innovation. That would undermine the excessive marketing and use of certain pharmaceutical products. The social benefits can be measured on public health benefits due to decreased illnesses, health care costs, nursing, and so on.[222]

Perhaps the prize system in medical biotechnology should be regarded as a supplement to the patent system, and not as a substitute. The prize system can address the issue of excessive marketing and production of generic drugs.

resistance, *Health Economics* Volume 13, Issue 6 pp. 575-83.

[222] See NICKAS, M. (2012). A Patent Prize System to Promote Development of New Antibiotics and Conservation of Existing Ones. *Pittsburg Journal of Technology Law & Policy*, Volume 12, Issue 5 pp 1-32. for his UADS model where he Uncouples Antibiotic Development from Sales. At first there is a patent buy-out where pharmaceutical companies develop new antibiotics and receive patents for the new compounds, formulations, or methods of use, which in return for FDA approval can be transferred to the government in exchange for a prize. Later in sales phase government licenses manufacturing companies.

3. ANALYSIS OF THE LEGAL SYSTEMS

In this chapter the positive analysis is primarily a discussion of the patenting requirements in the different legal systems (EU and USA), related jurisprudence with some examples from the case law.

A few basics about biotechnology are given below in order to have a better understanding of biotechnological materials, their importance and (potential) use in research and at a clinical setting. Some very serious medical conditions occur as a result of abnormal cell divisions and mutations and the thorough understanding of genetic material and molecular processes encourage the development of new therapies.

3.1 Some Basics on Biotechnology

Biotechnology can be defined as a set of techniques and processes using biological sciences to do research and provide products and services to meet human needs[223]. The term "biotechnology" dates back to 1919, as the Hungarian – German economist Karl Ereky used the term for the first time in his book "Biotechnologie der Fleich-, Fett- und Milcherzeugung im landwirtschaftlichen Grossbetriebe"[224] to define "products made from raw materials with the help of living organisms".[225] However, the application of biological sciences in different methods and processes to satisfy human needs is not a new concept. It was more than 10.000 years ago, as the humans started with crossing of plants and animal husbandry by selective breeding methods and later with processes of brewing beer and fermentation of milk to produce cheese and yoghurt. Today there are many application areas of biotechnology, sometimes referred with colors, such as red biotechnology (medical applications); green biotechnology (agricultural applications);

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[223] Compiled from various definitions from SMITH J. E., (2004), *Biotechnology 4th edition – Studies in biology*, Cambridge University Press, Cambridge pp. 3-5.

[224] EREKY, K. (1919). Biotechnologie der Fleich-, Fett- und Milcherzeugung im landwirtschaftlichen Grossbetriebe, Verlag P. P. Berlin.

[225] FÁRI, G., BUD R., KRALOVÁNSZKY, P. U. (2001). *The History of the Term Biotechnology: Károly Ereky and His Contribution*, presentation at the Fourth Congress of Redbio- Encuentro Latinoamericano de Biotecnologia Vegetal, Goiânia, Brazil, June 4-8.

white/grey biotechnology (applications to industrial processes to produce organisms that destroy hazardous chemicals in order to treat waste and to recycle) and most recently blue biotechnology (aquatic applications to increase marine and freshwater organisms in order to safeguard seafood and assure safety of aquatic species.)

Since red biotechnology lies at the core of this dissertation, it is better to give a short overview about the basics of biotechnology and its health and medical applications.[226]

Proteins, also called as polypeptides, are made of amino acids that are linked together covalently. They are organic compounds of enormous importance. They occur in nature only in little quantities or are difficult to purify from natural sources. Hence many biotechnological patents and patent applications entail specific proteins or methods for making and using proteins. There are only 20 amino acids, however, they are strung together in different orders to produce the hundreds of thousands of proteins found in nature.

In order to produce a protein molecule, a cell needs information about which amino acids should be used and the sequence in which the amino acids must be assembled. The cell uses a long polymeric molecule, DNA (deoxyriboneucleic acid), to store this information. The subunits of the DNA chain are called nucleotides. There are four nucleotides; namely adenine, guanine, cytosine, and thymine (abbreviated as A, G, C and T). They differ from each other in the base region of the molecule. The sequence of these bases along the DNA molecule specifies which amino acids will be inserted in sequence into the polypeptide chain of a protein. A gene is a sequence of these bases. A three-based sequence is called a codon and it codes for an amino acid. The four bases can be combined as triplets (4^3) in 64 different ways, but there are only 20 amino acids to be coded. Therefore, most amino acids are coded for by more than one codon. A one-to-one correspondence between codons and amino acids is not possible, that's why the DNA

[226] This part is compiled from Background part of the Case 853 F.2d 894 (Fed. Cir. 1988) In re O'Farrell, and SUTTON V. (2007). *Law and Biotechnology*, Durham, North Carolina: Carolina Academic Press, pp. 4-8.

sequence of a protein cannot be directly derived from its amino acid sequence. Still it is possible to obtain the DNA sequence by means of a complementary DNA (cDNA) library. cDNA library is a set of cDNA fragments that code for proteins actually expressed in a given cell. It is a library for reverse transcription. All the biotechnologist needs to do is then to develop a sample that will bind with the desired cDNA sequence of the protein and screen the cDNA library. This can be done if all or part of the amino acid sequence of the protein is known. The information on cDNA libraries is available to members / subscribers or upon purchase. The patentability criterion in granting patents to DNA sequences is a very controversial issue as addressed in this dissertation.[227]

Alone biopharmaceuticals (pharmaceuticals developed by using biotechnological processes) have so far been used by over 325 million patients worldwide.[228] If we add other therapeutic and diagnostic uses of biotechnology, it is obvious that medical biotechnology and personalized medical care with targeted approach will be an integral part of the health system in the future. Therapies derived from the molecular profiles of the patients will replace the traditional medicine.[229]

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[227] See Sutton at Supra note 226 for some applications of medical biotechnology such as

Cell culture technology: Process of growing of cells outside the tissue from which they are obtained. The cells growing in artificial environment may be used therapeutically, in drug testing to find out the efficacy and safety of pharmaceutical products and in vaccines.

Monoclonal antibody technology: Process of using immune system cells and enzymes to produce proteins; namely antibodies. Antibodies are used by the immune system to detect and neutralize foreign substances.

Recombinant DNA (rDNA) technology: Also referred as genetic engineering technology, it is the production of an artificial kind of DNA by joining (recombining) of two or more sequences from different sources so that transfer of genes across species is possible.

Tissue engineering: is the technology of creating semi-synthetic tissues by combining living cells with different biodegradable materials to repair or replace the damaged tissues.

Antisense therapy: Antisense DNA is a strand of DNA. It transmits the information to make proteins by binding to a corresponding messenger RNA; which is the product transcribed from a DNA and which carries coding information to the cells that make proteins from amino acids; namely the ribosomes. This therapy is the process of turning a gene off e.g., genes causing particular diseases. This technology may be used in treatment of hereditary diseases.

[228] Trade Association-European Biopharmaceutical Enterprises- Facts, available at https://www.ebe-biopharma.eu/facts/ last visit 30.04.2020.

[229] GINSBURG, G.S. & MCCARTHY, J.J (2001). Personalized Medicine: Revolutionizing Drug discovery and Patient Care. *Trends in Biotechnology*, Volume 19, Issue 12, pp. 491 – 496.

3.2 TRIPS – Section 5

The Agreement on Trade Related Aspects of Intellectual Property Rights (TRIPS) of 1 January 1995 is a multilateral agreement on a wide range of intellectual property. It is administered by the World Trade Organization (WTO) and the enforcement of the agreement among the WTO members is assured by the WTO's dispute settlement mechanism.

Section 5 of Part II of the agreement deals with the patents. According to Article 27.1 product / process inventions in all fields of technology shall be granted patent protection if they are "new, involve an inventive step and are capable of industrial application." It is noted that "the terms "inventive step" and "capable of industrial application" may be deemed by a Member to be synonymous with the terms "non-obvious" and "useful" respectively". Besides patents shall be "available and patent rights enjoyable without discrimination as to the place of invention and whether products are imported or locally produced".

There are three exceptions to patentability. The first one is according to Article 27.2 for inventions (and their commercial exploitation) contrary to ordre public or morality, this includes inventions to protect human, animal or plant life or health or to prevent serious prejudice to the environment.

The second exception is according to Article 27.3(a) is that the Members states may exclude the patenting of diagnostic, therapeutic and surgical methods for the treatment of humans or animals.

The third exception according to Article 27.3(b) is on plants, animals other than micro-organisms and essentially biological processes for their production. However, plant varieties may be excluded provided that the member country offers "an effective sui generis system of protection".

On dissemination of information Article 29.1 requires that the disclosure of the invention shall be done by applicants in a way "sufficiently clear and complete for the

invention to be carried out by a person skilled in the art", the applicant may be required to "indicate the best mode for carrying out the invention known to the inventor at the filing date".

It must also be noted that the compulsory licensing and the use of invention without the authorization of the right holder by government or by parties authorized by the government (public non-commercial use) are also allowed under Article 31, but they are subject to various conditions. In general, these conditions are developed to protect the right-holder and the use without authorization shall be applied "only if an attempt has been made to acquire a voluntary license on reasonable terms and conditions within a reasonable period of time", but this attempt has been unsuccessful. It can be argued that the provision on such use is developed with some efficiency concerns. It is stated in Subparagraph (a) that "authorization shall be considered on its individual merits". Subparagraph (h) states that "the right holder shall be paid adequate remuneration in the circumstances of each case, taking into account the economic value of the authorization". Similarly, in Subparagraph (l) the issue of blocking patents is taken into consideration. If the (use of) "a patent ("the second patent") cannot be exploited without infringing another patent ("the first patent"), the owner of the first patent shall be entitled to a cross-license on reasonable terms to use the invention claimed in the second patent provided that the invention claimed in the second patent involves an important technical advance of considerable economic significance in relation to the invention claimed in the first patent. The use authorized in respect of the first patent shall be non-assignable except with the assignment of the second patent."

The flexibility in Article 31 to allow governments to authorize third parties to use the patents without the permission of the right holder is an important step in dissemination of information. By means of compulsory licensing or other administrative processes, the countries may decide according to their own legal systems to which scope this authorization shall apply. The two pre-requisites of this permission are to ensure an adequate remuneration for the right holder, as well as to ensure a fair treatment by judicial or independent review. Article 31 (i) and (j) state that decisions given on such use and renumeration will be subject to a judicial or independent review by a higher authority in

the member state.

These are two important provisions that allow members to choose either judicial or other independent review for appeals for decisions relating to the authorization of compulsory licensing. By these provisions the members have the possibility to keep the decision making and review processes out of the judicial system.

Similarly, Article 31(k) states that countries may choose judicial or administrative processes to decide whether a compulsory license is necessary to remedy practices that are found to be anticompetitive after the judiciary or administrative process.

Articles 41-44 of the Treaty refer to the establishment of just and reasonable procedures to enforce intellectual property rights. Article 41.2 states that these procedures "shall be fair and equitable and not unnecessarily complicated or costly or entail unreasonable time-limits or unwarranted delays." Article 44.2 also brings important provisions on injunction for compulsory licenses. It states that as long as TRIPS "provisions regarding use by governments or by third parties authorized by a government, without the authorization of the right holder are complied with, Members may limit the remedies available against such use to payment of remuneration in accordance with subparagraph (h) of Article 31". Hence it is possible to exclude injunctive relief for government use or compulsory licensing disputes.

Promotion of technological innovation and to the transfer and dissemination of technology is one of the major goals of TRIPS Agreement.[230] As stated by Ebermann (2012) the presence of an efficient and enforced intellectual property system can influence both innovation and transfer of technology. Trade in intellectual property creations accompanies transfer of technology. Licensing in this regard plays a central role for technology transfer as it enables the licensee to attain the technology without undertaking own research endeavors. Foreign direct investment (FDI) is another way of enabling learning by doing and knowledge spillovers. Right holders can be discouraged to make

[230] See Article 7 of TRIPS.

their technology available at places in absence of intellectual property. [231] Empirical findings suggest that developed countries benefit from strong intellectual property since innovative activity primarily originates from these countries. In developing countries intellectual property protection and enforcement has a positive role in attracting FDI and generating technology transfer, however patent protection does not ensure that new products will be supplied in the short run, but rather prevents the supply of imitated products. For developing countries, the benefits of intellectual property rights in terms of FDI attraction is likely to exceed the cost of implementation of such rights. But especially in countries with low per capita income the positive effects are expected to slow down in the long run.[232]

The issue as regards medical biotechnology can be the use of compulsory licenses by certain countries for the patented products such as biopharmaceuticals. But for this to happen, the countries should have the necessary manufacturing capacity of the patented medicine so that terms on licensing can be agreed upon by both parties. For instance, AIDS treatment in the developing world has been quite controversial. The weak access of AIDS patients to antiretroviral medicines in poor countries that are severely affected from the disease such as Africa has sparked a lot of debate about the role of patents and excessive monopoly rights of pharmaceutical companies. It is noted by Westerhaus and Castro (2006) that the compulsory licenses, the primary mechanism offered for public health protection by the TRIPS agreement have rarely been used till 2004 since exact procedures for issuing a compulsory license for antiretroviral production remained unclear and largely untested. In 2004 only four countries namely Malaysia, Indonesia, Zambia, and Mozambique had issued such compulsory licenses.[233] Indeed Doha Declaration of 2001 on the TRIPS Agreement and Public Health had also enabled the poor countries to import the patented drug, if they are unable to manufacture it. Later on,

[231] EBERMANN, P. (2012). *Patents as Protection of Traditional Medical Knowledge*, Cambridge, UK: Intersentia, pp 45-46.

[232] Ibid p. 51.

[233] WESTERHAUS, M. & CASTRO, A. (2006), How Do Intellectual Property Law and International Trade Agreements Affect Access to Antiretroviral Therapy? *PLoS Med,* Volume 3, Issue 8 pp. 1230-1236.

in order to avoid compulsory licensing, the pharmaceutical companies made voluntary efforts to make their medicines accessible for developing countries by making price reductions or providing royalty free licenses to other companies.[234]

When assigning compulsory licensing to third parties, governments should take public health issues, as well as rights of the patent holders into consideration. Assigning compulsory licensing too frequently may discourage the inventors from patenting their products.

Indeed in addition to TRIPS Agreement many nations have engaged in bilateral agreements, known as TRIPS-Plus measures to ensure a higher standard of patent protection; extending the patent protection beyond the 20-year period, increasing data exclusivity (protection of the manufacturers' drug testing data) and bringing more restrictions on compulsory licenses.[235] For instance in Guatemala legislation allowed 15 years of test data exclusivity, a term way beyond what was required by TRIPS Agreement and the Central American Free Trade Agreement (CAFTA) requirement of 5 years.[236]

Compulsory licensing and production of generic drugs are related to the production

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[234] KAUR, A. & CHATURVEDI, R. (2015), Compulsory Licensing of Drugs and Pharmaceuticals: Issues and Dilemma, *Journal of Intellectual Property Rights* Volume 20, Issue 5, pp.279-287.

[235] The Central American Free Trade Agreement (CAFTA) between the US, Costa Rica, El Salvador, Guatemala, Honduras, and Nicaragua and the Dominican Republic requires both data exclusivity of five years and patent extensions beyond 20 years term to compensate the patent owner for unreasonable administrative delays, either in granting patents or in marketing approval process for pharmaceuticals.

[236] Pharmaceutical companies need to provide information about the safety and efficacy of their products to get market approval from regulatory bodies. Data exclusivity requirement ensures that manufacturers' drug testing data where pre-clinical and/or clinical results of the drug are disclosed, cannot be used by another (mostly a generic) company to get market approval. Due to the length of the drug-development and market-approval processes, the patent protection does not correspond to market approval of the product, and pharmaceutical companies may be faced with patent expiry shortly before or after the product enters the market. Article 39.3 of TRIPS Agreement only foresees that countries should "protect such data against unfair commercial use with the exception where necessary to protect the public". This Article was enjoyed by some countries to approve a generic product on the market on the basis of an earlier approval of a branded product. TRIPS – plus measures restrict such authorizations. See GODOY, A. S. & CERÓN, A. (2011). Changing Drug Markets Under New Intellectual Property Regimes: The View from Central America. *American Journal of Public Health*, Volume 101, Issue 7, pp 1186–1191 for a full discussion of how implementation of CAFTA differed in four Central American countries, although they were subject to the same requirements. It is noted that these laws generated little discussion in Central America at the time of their introduction.

and supply capabilities of the relevant country, as well as the global political economy to create the necessary legal, political, and economic incentives to address the pricing and undersupply problems in pharmaceuticals. The law should focus on the economic interests of all stakeholders and find a balance between extending treatment possibilities and creating further incentives for innovation.

In the WTO dispute between Canada and the EU over the Canadian patent protection of pharmaceutical products we see the importance of allowing generic drug producers certain rights over the rights of the patent holder.[237] The dispute arose around two provisions of the Canadian Patent Act. The first one (Section 55.2(1) of the Act) allowed generic drug manufacturers to use the patented invention before the expiry of the patent so that the generic manufacturers could develop and test drugs to gain regulatory approval. Also known as the regulatory review provision, this Section accelerated the review and approval processes of new drugs. The second disputed provision of the Canadian Patent Act (Section 55.2(2)) allowed generic drug manufacturers to make the drug and stockpile it six months prior to the patent expiry date. As a result of these two main provisions (and certain regulations about the implementation of these two Sections) generics could be placed on the market immediately or very shortly after the expiry of the patented pharmaceuticals.

The EU filed a complaint at the WTO that Canada was in breach of TRIPS Article 27.1 on non-discriminatory nature of patentable subject matter, Article 28.1 on rights conferred to patent owners and Article 33 on 20 years term of protection (that Canada was making discrimination based on technological field, i.e. holding pharmaceutical patent holders less favorable than those ones in other fields of technology, allowed for activities to obtain market approval without the consent of the patent holder and reducing the 20-year patent term.) In the complaint of the European Communities and their member states, the economic loss of the EU pharmaceutical industry due to these

[237] WTO dispute settlement body report No: WT/DS114/R of 17 March 2000, adopted on April 7, 2000. Canada – Patent Protection of Pharmaceutical Products, Complaint by the European Communities and their member States, Report of the panel.

provisions was also estimated to be around C$ 100 million annually .

Canada on the other hand argued that these provisions were in line with TRIPS Article 30 on limited exceptions to conferred rights when the legitimate interests of third parties were at stake. In this case third parties were patients in the Canadian health systems and public and private sector entities paying for it. It was emphasized that the Patent Act took into account social welfare and finding a balance between rights and obligations in protecting public health and promoting cost-effective access to generic drugs after patent expiry (referring to objectives and principles of TRIPS in Articles 7 &8) . Moreover it was mentioned that since Section 55.2(1) of the Patent Act was limited to a narrow circumstance solely for the purpose of regulatory review, and the second provision on stockpiling (Section 55.2(2)) could only be invoked by the same generic drug manufacturer after the first exception, neither the commercial activities of the patent holder on the sales , licensing agreements and royalties (i.e. normal exploitation of a patent) were not affected, nor the effective patent term was reduced.

On regulatory review exception of Section 55.2(1), the WTO panel referred to the information provided by Canada (and not contested by the European Communities) that development and regulatory approval of a new patented drug takes 8-12 years, whereas the generics require 2-4 years of development and 1-2,5 years of approval process. If no exception was given in development and regulatory review during the patent term, the generic drug manufacturers would be forced to wait 3-6,5 years after the patent expiry. Besides a possibility of de jure discrimination was dismissed since Canada declared that this provision should apply to any technological field in need of regulatory approval and the EC Communities failed to provide evidence of de facto discrimination against pharmaceutical sector. Hence this provision of the Patent Act was found to be justified under TRIPS Article 30 on exceptions.

However, the Panel had a different view on Section 55.2(2) on stockpiling and did not accept Canada's arguments that the exception was "limited" in the sense that it was given for a period of six months, to be invoked by the same person who relied on the exception in Section 55.2(1) and the exclusive right to sell to the ultimate consumer

during the patent term was preserved to the right-holder. First, the Panel stated that TRIPS does not create a hierarchy of patent rights in which "selling" is primary and "making", and "using" are secondary. Next, market advantage of the patent holder after the patent expiry is viewed as an extended market exclusivity and the provision did not provide any limitation on the quantity of the products that can be manufactured and having barely a reference to a 6-months period would not render the provision "limited". Last, the fact that the stockpiling provision was tied to regulatory approval provision would not qualify the provision to be eligible to a general exception under Article 30; "each exception must be evaluated with regard to its impact on each affected patent, independently."[238] Hence the Panel found the stockpiling provision to be inconsistent with Article 28.1 and asked Canada to bring Section 55.2(2) of the Patent Act in conformity with TRIPS. Canada informed WTO on April 25, 2000 that it would do so in a "reasonable period of time", which was determined by the Arbitrator between Canada and the EU for a period of six months.[239]

From law and economics point of view the approach of the Panel towards de jure and de facto discrimination is of significance. Canada denied any de jure discrimination limited to pharmaceuticals and gave evidence from a court case of a medical device manufacturer involving Section 55.2.(1) as a defense claim to an infringement. The Panel referred to some rulings of Appellate Body, where defined forms of de facto and de jure discriminations were prohibited, and each ruling was based on the precise legal text concerned. Hence not all differential treatment could be deemed discriminatory. The Panel then asked the complainant to prove de facto discrimination by either empirical evidence of disadvantageous effects or by a discriminatory purpose that the legislator had intended. Since there was no such evidence, and the incentive effects aimed by the legislator could not be the provision of an exception only to the detriment of pharmaceutical patent holders, the discrimination claims of the EC were rejected. Since

[238] Ibid p. 156 Par. 7.37.

[239] WTO Award of the Arbitrator WT/DS114/13 of 18 August 2000; Canada – Patent Protection of Pharmaceutical Products, Arbitration under Article 21.3(c) of the Understanding on Rules and Procedures Governing the Settlement of Disputes.

this decision of the Dispute Settlement Body was not appealed, there is not a follow-up decision of the Appellate Body. Still, we see that the social welfare incentives of Canadian legislators in finding a balance between patent holders and the cost- effective access to pharmaceuticals were recognized by the WTO to a great extent. Likewise, the WTO Dispute Settlement Body also exercised a balance of rights and obligations to promote innovation, dissemination of technology, social and economic welfare by allowing member states to take necessary measures to protect their public health as set forth in Articles 7&8 of TRIPS. The Panel relied on Appellate Body decisions and weighed on the facts of the case: Concerning the first exception on regulatory review, the Panel confided in the declaration and evidence of Canada that the law had no discriminatory purpose, regulatory review exception was not intended solely for the pharmaceutical sector, and the discriminatory effect could also not be proven by the complainant. Concerning the second exception on stockpiling the Panel concluded that the measure was not consistent with TRIPS Article 30 criteria on being "limited, not unreasonably conflicting with the normal exploitation of a patent and not unreasonably prejudice the legitimate interests of the patent owner, taking account of the legitimate interests of third parties".[240]

3.3 Patentability of Biotechnological Inventions – Legal Basis in the EU

In addition to Section 5 of the TRIPS, the legal basis for the patentability of biotechnological inventions in the EU consists of European Patent Convention (EPC) and the Directive 98/44/EC.

3.3.1 European Patent Convention

The Convention on the Grant of European Patents of 5th of October 1973, commonly known as European Patent Convention (EPC), is a multilateral treaty set up

[240] DSB report at supra note 237 pp. 56-59.

by the Council of Europe and both EU and non-EU countries are party to it.[241] It is the basis of the foundation of the European Patent Organization, which has two bodies, namely the European Patent Office (EPO) and the Administrative Council that has the role of supervising the activities of the EPO. The EPC brings a single procedure for granting "European" patents. The application for a patent can be filed in one of the 3 official languages directly to EPO or to one of the national patent offices of EPC contracting states.

The revised version of the Convention EPC 2000 came into force on December 13, 2007. The revised convention did not bring about any major changes in substantive patent law, however introduced a considerable number of smaller amendments such as late claiming of priority, late submission of claims, filing by reference to an earlier application, post-grant limitation and complete renumbering of the "Rules".[242]

The term EPC will refer to EPC 2000 throughout the dissertation, unless otherwise indicated.

On patentability of inventions Article 52 (1) of the EPC states that "European patents shall be granted for any inventions which are susceptible of industrial application, which are new, and which involve an inventive step".[243]

Article 54 of the EPC specifies the novelty requirement where the new invention should not form state of the art, which is considered to be everything that has been disclosed to the public by written or oral description before the date of filing of the

[241] Non-EU countries include Albania, Iceland, Lichtenstein, Monaco, Norway, the Republic of North Macedonia, San Marino, Serbia, Switzerland and Turkey.

[242] "EPC 2000 and its impact for patent searchers", EPO Patent Information News, Issue 1/2007 pp. 1-2 available at http://documents.epo.org/projects/babylon/eponet.nsf/0/FDFF591CF37EBF48C12572A5004BD30C/$File/Patentinfo_news_0701_en.pdf, last visit 30.04.2020.

[243]Article 52 (2) of the EPC regards the following material as "non-patentable subject matter: (a) discoveries, scientific theories and mathematical methods; (b) aesthetic creations; (c) schemes, rules and methods for performing mental acts, playing games or doing business, and programs for computers; (d) presentations of information". Similarly, Article 52 (4) reads as follows: "Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods."

European patent application.

Article 56 of the EPC specifies the rule of inventive step as not being "obvious to a person skilled in the art" regarding the state of the art.

Article 57's rule on industrial application indicates that if the inventions "can be made or used in any kind of industry, including agriculture", they shall be considered to be capable of industrial application.

Thus, EPC excludes general discoveries from patentable subject matters. As it will be analyzed in the next chapter, according to the Directive 98/44/EC, although biological materials have previously occurred in nature their patentability is possible given that they are "isolated from their natural environment or produced by means of a technical process, which may be the subject of an invention."[244] Hence there is a difference between isolated form of biological material and the material found in its natural environment.[245] As a result patenting of human genes is possible with disclosed industrial application. This has resulted in public disturbance regarding the patentability of human genes. Although the EPC excludes mere discoveries from patentability, Rule 23b of Chapter VI on Biotechnological Inventions states that the classical patentability requirements will apply to biotechnological inventions.

It is apparent that patents are to be granted only for new inventions clearly disclosed with useful application. Novelty requirement is challenged when the technical features of a new invention have been disclosed to the public before the patent application. This is then considered to be prior art. After prior art analysis, it must be assessed whether the

[244] Article 3 (2) of the Directive

[245] Article 5 (2): "An element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, may constitute a patentable invention, even if the structure of that element is identical to that of a natural element". Again Recital 20 of the Directive states: "… 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."

invention is obvious to a person having ordinary skills in the art. Finally, an assessment is made on the industrial application of the invention. With regards to patentability of biotechnological inventions the question is whether techniques used to isolate genes today can be subject to the same patentability criteria taking into account the increased use of highly advanced computer technologies. In the EU, this question was to some extend addressed by having a separate directive on biotech inventions, as explained in the next chapter. But more importantly the interpretation of the patent office and the courts on the patentability requirements for gene patents has shaped the law considerably.

3.3.2 Directive 98/44/EC

The public opinion in the EU is rather skeptic towards biotechnology. A Eurobarometer survey on biotechnology (2005) shows that the EU citizens regard gene therapy (the red biotechnology) and genetically modified (GM) food (the green biotechnology) as "risky".[246] In a later survey carried out by the European Commission in 2010, Europeans seem to have developed a bit more positive attitude towards biotechnology, but still have divided opinions on different uses of biotechnology. A slim majority of 53% of the respondents see that biotechnology and genetic engineering will have a positive effect of life in the next 20 years. On one hand, GM food has the least support of 23% (down from 27% in 2005), interestingly, the majority of the respondents with a degree in science is not willing to support the development of GM food. On the other hand, medical applications of biotechnology and regenerative medicine has attracted considerable support across EU countries; 69% approve stem cell research, 63% approve embryonic stem cell research, 63% approve gene therapy. This support is mostly conditioned upon strict laws to regulate monitoring and control.[247]

[246] Europeans and Biotechnology in 2005: Patterns and Trends, (2006), Eurobarometer 64.3, European Commission Directorate-General for Research, Brussels, Belgium p. 4

[247] Europeans and Biotechnology in 2010, Winds of Change? (2010), European Commission Directorate-General for Research, Brussels, Belgium pp. 39, 54.

The Commission and the Parliament have considered biotechnology to be of fundamental importance for the Community's industrial development.[248]

The main objective of the Directive 98/44/EC (the EU Biotech Directive) is the harmonized protection and enforcement of biotechnological inventions within the EU regarding patentability requirements and scope of protection.[249]

A discovery cannot be the subject matter of a patent, as they do not extend the human ability, but only human knowledge. So, it is only an invention to be the subject matter of a patent. It is often argued that biotechnological inventions dealing with genes, involve resources which already occur in nature and therefore they are discoveries and not inventions. As a result, a simple sequencing of a genome is a discovery, and should not be granted patent protection. However, the European Commission clarified these points and stated that if a DNA sequence is released from its natural surrounding by means of a technical procedure and made available for a new commercial use, it involves an inventive step, and the new material could be patented.[250]

Directive 98/44/EC is in line with this view.[251] It requires member states to protect biotechnological inventions under national patent law.[252] In doing this it defines what constitutes biotechnological inventions. Accordingly "inventions which are new, which

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[248] Recital 1 of the Directive 98/44/EC.

[249] Recital 8 of the Directive states: "…legal protection of biotechnological inventions does not necessitate the creation of a separate body of law in place of the rules of national patent law". Recital 9 of the Directive states: *"...*certain concepts in national laws based upon international patent and plant variety conventions have created uncertainty regarding the protection of biotechnological and certain microbiological inventions; whereas harmonization is necessary to clarify the said uncertainty."

[250] See the answer given by the Commission to the EP on the question of patentability of genes (dated 27.07.2000) available at https://www.europarl.europa.eu/sides/getAllAnswers.do?reference=P-2000-2281&language=EN last visit 30.04.2020.

[251] Recital 22 of the directive reads as:" … the discussion on the patentability of sequences or partial sequences of genes is controversial; whereas, according to this Directive, the granting of a patent for inventions which concern such sequences or partial sequences should be subject to the same criteria of patentability as in all other areas of technology: novelty, inventive step and industrial application; whereas the industrial application of a sequence or partial sequence must be disclosed in the patent application as filed."

[252] Article 1(1)

involve an inventive step and which are susceptible of industrial application are patentable, even if they concern a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used".[253] Biological material is defined as "any material containing genetic information and capable of reproducing itself or being reproduced in a biological system".[254] "Biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature".[255] Furthermore, the Directive also enables the patentability of "an element isolated from the human body or otherwise produced by means of a technical process, including the sequence or partial sequence of a gene, even if the structure of that element is identical to that of a natural element".[256]

The Directive does not enable the patenting of the following:

- processes for cloning human beings[257]
- processes for modifying the germ line genetic identity of human beings[258]
- uses of human embryos for industrial or commercial purposes[259]
- 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[260]
- inventions where their commercial exploitation would be contrary to ordre public

[253] Article 3(1)

[254] Article 2(1)(a)

[255] Article 3(2)

[256] Article 5(2)

[257] Article 6(2)(a)

[258] Article 6(2)(b)

[259] Article 6(2)(b)

[260] Article 6(2)(d)

or morality[261]

- plant and animal varieties[262]
- essentially biological processes for the production of plants or animals[263]
- the human body, at the various stages of its formation and development, and the simple discovery of one of its elements, including the sequence or partial sequence of a gene[264].

The Directive had to be implemented by the member states as of 30.07.2000. But due to the reasons explained in Chapter 4.1.1 it took almost 20 years to come into effect from the first draft in 1988 till 2006 when all member states had finally implemented.

3.3.3 Unified Patents and Unified Patent Court

In theory the European Patent Office (EPO) was founded to grant "European" patents. However, after the patents are granted at EPO, their validation and enforcement must take place separately in each EPC signatory state where patent protection is sought. Although the validation is an administrative procedure and does not involve a thorough examination of claims at national patent offices, each of these member states may still refuse to grant patents on administrative grounds such as failure to meet deadlines, provide translation, pay related fees, etc. Invalidation of patents (after the grant of patent at EPO and the 9-month period for opposition has passed), infringement cases are matters of national jurisdictions and they are carried out by member states out of the scope of the EPO.

Although there have been improvements in innovation performances of the EU

[261] Article 6(1)

[262] Article 4(1)(a)

[263] Article 4(1)(b)

[264] Article 5(1)

member states in recent years, EU still lags behind the US in innovation.[265] Fragmentation of the European patent system allowing for prevalence of several member state jurisdictions and the costs associated with the application and enforcement of patents in different member states were seen as one of the factors of EU's lagging behind in terms of innovation.[266] The reply of the EU to this problem was the establishment of the Unified Patent Court and the Unitary Patent offering a more efficient and rationalized system with cost advantages and reduced administrative burden to be able to unify the European patent granting and jurisdiction as much as possible.[267]

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[265] See European Innovation Scoreboard 2017 by the European Commission available at http://ec.europa.eu/growth/industry/innovation/facts-figures/scoreboards/last visit, 30.04.2020. It is stated in the main report at p. 6 that EU is catching up with Canada and the US, whereas South Korea and Japan are the forerunners in innovation. At the global level, the EU is less innovative than Australia, Canada, Japan, South Korea, and the US. Performance differences with the US and Canada have become smaller compared to 2010. According to 2019 scoreboard results, the EU has overtaken the US, but is still lagging behind Australia, Canada, Japan and South Korea.

[266] See MEJER M. & VAN POTTELSBERGHE DE LA POTTERIE B. (2012). Economic incongruities in the European patent system. *European Journal of Law and Economics*, Volume 34, Issue 1, pp 215-234. Also HARHOFF, D. et al. (2009). Patent validation at the country level - The role of fees and translation costs. *Research Policy*, Volume 38, Issue 9, pp 1423-1437 concluding that fees and translation costs indeed influence the patenting behavior of firms. Also VAN POTTELSBERGHE DE LA POTTERIE B. & FRANÇOIS, D. (2009). The cost factor in patent systems. *Journal of Industry, Competition and Trade*, Volume 9, p.339 showing that the European patent system is much more expensive than the US, where a European patent that is renewed for 20 years in 3 (13) EPC Member states costs more than EUR 40,000 (120,000), compared to EUR 14,500 in the US patent system. To reduce the translation costs of European patents granted under the EPC the Agreement on the application of Article 65 of the Convention on the Grant of European Patents (the London Agreement) was signed in October 2000 and it entered into force in May 2008. However despite the savings in translation costs, it was shown that the relative cost of a European patent validated in 6 (13) countries was still at least 5 (7) times higher than in the US. See VAN POTTELSBERGHE DE LA POTTERİE, B. & MEJER, M., (2008) The London Agreement and the Cost of Patenting in Europe, *CEPR Discussion Paper* No. DP7033 available at SSRN: https://ssrn.com/abstract=1311157, last visit 30.04.2020.

[267] See the press release of the European Commission from 11.12.2012 on advantages of the then proposed unitary patent package; one of which being creating "a unified and specialized jurisdiction in patent matters for the participating Member States, and thus avoiding an unnecessary duplication of litigation cases before the various courts of the various Member States concerned, and enhancing legal certainty". FAQ from 11.12.2012 available at http://europa.eu/rapid/press-release_MEMO-12-970_en.htm?locale=en, last visit 30.04.2020. Long before this the Commission had presented in 1997 a green paper on the Community patent and the patent system in Europe - Promoting innovation through patents (COM(97) 314 final, 24.06.97) to launch a discussion with stakeholders for the necessary measures to be taken for a Community patent. As a follow up to this Green Paper the Communication from the Commission to the Council, the European Parliament and the Economic and Social Committee was released in 1999 (Communication from the Commission of 5 February 1999. Promoting Innovation through Patents) to make proposals in the future to make the patent system attractive for promoting innovation in Europe. (See p. 7 of the Communication.) The Green Paper especially addressed the question of costs such as procedural fees, translation costs and distribution of renewal fees; as the use of the revenue from renewal fees for European patents varied greatly between the Contracting States, where in some states the revenue was not allocated into activities such as

After a political agreement at the European Council in June 2012, EU Regulation No: 1257/2012 was enacted in December 2012 creating a "Unitary Patent".[268] All EU Member states except Poland, Croatia and Spain have signed the Unified Patent Court (UPC) agreement. [269]

The main feature of the unitary patent is that it is still based on the European patent granted by EPO according to rules and procedures of EPC. However, after the patent is granted by EPO, the unitary effect of it can be validated in all 25 participating EU member states. There are no fees for such validation requests, which has a significant effect on the former costs of validation in each member state. Besides the annual renewal fees will be paid to EPO, which eliminates the necessity of national renewal fee payments in different currencies and at different time periods.

Although EU Regulation No: 1257/2012 came into effect in January 2013, the unitary patent was expected to become operational in 2018, only after UPC Agreement[270] enters into force. The UPC will be the new supranational European court dealing with the validity of unitary patents, as well as former "European" patents, besides with infringement cases. With UPC the costs associated with multiple national litigation cases plus the risk of having contradicting rulings will be eliminated. In order to enter into effect, it must be ratified by at least 13 member states, including France, Germany, and

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covering the operating costs of National Patent Offices or promoting innovation, since the revenue went straight into general budget.

[268] Regulation (EU) No 1257/2012 of the European Parliament and of the Council of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection. Besides EU Regulation No 1260/2012 (COUNCIL REGULATION (EU) No 1260/2012 of 17 December 2012 implementing enhanced cooperation in the area of the creation of unitary patent protection with regard to the applicable translation arrangement) brings new rules in translation arrangements removing the necessity of further translations after the application at EPO is done in one of the three official languages; namely English, German or French, which become the language of proceedings as set forth in Article 14(3) of EPC, and also bringing some compensation schemes for SMEs, natural persons, NGOs and universities & public research organizations.

[269] See the Council website on status of ratifications https://www.consilium.europa.eu/en/documents-publications/treaties-agreements/agreement/?id=2013001 last visit 29.04.2020.

[270] Agreement on a Unified Patent Court (UPC Agreement) of 19 February 2013 (OJ EPO 2013, 287). The UPC Agreement was signed by 25 EU Member states except Croatia, Poland and Spain. See the Council document on the UPC agreement at https://www.consilium.europa.eu/en/documents-publications/treaties-agreements/agreement/?id=2013001&DocLanguage=en last visit 30.04.2020.

the United Kingdom (in which the highest number of European patents had effect in 2012). As of April 2020, 16 countries including France and the UK had ratified the Agreement.[271] The UK vote to leave the EU (Brexit) will have consequences for the UPC Agreement. The exit agreement between the EU and the UK would need provisions on extending the unitary patent protection to UK territory and also for letting the UK to stay in the UPC Agreement. On the other hand, the UK government announced in February 2020 that UK will not stay in the UPC system. [272] The target date for the UPC to become operational was December 2017, however it was announced in June 2017 that this timeline will not be met. [273] In June 2019 it was announced that the Court will re-open the recruitment process for judicial positions,[274] after the initial process carried out back in 2016 had stalled, as the constitutional complaint against the UPC Agreement was submitted in Germany in June 2017. The complaint concerns the constitutionality of German law enabling ratification to transfer sovereign rights to the EU. On the other hand, the Court of Justice of the EU (CJEU) ruled in its April 2019 opinion on Investor-State Dispute Settlement (ISDS) mechanism in EU- Canada Comprehensive Economic and

[271] See the Council website at supra note 270.

[272] See the message from, UPC preparatory committee chair dated March 5,2020 available at https://www.unified-patent-court.org/news/message-preparatory-committee-chair-alexander-ramsay-march-2020 last visit 30.04.2020.

[273] See UPC Timetable update from 07.06.2017 available at https://www.unified-patent-court.org/news/upc-timetable-update-june-2017. It was also announced on 07.07.2017 that the UK has deposited the document required to apply the Protocol to the Agreement on a Unified Patent Court on provisional application (PPA) with the depository for the UPC Agreement. See https://www.unified-patent-court.org/news/update-provisional-application-phase . The Protocol to the UPC Agreement signed in October 2015 allows for the institutional, organizational, and financial provisions of the UPC Agreement to be applied before the agreement enters into force so that for instance the judges and other staff can be recruited and moving to Court's premises can be finalized and UPC becomes operational already on day one. Indeed, there is also an action brought to the German Constitutional Court concerning the ratification of the UPC Agreement and the PPA (Protocol on Provisional Application). The case was on the list of cases to be decided in 2019 by the German Constitutional Court, but no decision has been given in 2019. See https://www.bundesverfassungsgericht.de/DE/Verfahren/Jahresvorausschau/vs_2019/vorausschau_2019_node.html last visit 30.04.2020. The German President suspended the ratification process in Germany at the request of the Constitutional Court until a decision has been given. The Court delivered its decision on February 13, 2020 declaring the German Parliament's act of approval void. The reason is that the Parliament did not adopt the act with qualified majority. See the Decision at https://www.bundesverfassungsgericht.de/SharedDocs/Entscheidungen/DE/2020/02/rs20200213_2bvr073917.html last visit 29.04.2020. This decision means further delays for the operation of Unified Patent Court.

[274] See the UPC announcement dated 03.06.2019 https://www.unified-patent-court.org/news/upc-judicial-recruitment-2019-top-campaign-now-open last visit 30.04.2020.

Trade Agreement (CETA) that CETA's investment court system was compatible with the Union law.[275] In a previous case in 2011 on the compatibility of the provisions of the EU Treaties with the draft agreement on European and Community Patents Court to be concluded among the EU, member states and third countries party to the EPC, the CJEU had given the opinion that creating such a unified patent litigation system is not compatible with the EU law, since it would have deprived the powers of the courts of the EU member states in relation to the interpretation and application of EU law, which is an essential character of the EU judicial system.[276] The CETA opinion of CJEU is therefore important regarding the requirements as to the protection of the principle of EU law autonomy in relation to international courts. The creation of an international court within the framework of an external EU agreement can be easier in the future. After the UPC Opinion of the CJEU, the negotiations between the member states were relaunched and they reached an agreement to allow Regulation 1257/2012/EU to come into effect. As a result, the patent jurisdiction was not transferred to CFEU or to national courts, but to an international court created via an international agreement that was concluded among the EU member states. This agreement is not open to third countries outside of the EU.

Once operational, the UPC will have exclusive competence to hear actions concerning decisions of the EPO in carrying out the administrative tasks,[277] actual or threatened infringement actions related to patents and supplementary protection certificates,[278] actions for declarations of non- infringement of patents, actions for provisional and protective measures and injunctions, actions for damages or compensation derived from the provisional protection conferred by a published European patent application, revocation actions, actions relating to rights based on prior use of an

[275] Opinion 1/17 of the Court of 30.04.2019 pursuant to Article 218(11) TFEU (CETA) — Investor-State Dispute Settlement (ISDS) — Establishment of a Tribunal and an Appellate Tribunal — Compatibility with primary EU law — Requirement to respect the autonomy of the EU legal order.

[276] Opinion 1/09 of 08.03.2011 delivered pursuant to Article 218(11) TFEU - Draft agreement - Creation of a unified patent litigation system - European and Community Patents Court - Compatibility of the draft agreement with the Treaties.

[277] As referred to in Article 9 of EU Regulation No 1257/2012.

[278] Actions for infringement or for revocation of previous "European" patents may still be brought before national courts for a transitional period of seven years, which may be prolonged by up to a further seven years, see Article 83(1) of the UPC Agreement.

invention and, actions for compensation for licenses of right, actions for compensation for licenses, actions for counterclaims for revocation and other defenses.[279] The Member States' national courts will remain competent for actions which do not come within the exclusive competence of the UPC, e.g. cases relating to compulsory licensing of Unitary Patents (in their own territory).[280] In the current situation during a period of 9 months after the grant of the patent, an opposition procedure on the validity of the patent can still be brought to the EPO.[281] In the UPC structure, the appeals to the decisions of EPO regarding the unitary patents will be brought before the Court of Appeal of UPC, which will be located in Luxembourg. The UPC will not have any competence regarding national patents.

Applicants /holders of a European patent, who has been granted / has applied before the end of the transitional period of seven years, will be able to opt out of the UPC's jurisdiction unless an action has already been brought to the UPC.[282] The opt-out scheme will not be applicable to unitary patents.

An empirical study comparing around 9,000 patent suits from seven of the largest and most judicially active countries in the EU during 2000 to 2010 period shows that the incidence of litigation, revocation and infringement proceedings, evidence on patent validity and the bases of judicial outcomes diverge radically across the different countries and sector of patented technologies. This is a very ambiguous result for the EU in terms of legal certainty.[283] The UPC and the unitary patent seem to allow for a better application,

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[279] Article 32(1) of the UPC Agreement.

[280] Article 32(2) of the UPC Agreement, see also *Patent Litigation in Europe -An overview of national law and practice in the EPC contracting states*, 2016, European Patent Academy, 4th edition Munich, Germany p.135.

[281] The opposition procedure before the EPO can be initiated within 9 months after the grant on the grounds of unpatentability of claims, insufficient disclosure, or extension of the subject matter beyond the content of the application. In 2016 at EPO 1,814 opposition cases were concluded for 95,940 patents granted in the same year, where 316 of them were dismissed. See the 2016 Annual Report of EPO available at http://documents.epo.org/projects/babylon/eponet.nsf/0/35E90F1C530D8067C12580D8005B458F/$File/boards_of_appeal_en.pdf last visit 30.04.2020.

[282] Articles 83(3) and 83(4) of the UPC Agreement.

[283] GRAHAM, S. J.H. & VAN ZEEBROECK, N. (2014). Comparing Patent Litigation Across Europe: A First Look. *Stanford Technology Law Review*, Volume 17, pp. 655-708. For instance, in Spain 5% of the litigation cases were subject to a decision in the courts of more than one country, whereas this ratio was

validity, and enforcement of patents at the EU level. Patents for biotechnological and pharmaceutical inventions are validated in different jurisdictions. So, for these sectors one can expect that the grant of a unitary patent will be appealing taking into the costs associated with such validation. Of course, the patent holders can still apply for patent protection in unitary terms, as well as in the "classical European" terms with a different illustration of claims. Hence the system is not flawless.

First of all, the EPC is an international treaty, where non- EU countries are also parties to it.[284] Allowing to have a unitary patent at the same time with a bundle of European patents, even in the EU member states may weaken the positive effects of unitary patent and the UPC in terms of efficiency and cost reduction. Trying to increase the efficiencies of patent law in pre-grant and post-grant period is not a straightforward task. In the new system of unitary patents, the pre-grant tasks related to obtaining of patent protection are still within the jurisdiction of EPO under the provisions of EPC. However, a unitary patent needs to have the same set of claims in every signatory member state to be valid.[285] The risk here for biotechnological patent claims is that the innovators for certain biotechnological subject matter will not seek a unified patent protection, if there is doubt that their set of claims will be granted patent protection in each member state. Alternatively, in order to make a unified patent application the innovators may choose the least common denominator set of claims in all participating EU member states' patent legislation. The invalidation or revocation of patents may also be an important issue for innovators. Under national systems, if a patent is invalidated in one country, it may still be enforced in another one. Under unified patent system invalidation would mean losing the patent right in all signatory member states. This difference is important for all innovators but especially in terms of patent protection in medical biotechnology, it may

31% in Belgium and 34% in the UK. The authors conclude that patent disputes in Spain, France and Germany are more likely to be purely national, whereas Belgium and the UK have more multinational disputes. In invalidity actions 10% of the cases were found to be not novel in Spain, 18% in France and 22% in Germany, whereas 43% in the Netherlands, 32% in the UK. Lack of inventive step varied between 33% of the cases in France, and 64% of cases in the Netherlands.

[284] See supra note 241 for contracting states.

[285] See Article 3(1) of the EU Regulation 1257/2012 read as "A European patent granted with different sets of claims for different participating Member States shall not benefit from unitary effect."

even be more crucial. We see that biotechnological patents can be granted to very broad claims, where performing research in the field or even patient access to treatment can be tied to licensing agreements. Apart from the concern that competition authorities may have, due to the anti-competitive behavior of patent pools and licensing agreements; innovators may wish to assert their rights by applying for patent protection in different jurisdictions, although it is more costly than unified patent application, if they are certain that these costs will be offset by the benefits of having broader patent protection in different markets for biotechnological innovation. Patent thickets in biotechnology are a serious concern for the inventors. There are a lot of complementary patent rights in the field, where patent thickets merge as a result, and the returns on investment can be better accrued by accessing to several patents.

Some scholars argue that the Unified Patent Court will be similar to the Court of Appeals for the Federal Circuit in the US.[286] The Federal Circuit was created by the US Congress in order to bring uniformity in patent law at a national level.[287] Having numerous jurisdictions clearly creates legal uncertainty. However, there are some points that hint that the Unified Patent Court (UPC) will still rule under fragmented set of rules.

First, UPC will be operative after the national ratifications. It was certainly not necessary for the circuit courts of the US to ratify the Federal Circuit to become operational. And the UPC and unitary patent regulation will cover only 25 of the 28 member states of the current EU. Signatory states, other than the EU members to the European Patent Convention will not be covered by the new regulation.[288] In addition to the fragmentation of the internal market in the EU due to non-participating states being Spain and Poland, the bigger European market will also be fragmented having national patents, granted both nationally and by the EPO and European patents with unitary effect.

Secondly the jurisdiction will also not be unified; UPC being competent for unitary

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[286] SWANSON, R.D. (2013). Implementing the EU Unifies Patent Court: Lessons from the Federal Circuit. *Brigham Young University International Law & Management Review*, Volume 9, Issue 2 pp. 169-199.

[287] DREYFUSS R.C. (1989). The Federal Circuit: A Case Study in Specialized Courts, *New York University Law Review*, Volume 64, Issue 1. pp.1-77.

[288] See supra note 241 for these countries.

patents and national courts being competent for EU member states not participating to the unitary patent regulation, as well as for cases regarding national patents. Hence, even if all the EU member states would participate to the unitary patent regulation, national patent rights will not allow the system to be fully unified. Besides cases relating to compulsory licensing of unitary patents will still be under competence of national courts. The UPC will be able to request a preliminary ruling from the Court of Justice of the European Union in cases for an interpretation to EU law, where this can be of particular importance for cases involving, among the others, the EU Biotech Directive 98/44/EC.[289]

Thirdly oppositions at EPO will still be possible after the UPC becomes operational, parties shall inform UPC of any pending opposition, revocation, limitation proceeding before the EPO.[290]

Having both EPO opposition and UPC revocation procedures to decide on the validity of the patent may create further uncertainties. At EPO the opposition can be made due to being an unpatentable subject matter such as discoveries, plant animal varieties, inventions against ordre public and morality or due to lack of novelty , inventive step, or industrial application, and insufficient disclosure of the subject matter. Article 3(1) of Regulation 1257/2012 on unitary patent protection confirms that the unitary patents shall have the same set of claims; a prior art in a member state can invalidate a unitary patent entirely. Also, Article 65(2) of the UPC Agreement states that revocation can be done on the grounds referred in EPC Articles 138(1) and 139 (2). Article 138 (1) of EPC on revocation of European patents lists the grounds of revocation with effect for a contracting state such as being an unpatentable subject matter, lack of sufficient disclosure, extension of scope of protection, extension of subject matter after the filing and lack of entitlement, and Article 139 (2) deals with revocations on the grounds of prior art at a limited territory in a specific contracting state stating that if one has a priority date in one contracting state, it applies to all.

This article concerns prior art regarding a national patent application prior to the

[289] See UPC Agreement Article 21, as well as Patent Litigation in Europe at supra note 280 p. 136.

[290] See UPC Agreement Article 33(10).

application at EPO. This may be a concern for the biotechnology industry, as it is costly to indicate the incidence of national prior rights, and especially unpublished national applications. Indeed, once a patent becomes unitary patent, its national effect is abolished.[291] Hence, if a unitary patent is revoked, it is unclear how to re-establish the national effect of the patent.

The opposition period at EPO is 9 months after the grant of a patent. [292] At UPC the validity of the patent shall be decided by the Court on the basis of an action for revocation or a counterclaim for revocation.[293] Hence: the time limit is not strict as at EPO.

At EPO, any person is entitled to bring an opposition.[294] The opposition to UPC can be made by any other natural or legal person, *who is concerned by the patent* (emphasis added).[295] According to this formulation it is unclear, whether persons, who cannot show certain legal and/or economic benefits/losses will be able to bring actions.

The fees for the opposition at EPO or revocation at the UPC also differ considerably. The opposition fee at EPO is 785 EUR and the appeal fee is 1,880 EUR.[296]

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[291] See Article 4(2) of the Regulation 1257/2012: "The participating Member States shall take the necessary measures to ensure that, where the unitary effect of a European patent has been registered and extends to their territory, that European patent is deemed not to have taken effect as a national patent in their territory on the date of publication of the mention of the grant in the European Patent Bulletin."

[292] See Article 99(1) of the EPC.

[293] See Article 65(1) of the UPC Agreement.

[294] See Article 99(1) of the EPC. In Decision G 3/99 on the invention "Molecular cloning and characterization of a further gene sequence coding for human relaxin" from the Patentee - Howard Florey Institute of Experimental Physiology and Medicine, it is stated that the opposition was filed in common by two or more persons (indeed by some MEPs from the "Greens" of the European Parliament) represented by the common representative in accordance with Article 99 of EPC. Indeed, representation can be made by a professional representative according to Article 133(2) of the EPC. UPC Agreement is more specific on who can be such a representative in Article 48; namely lawyers and European patent attorneys with appropriate qualifications such as a European Patent Litigation Certificate. The representatives can be assisted by patent attorneys, who will be allowed to speak at hearings of the Court. Although the UPC regulation is more specific, it can be more costly for the persons filing opposition as well and may deter them from doing so. At EPO the representation can be made by an authorized employee, as well, which definitely has lower cost advantages. See Decision G 4/95, G 3/99 referring to Article 133(3) of the EPC on such representation by an employee who is authorized in accordance with the Implementing Regulation.

[295] See Article 47 (6) of the UPC Agreement.

[296] See EPO Rules No 10 and 11 relating to fees available at https://www.epo.org/law-practice/legal-

Whereas at the UPC the revocation action and the appeal both have fees of 20,000 EUR each.[297] Besides the costs of legal representation also borne differently. At EPO, each party to the opposition proceedings bears the costs it has incurred.[298]At UPC proceedings legal costs and other expenses incurred by the successful party will need to be borne by the unsuccessful party.[299] This may also deter parties from filing an opposition, if they doubt the success in the proceeding.

The speed of the UPC in hearing cases will definitely be one of the advantages of the new system. At EPO the average length of an opposition (inter partes) proceeding is 34 months in 2016.[300] The Rules of Procedure of the UPC foresee that proceedings at the First Instance will be concluded within one year.[301]

It is difficult to conclude which proceeding whether at EPO or at UPC, the patent disputes concerning biotechnological subject matter will be brought to. If the opponents are still within the 9 months period after the grant of the patent, and they have budgetary limitation, but can wait longer for a decision, and especially when they are interested in revocation of the patent in non-UPC countries, these being EU member states or not, they can start and opposition proceeding at EPO. However, they should be in a position where

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texts/html/epc/2016/e/ma6.html last visit 30.04.2020.

[297] See the fee document of UPC available at https://www.unified-patent-court.org/sites/default/files/UPC_Court_Fees_and_Recoverable_Costs_Consultation_Document_FINAL.pdf last visit 30.04.2020.

[298] See Article 104(1) of the EPC stating, "Each party to the opposition proceedings shall bear the costs it has incurred, unless the Opposition Division, for reasons of equity, orders, in accordance with the Implementing Regulations, a different apportionment of costs."

[299]See Article 69(1) of the UPC Agreement stating: "Reasonable and proportionate legal costs and other expenses incurred by the successful party shall, as a general rule, be borne by the unsuccessful party, unless equity requires otherwise, up to a ceiling set in accordance with the Rules of Procedure". The ceiling is set between EUR 38.000 and EUR 2.000.000 for proceedings varying up to EUR 250.000 and more than EUR 50.000.000. See the fee document in supra note 297.

[300] See the 2016 Annual Report of EPO Boards of Appeal available at http://www.epo.org/law-practice/legal-texts/official-journal/2017/etc/se3/p1.html last visit 30.04.2020.

[301] See the latest version (updated in March 2017) Rules of Procedure of the UPC available at https://www.unified-patent-court.org/sites/default/files/upc_rules_of_procedure_18th_draft_15_march_2017_final_clear.pdf Preamble p.19 last visit 30.04.2020.

the prior art obviously leads to the claims in the patent. In determining the inventive step, the EPO applies problem-solution approach by identifying the closest prior art, assessing the technical effect of the invention compared with state of the art, defining the technical problem that the invention aims to solve and determining whether claimed technical features are obvious to a skilled person.[302] If the opponents cannot prove lack of inventive step by using this approach, yet have no budgetary constraints and wish to have a quick decision, believe that they can get their costs recovered, because they have strong arguments, and can win the case then they can use a revocation procedure at the UPC. If they have missed the opposition period of 9 months and the patent is deemed invalid after the grant due to scope extension, or there is a lack of entitlement due to some national applications that were filed earlier but were unpublished, then they have to choose the UPC option. Of course, the opponents may use both options if the costs of starting a procedure do not matter and have already won the EPO opposition proceeding but want some their legal costs to be recovered. This may include cases of having found some new prior art that cannot be brought into pending proceedings, which is very likely in the gene patents, where the pace of innovation is immense, and one can easily come up with some later search techniques revealing prior art reference. If opponents file both at EPO and UPC especially in major cases, it is very likely that accumulation of cases will further increase despite the relatively speedy decision-making procedures at UPC.

As a result, although the Regulation on unified patent protection and the UPC Agreement intend to decrease costs, promote innovation in the EU by unifying the patent enforcement, the patent environment may become more costly for innovators dealing with fragmented structures of EPO, UPC and national courts and for not having legal certainty on especially on revocation and opposition cases. The applicable law at the EPO is the

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[302] See EPO Guidelines for Examination available at https://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_vii_5.htm last visit 30.04.2020.

The problem and solution approach was explained as such in Decision T 824/07 EPO. To define inventive step, the Boards of Appeal also applies the "could-would approach" asking the question, whether the person skilled in the art **would** have carried out the invention to solve the underlying technical problem or for some improvement or advantage, and not the question whether he/she **could** have carried out the invention. See EPO case law of the Boards of Appeal available at https://www.epo.org/law-practice/legal-texts/html/caselaw/2016/e/clr_i_d_5.htm last visit 30.04.2020.

EPC and the case law derived from Boards of Appeal Decisions. At the UPC the applicable law will be the EU law, UPC Agreement, EPC, national law and other international agreements applicable to patents and binding on all the Contracting Member States.[303]

Indeed in the UPC Agreement there is also the possibility of opting out from the exclusive jurisdiction of the UPC for European patents granted before the end of a seven-year transitional period and European patent applications filed before the end of this period.[304] Transitional period will start on the date of entry into force of the UPC Agreement.[305] Although the opt-out scheme will only be available for European patents and patent applications and not for unitary patents, we may still expect a significant number of gene patents to be opted-out. The reasons for this are two-hold. Firstly, although we associate cost of litigation with a negative connotation, this is not a huge concern for proprietors holding gene patents, especially for corporations, given the value of and expected benefit from the patent in question. Secondly, UPC will be a new court with new procedures but no case law, and litigation in non-participating countries will be necessary, nonetheless. Harmonization of European patentability requirements has been achieved during the grant period at EPO, but enforcement after grant is still diversified; EPO having developed its own case law and member states having different legal systems and they are not bound by EPO decisions. European patents without unitary effect cannot be enforced till they are turned into national patent rights, where national laws are applicable. The problem about filing of gene patents is that if they are filed too early, they may lack industrial application, and if too late they may be obvious by competitors' applications and publications. Indeed, this is the very reason why the BioIndustry Association of the UK (the BIA), describing itself as "a trade association for innovative enterprises in the UK's bioscience sector with hundreds of member companies, an

[303] See Article 24 of the UPC Agreement.

[304] See Article 83(3) of the UPC Agreement.

[305] See Article 83(1) of the UPC Agreement.

aggregate turnover in 2010 of about £5.5 billion, and around 36,000 employees"[306] intervened in the proceedings of the Case Human Genome Sciences Inc. (HGS) v. Eli Lilly in the UK.[307]

In Case HGS v. Eli Lilly, the patent granted by EPO to HGS in 2005 consisted of a gene sequence, that was encoded in 1996 using expressed sequence tags (EST) [308], but also a new method called bioinformatics[309] and whose function was not known at the time, placed into a protein that is expected to have significant impacts on immune system. The specification in the patent application gave "an identification of Neutrokine- α as a member of the TNF ligand superfamily[310] and disclosed further technical data on tissue distribution of Neutrokine- α mRNA expression using the nucleic acid sequence encoding the Neutrokine- α protein as a cDNA probe and, reported the expression of Neutrokine-

[306] See infra note 307 par. 96-97.

[307] UK Supreme Court Decision [2011] UKSC 51 Human Genome Sciences Inc. (HGS) v. Eli Lilly and Company.

[308] An EST is a short nucleotide (200-800 bases in length) sequence derived from the cDNA libraries, capable of identification of the full-length complimentary gene and mostly used for the identification of an expressed gene. See BEHERA, P, M, et al. (2013). In silico expressed sequence tag analysis in identification of probable diabetic genes as virtual therapeutic targets." *BioMed Research International*, Volume 2013 704818. doi:10.1155/2013/704818 last visit 30.04.2020. They can be generated at a reasonably low cost and since 1990s there has been an exponential growth in their generation and accumulation to enable gene discovery, complement genome annotation, aid gene structure identification, establish the viability of alternative transcripts. See NAGARAJ et al. (2007), A hitchhiker's guide to expressed sequence tag (EST) analysis, *Briefings in Bioinformatics*, Volume 8, Issue 1, pp. 6–21.

[309] The method allows "researchers to identify genes and the proteins for which they encode by comparing sequences with previously identified and characterized genes". See Case [2011] UKSC 51 Introduction Par.17.

[310] The TNF (Tumor Necrosis Factor) is a group of proteins found in the body that causes inflammation and apoptosis (cell death). The TNF ligand superfamily is composed of 19 ligands and 29 receptors. These receptors bind the TNF-related ligands and act on the immune system. Although they induce apoptosis, many TNF superfamily members may also induce lymphocyte proliferation and have hence been targeted for use in combination with chemotherapy in cancer treatment, especially where they were capable of killing selectively cancer cells but not normal cells. Inibition of TNF with neutralizing antibodies are also found to improve the state of the patients with immunological diseases. See GRANDHI, T.S. et al. (2014), Sensitizing cancer cells to TRAIL-induced death by micellar delivery of mitoxantrone, *Nanomedicine*, Vol. 9 Issue 12 pp 1775 – 1788. FISCHER J.A.et al. (2015). Combined Inhibition of Tumor Necrosis Factor α and Interleukin-17 As a Therapeutic Opportunity in Rheumatoid Arthritis: Development and Characterization of a Novel Bispecific Antibody. *Arthritis& Rheumatology*. Volume 67, Issue 12, pp.51-62. GRUSS, H.J. et al. (1996). Structural and biological features of the TNF receptor and TNF ligand superfamilies: interactive signals in the pathobiology of Hodgkin's disease. *Annals of Oncology*, Volume 7, Suppl 4, pp 19-26.

α in activated T-cells." [311]

Eli Lilly challenged the patent at an opposition proceeding at EPO, as well as by a revocation proceeding at the UK courts. The first instance decision at the UK Court concluded in 2008 that the patent was invalid due to lack of industrial application and inventive step.[312] After the hearing at the Opposition Division at EPO, the patent was revoked in December 2008, as the claim (protein Neutrokine-α claimed by HGS) was found to be obvious, being a member of the TNF ligand superfamily. HGS then appealed against this decision, where the Board of Appeal in return decided in 2009 that[313] in light of the evidence put forward by the patentee, prior art could not enable a person skilled in the art to find the Neutrokine-α sequence and that "in the light of the common general knowledge of the TNF ligand superfamily and its properties, the presence of Neutrokine-α in activating T-cells and directing the proliferation, differentiation, and migration of these cells", is plausible backed with evidence. Thus, the patent is justified under Article 57 EPC (on industrial application) with these functions.

On the objection based on insufficient disclosure the Board stated that serious doubts must be substantiated by verifiable facts adding:

> "…in relation to the issue of industrial applicability of the teachings of the invention, the board believes that the plausibility of the overall disclosure in relation to the prospects of a real possibility of exploitation in the pharmaceutical and/or diagnostic fields has positive reflections also on the evaluation of the sufficiency of disclosure of the claimed invention. The claimed subject-matter is thus considered to fulfil the requirements of Article 83 EPC (on disclosure of the invention)."

The Board stated that the information in patent specification cannot be taken as "a mere theoretical or purely hypothetical assumption." Hence the objections on lack of

[311] See infra note 313 reasons point 24.

[312] Case [2008] EWHC 1903 Eli Lilly and Company v. Human Genome Sciences, Inc.

[313] Decision T 18/09 Neutrokine/HUMAN GENOME SCIENCES of 21.10.2009

industrial application (Article 57 EPC) and on insufficient disclosure (Article 83 EPC) were not accepted by the Board. It was concluded that the "description of the patent delivered sufficient technical information on the effect of Neutrokine- α on T-cells and the tissue distribution of Neutrokine- α mRNA, to satisfy the requirement of disclosing the nature and purpose of the invention and how it can be used in industrial practice." [314]

The case was referred back to Opposition Division for the patent to be maintained.

HGS also appealed in the UK to the Court of Appeal, which dismissed the case, and the decision came after the decision of the EPO Board of Appeal decision of T 0018/09. In dismissing the case the judges used the similar arguments as in First Instance Court and concluded that the first instance Court was right to hold that the invention failed to comply with Art. 57 EPC.

> "…nearly 9 years after the date of the patent, that it was not known what significance the T-cell activity had – that seems rather a long way from "an immediate and concrete benefit.""[315]

In appealing to this Decision of Court of Appeal, HGS argued that the First Instance Court and the Court of Appeal had set industrial applicability standard too high. In hearing the case the UK Supreme Court made a review of the EU, UK and US jurisdictions. Referring to EU law, Article 5 of the EU Biotech Directive was cited that "a naturally occurring gene is patentable, but its industrial application must be disclosed in the patent application".[316] As for the US approach it was mentioned that the Court of Appeal Judge quoted the US Supreme Court decision Brenner v Manson[317], and the

[314] Ibid reasons point 27.

[315] Human Genome Sciences Inc. v. Elli Lilly and Company, Court of Appeal Decision [2010] EWCA Civ 33

[316] UK Supreme Court Decision [2011] UKSC 51 par. 35. It goes on quoting the Judge from the Court of Appeal "However clever and inventive you may have been in discovering a gene sequence, you cannot have a patent for it or for the protein for which it encodes if you do not disclose how it can be used."

[317] US Supreme Court Decision 383 US 519 (1966) Brenner v. Manson.

Federal Circuit decision In re Fisher and Lalgudi[318] on what constitutes "any new and useful … composition of matter" under 35 USC § 101.[319]

The UK Supreme Court also held that the invalidity decision by EPO is applied throughout all signatory states of EPC. However, when EPO decides a particular claim to be valid, "it is still up to a national court to decide whether the patent or claim is invalid within its territorial jurisdiction. Although both EPO and the national courts are applying the principles contained in EPC, it is highly desirable in practice, that national courts align their decisions with EPO."[320]

In allowing the appeal, the Supreme Court concluded that the general principles of industrial application to be held are that:

- "the patent must disclose "a practical application" and "some profitable use" for the claimed substance, so that the ensuing monopoly "can be expected [to lead to] some … commercial benefit."
- a "concrete benefit"; the invention's "use … in industrial practice" must be "derivable directly from the description", coupled with common general knowledge.
- A merely speculative use is not sufficient.
- The patent and the common general knowledge must enable person skilled in the art to reproduce the invention without undue burden. [321]

[318] Decision 421 F 3d 1365 (Fed. Cir. 2005) In Re Dane K. Fisher and Raghunath v. Lalgudi – the invention must be useful in its current state and not at a later stage after further research can be conducted.

[319] UK Supreme Court Decision [2011] UKSC 51 par. 38.

[320] Ibid par. 83, also par. 86 quoting Decision Conor Medsystems Inc v Angiotech Pharmaceuticals Inc. [2008] UKHL 49, [2008] RPC 28, para 3: "A European patent takes effect as a bundle of national patents over which the national courts have jurisdiction. It is therefore inevitable that they will occasionally give inconsistent decisions about the same patent. Sometimes this is because the evidence is different. In most continental jurisdictions, including the [EPO], cross-examination is limited or unknown. Sometimes one is dealing with questions of degree over which judges may legitimately differ. Obviousness is often in this category. But when the question is one of principle, it is desirable that so far as possible there should be uniformity in the way the national courts and the EPO interpret the [EPC]."

[321] Ibid par. 107 (i)-(iv).

Further principles are cited depending on whether the patent "discloses a new protein and its encoding gene", or "the protein is a member of a family or superfamily". The Supreme Court stated that the patent court did not follow these principles when ruling that the patent is invalid due to lack of industrial application. This decision was upheld by the Court of Appeal.

The UK Supreme Court was looking also at the wider picture; consistency and policy implications manifested on the concerns of the BIA that legal certainty is essential for bioscience companies to attract investment referring to their patent portfolios and that funders should be reasonably confident that the patent shall be granted in order to fund R&D activities on "the potential therapeutic value of a newly discovered protein or its antibodies."[322]

Further note was given on the need to give a temporary monopoly in return for incentives to innovate and dissemination of knowledge referring to public interest and commercial need of patent protection. The reasoning of the Court of Appeal was found to be risking that it would be rather hard for applicants to satisfy the industrial application requirement in the future making it difficult for UK bioscience companies to attract investment at an early stage in the R&D process.[323] BIA had also argued that the therapeutic value of a protein or its encoding gene can only be determined at a later stage of R&D and that the timing of the patent application is very important: If it is too early there will be early disclosure without a patent, if it is too late, competitors might have already filed an application.[324] Avoiding longer application periods is especially relevant for the first to file patent systems.

In doing so the UK Supreme Court gave a clear message to UK courts to use a lower threshold for industrial application requirement concerning biotech patents and align their interpretation of patentability criteria with that of EPO jurisprudence.[325] It was

[322] Ibid par. 98.

[323] Ibid par. 99-100.

[324] Ibid par. 97.

[325] See the Judgment par.84 and 171.

emphasized "EPO Boards of Appeal are not a court or a tribunal of an EU member state, and they do not have the status to refer a question to the CJEU".[326]As such EPO decisions are also not under scrutiny of CJEU or any other EU Court. The UPC on the other hand will have the same obligation as any national court to ask for preliminary rulings in accordance with Article 267 –TFEU and must cooperate with CJEU relying on CJEU case law for the interpretation of law [327]. However, the unified patent system in the EU still does not provide tools to qualify for a legal monitoring and review of EPO patenting policies. UPC's decisions will still be non-binding on EPO, which will create further legal uncertainty.

3.4 Patentability of Biotechnological Inventions – Legal Basis in the US

The U. S. Constitution has had as early as 1787 a provision to protect intellectual property and the first Patent Act was introduced in 1790 based on the utilitarian ideas of the US President Thomas Jefferson, who himself was an inventor and one of the first members of the Patent Board, who had the right to grant patents. The subject matter of a patent was then defined as "any useful art, manufacture, engine, machine, or device, or any improvement thereon not before known or used."[328] The first Patent Board was also created with this patent act.[329]

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[326] See EPO Decision T 276/99 - Publication of patent specification/PHILIPS of 26.9.2001 at par. 17 The Board "The provisions of the EPC, (forbidding the replacement of description of the patent specification by a mere reference to a publication) and no serious arguments based on the EC Treaty or the TRIPS Agreement exist which throw doubt on the matter or which raise anything that can be regarded as an important point of law that should be referred to the Enlarged Board of Appeal, let alone the Court of Justice of the European Communities. A reference to the latter would in any case appear to have no basis under the EPC or the EC Treaty Article 234" (now Art. 267 TFEU).

[327] See the competence of the UPC at https://www.unified-patent-court.org/faq/competence-upc-0 last visit 29.04.2020, as well as UPC Agreement preamble and Art. 21.

[328] USPTO Press release 9.4.2002 https://www.uspto.gov/about-us/news-updates/us-patent-system-celebrates-212-years. last visit 30.04.2020. Also, WALTERSCHEID, E.C. (1999). The Use and Abuse of History: The Supreme Court's Interpretation of Thomas Jefferson's Influence on the Patent Law. *The Journal of Law and Technology,* Volume 39, pp. 195-236.

[329] The first Board members included the Secretary of State, Thomas Jefferson, who was considered the first administrator of the American patent system and the first patent examiner; the Secretary of War Henry Knox, and the Attorney General Edmund Randolph. Their authority was absolute and could not be appealed

The next patent act of 1793 was introduced to simplify the process of patent application and granting. The review was very limited if it was ensured that the application was in good order.[330] As a result the Patent Board in issuing patents, could not certify standard patentability criteria and it became merely a registration system.[331] In the previous Patent Act of 1790 it was the duty of the Patent Board officers to inquire into the utility and the importance of the patent before the patent was granted.[332] After 1793 the Courts became the main institutions to review and shape patents where all substantive decisions regarding patents were made.[333] The problem of proliferation of patent litigation cases in courts[334] and the increase in number of patents granted with the quality of the patents questioned, ended in introduction of the next Patent Act of 1836.[335] The new act also created the Patent Office with the duty of the examination of the alleged new invention and decide on the usefulness and importance of it.[336]

The Patent Act of 1952 is considered to be the modern patent act of the US,[337] which

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and they decided also on the duration of each patent, not exceeding 14 years. See the press release at supra note 328.

[330] HOVENKAMP, H.J. (2016). The Emergence of Classical American Patent Law. *Arizona Law Review*, Volume 58, Issue 2, pp. 263-306.

[331] BRACHA O. (2004). The Commodification of Patents 1600-1836: How Patents Became Rights and Why We Should Care. *Loyola of Los Angeles Law Review*, Volume 38, Issue 1. pp 177-244, p 227.

[332] Ibid p. 229.

[333] Ibid pp. 228-229.

[334] In the 1820s the patentees were losing as many as 75% of the litigated cases. See Hovenkamp supra note 330 at p. 269.Roughly a third of patent validity challenges during the period 1800–1839 were based on lack of novelty p. 276.

[335]A 1836 report to the Senate by Senator Ruggles concluded that the 1793 regime of granting patents with put through examination had resulted in a considerable portion of worthless patents that give little protection to inventors due to infringement and fraud and that "a great number of law suits arise, which are daily increasing in an alarming degree, onerous to the courts, ruinous to the parties, and injurious to society". See BERRY, R.(2015), Researching the Early History of the Patent Policy: Getting Started, *Journal of the Patent & Trademark Resource Center Association*, Volume 25 available at http://ptrca.org/newsletters/2015/berry at p. 6 last visit 30.04.2020.

[336] See Berry supra note 335 pp.3-4.

[337] Bayh-Dole Act (Pub. L. 96-517, December 12, 1980) Leahy- Smith America Invents Act (Pub. L. 112–29, September 16, 2011) are the two major amendments to the US patent system since then.

The Bayh-Dole Act facilitated the patenting of SMEs, non-profits (especially universities) for their inventions carried out with federal funding and thus promoted commercialization of them. Before the Act,

is also codified in Title 35 of the US Code. The new patent law in the US in particular was designed to strengthen rather than to curtail the rights of the patent owner.[338] It must be recalled that before World War II and especially during the great depression period, the patent system had come under big criticism about the abuse of patents due to patent-based cartels and downward price rigidities enforced by monopolistic sellers.[339]

In addition to Section 5 of the TRIPS, according to Title 35 of the US Code the

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it was the federal government and its agencies which owned the patents. The Act also aimed to allow federal agencies to grant exclusive licenses for their technology to provide more incentive to businesses. Apparently before the Act, fewer than 5 % of the 28,000 patents being held by federal agencies had been licensed, compared with 25 % to 30 % of the small number of federal patents for which the government had allowed companies to retain title to the invention. See United States General Accounting Office (GAO) Report to Congressional Committees, May 1998, Technology Transfer, Administration of the Bayh-Dole Act by Research Universities p.3 available at https://www.gao.gov/archive/1998/rc98126.pdf last visit 30.04.2020.

There are controversial discussions on the effects of the Bayh-Dole Act on university / academic patenting. An empirical analysis suggested that the effect of the Act on three major universities in the US (the University of California, Stanford and Columbia Universities) remained modest for Stanford and California except for significant increase in patenting and licensing of biomedical research, but it is argued in the paper that the Bayh-Dole Act has little to do with this increase and it was merely the intensified efforts of the university administrators to make more inventions in the wake of the Act. An overall analysis with all university patents showed that the patents issued after the Act seemed to be more general in nature and less significant in terms of breadth and rate of their citations. See MOWERY, D. & ZIEDONIS, A. (2002). Academic Patent Quality and Quantity Before and After the Bayh-Dole Act in the United States, *Research Policy*, Volume 31, Issue 3, pp 399-418. On the other hand, the Act is also seen as the final step in institutionalizing the technology transfer to explain the rise of the university patenting as a process of institution building. See POPP BERMAN, E. (2008). Why Did Universities Start Patenting?: Institution-building and the Road to the Bayh-Dole Act. *Social Studies of Science*, Volume 38, Issue 6, pp. 835–871.

The Leahy Smith American Invents Act on the other hand changed the US patent system from "first to invent" to "first inventor to file" system, eliminated the interference proceedings at the USPTO since the priority after this Act would be based on filing date. Post – grant oppositions are still allowed under certain requirements. There was a concern over the new system that the small businesses would not be able to rush to the patent office to file, as they lack the resources such as financing, patent lawyers, etc. that bigger companies possess and that's why the bigger ones were considered to be able to prepare the applications more quickly. See RANTANEN J. & PETHERBRIDGE L. (2012), The America Invents Act Jeopardizes American Innovation, Opening Statement in *"Debate: America Invents, More or Less?", University of Pennsylvania Law Review*, Volume 160, pp. 229- 253 at pp. 231-232 available at https://scholarship.law.upenn.edu/cgi/viewcontent.cgi?article=1068&context=penn_law_review_online last visit 30.04.2020. Since the new Act affects patent applications filed after March 16, 2013, its impact on patenting is still to be determined.

[338] RIESENFELD, S.A. (1954). The New United States Patent Act in the Light of Comparative Law I. *University of Pennsylvania Law Review*, Vol 102 No:3, pp. 291-322.

[339] Ibid p. 294, see also SCHERER F.M. (2007). The Political Economy of Patent Policy Reform in the United States. *Harvard University, John F. Kennedy School of Government Faculty Research Working Papers* Series, RWP07-042 at p. 3.

inventions must also fulfill the requirements of utility[340], novelty[341], non-obviousness[342] and must be specified adequately.[343]

3.4.1 Utility Requirement

Title 35, §101 of the US Code brings the utility requirement for patentable subject matter. Accordingly, "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title."

The U.S. Supreme Court held in Brenner v. Manson[344] case that the invention must show an immediate, definite utility that must be demonstrated within the scope of the utility requirement of §101. It was not allowed to grant patents to chemical compounds that only facilitated future research. Upon this decision the USPTO brought Brenner standards for biotechnological patent examinations and it became essential for the applicants to reveal clinical data demonstrating utility of the invention. Hence, claims on the basis of sole theoretical utility could be rejected. These standards were used until the USPTO issued the Utility Examination Guidelines in 1995[345], Revised Utility Examinations Guidelines in 1999[346] in 2000[347] and in 2001 finally.[348] The revised guidelines were developed after comments and corrections and aimed to allow patent examiners to reject a claim unless the applicants can explicitly show *specific, substantial,*

[340] United States Code, Title 35, Section 101; 35 USC § 101.

[341] 35 USC § 102.

[342] 35 USC § 103.

[343] 35 USC § 112.

[344] Case 383 U.S. 519, 534 (1966) Brenner v. Manson.

[345] 60 Fed. Reg. 36, 263

[346] 64 Fed. Reg. 71, 440

[347] 65 Fed. Reg. 3, 425

[348] 66 Fed. Reg. 1, 092

credible and well-established utility (emphasis added). Such a requirement allows the patent examiners to omit negligible utility in granting patents.

However, it is not precisely explained what constitutes "specific, substantial and credible utility". Clinical utility and not only fundamental knowledge is essential for patent claims. According to USPTO gene sequences isolated from their natural state as a result of human intervention can be patentable subject matter.

By the enactment of Leahy- Smith American Invents Act (AIA) on March 16, 2013, 35 USC §102 conditions on novelty were revised and the prior art preclusion of patenting (unless exceptions are applicable) has changed.[349] However, these changes do not affect applications filed before this date, to which pre-AIA provisions still apply. Similarly, the USPTO Manual of Patent Examining Procedure (MPEP) sets forth the criteria both for the applications subject to examination under AIA or pre-AIA provisions.[350]

The utility requirement can be achieved if one product is altered to resemble another one, which itself has a benefit. Hence there is not a high threshold. To lack utility, the claim must be "totally incapable of achieving a useful result".[351]As long as the claim has even a partial utility, it is enough to satisfy the utility requirement.

3.4.2 Novelty Requirement

Title 35, § 102 of the US Code brings novelty requirement. In order for the claims not infringe an existing patent, they need to be novel and not anticipated by a prior art reference.

Before the enactment of AIA on 16 March 2013 this requirement necessitated the invention to be new and not similar to what has been known, published or used before,

[349] See the Leah- Smith America Invents Act at supra note 337.

[350] See USPTO Manual of Patent Examining Procedure (MPEP) Sections 2138, 2152 and 2163

[351] See Case 185 F.3d 1364, (1999) Juicy Whip, Inc. v. Orange Bang, Inc.

and must not have been in public use for more than 1 year than the date of application. In the US, until recently the patentee was the one that was first to invent. If there are various patent applicants that claim to have invented the same item, there is interference among them, as stated in § 102 (g). To be the first to invent the applicant must have been the first one who has reduced the invention to practice and must have not abandoned the invention.[352] Date of reduction to practice was usually the date of filing if an earlier date of conception cannot be proven. In case of interference the Patent Office had to consider the respective dates of conception and reduction to practice. If for instance the publication date was more than 1 year prior to the effective filing date of the application, the reference was regarded as prior art[353]. So USPTO would consider the first one to invent, not the first one to file as the inventor. The inventor herself did not need to be personally involved in the reduction to practice, because she would be the one who has contributed to the conception of invention.[354] However the conception was not enough to prove an earlier date of invention, an actual reduction to practice needed to be proven showing that the claimed invention works for its intended purpose.[355]

Similar to the EU's first to file system, AIA changed the US patent system from "first to invent" to "first inventor to file" for inventions filed after 16 March 2013. The difference between the two is that first to file system requires absolute novelty; if there is any disclosure of information by public use, sale or publication of the claimed invention

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[352] Reduction to practice refers to either actual reduction by physical construction of the invention in its material form or to constructive reduction by patent filing and sufficient disclosure of invention so that a person with ordinary skills in the art can construct the invention without undue experimentation. See USPTO - MPEP Section 715 available at https://www.uspto.gov/web/offices/pac/mpep/s715.html (last visit 30.04.2020) for an effective declaration of prior art using the doctrine and supra notes 354 and 355 for application of this doctrine in the US court cases. More information will be given in Chapter 4.2.1 of the dissertation.

[353] See MPEP section 2138.

[354] See Case 333 F.3d 1330 (Fed. Cir. 2003) Board of Education v. American Bioscience Inc.

[355] See Case 849 F.Supp. 740 (S.D. Cal. 1994) The Regents of The University of California, v. Synbiotics Corporation, citing 802 F.2d 1367, 1376 (Fed.Cir. 1986) Hybritech Inc. v. Monoclonal Antibodies, Inc., "Conception is defined as the "formation in the mind of the inventor, of a definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice." and citing Case 927 F.2d 1200 1206 (Fed.Cir.1991) Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd. "Actual reduction to practice requires that the claimed invention work for its intended purposes. Accordingly, conception requires both the idea of the invention's structure and possession of an operative method of making it."

before the filing date, then the patent cannot be granted. In the first inventor to file system, if the disclosure was made within 1 year of filing of the patent at USPTO by the inventor, it may be disregarded as prior art. If the disclosure was made by third parties, it will still be regarded as prior art. In a way the inventor is granted a grace period of 1 year for its own disclosures, in which such disclosures cannot be counted as prior art. The inventor, who disclosed information will also be not prohibited from patent grant, if a third party obtained a subsequent disclosure from the patent.[356] From law and economics point of view, this is a significant difference. At EPO there is no such grace period. Hence an early disclosure under first inventor to file system at USPTO means no patentability at EPO. Besides, independent disclosure of third parties can still be used against the inventor.

Having said that disclosures in the grace period are not taken into account when assessing whether the claimed invention meets novelty criteria, it is important to note that the inventor will have to make sure that materials offered for experimental use and / or prototypes are confidential. There is always the risk of having unwanted public disclosure of experimental material. Experimental use is regarded as the exception to public use. However, the scope of experimental use exception has been very narrow at the US Courts, and this results especially for gene patents in higher royalty obligations and transactions costs and restricted access to biomedical research tools for scientists.[357]

AIA clearly encourages inventors to disclose the new invention by filing or by publishing, hence bringing into public use. The pre-AIA and AIA conduct of public use was also analyzed by Lemley (2014)[358] and hints to immense differences from a law and economics point of view. Before AIA the term "public use" was interpreted by the US

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[356] See USPTO Manual of Patent Examining Procedure Chapter 717 Prior Art Exceptions under AIA 35 USC 102(b)(1) and (2) stating "For example, if the inventor or a joint inventor had publicly disclosed elements A, B, and C, and a subsequent intervening grace period disclosure discloses elements A, B, C, and D, then only element D of the intervening grace period disclosure is available as prior art under 35 USC 102(a)(1)." available at https://www.uspto.gov/web/offices/pac/mpep/s717.html - last visit 30.04.2020.

[357] MÜLLER, J. M. (2001). No Dilettante Affair: Rethinking the Experimental Use Exception to Patent Infringement for Biomedical Research Tools. *Washington Law Review* Volume 76, Issue 1, pp 1-66.

[358] LEMLEY, M.A. (2014). Does "Public Use" Mean the Same Thing It Did Last Year. *Stanford Public Law Working Paper No*. 2394153. Available at SSRN: https://ssrn.com/abstract=2394153 , last visit 30.04.2020

Courts as publicly known or used.[359] Besides, regulators also wanted to prevent inventors from making commercial use of the invention while keeping secret, hence if the patent has been "on sale" or in "public use" for more than a year before the filing of application, the invention would not be granted patent protection.[360] The AIA gives the inventor one-year grace period for disclosures made through inventor's own conduct.[361]

3.4.3 Disclosure requirement:

Title 35, § 112 of the US Code lays down the requirements for the adequate specification of the patentable subject matter. Accordingly, the disclosure is satisfied by written description (adequate description of the invention), enablement (description of the process of making and using of the invention) and best mode (best manner considered by the inventor to make the invention) requirements. According to the USPTO Guidelines for Examination of Patent Applications under the 35 USC § 112, "Written Description" requirement ensures that the patent examiners can agree that "a person skilled in the art can possess the claimed invention". The applicants must also include in their specifications the best mode to carry out the invention.[362] The rationale of this requirement is to ensure that the inventors enable persons skilled in the art to use the invention, hence information on the invention may be practiced after the expiry of the patent protection term.

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[359] Ibid p. 3.

[360] Ibid. pp 4-5. Indeed, the inventor could avoid the one-year statutory bar by commercializing the invention but keeping it as a secret. Secret commercial use was not prior art that bars a third party from later obtaining a patent, but it did start the one-year clock running for the user. This was the rule developed in 1946 by Judge Learned Hand in Case 153 F.2d 516, 520 (2d Cir.1946) Metallizing Engineering v. Kenyon Bearing & Auto Parts Co. with the reasoning that the intent of the statute was not to encourage secrecy, but instead to encourage disclosure of information.

[361] Ibid p. 7.

[362] 2163 Guidelines for the Examination of Patent Applications Under the 35 USC §112, "Written Description" Requirement available at http://www.uspto.gov/web/offices/pac/mpep/documents/2100_2163.htm, last visit 30.04.2020.

With regards to genes and expressed sequence tags (EST), the enablement requires more than a listing of the sequence, since it is possible by using computerized techniques to synthesize molecules chemically. The enablement requirement ensures that a person of ordinary skill will be able to practice the invention without making undue experimentation.[363]

The written description should ensure that the applicant has actually made the claimed invention.

Some claims were rejected since the applicant was not in possession of the claimed invention.[364] Thus it is seen appropriate for the patent examiners not to grant a patent even if a specification may enable someone skilled in the art to make the claimed invention, but it does not adequately indicate whether the applicant was in possession of the claimed invention at the time of filing the application.[365]

An adequate disclosure guarantees a person skilled in the art is enabled to make, construct, or use the same and that the public will receive the full benefit of the knowledge of the patent after the expiration of the patent term in return of the limited monopoly rights granted to the inventor. [366] Hence the written description and enabling requirements are two different requirements.[367] The patent applicants must have and disclose all the complete sequence of a gene to comply with the written description requirement.[368]

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[363] In re Wands Case, 858 F.2d 731, 736 (Fed. Cir. 1988). The Wands criteria on undue experimentation are quantity of the required experimentation, amount of the provided guidance, existence of functioning examples, the nature of the invention, state of the prior art, relative skills of the persons in that art, predictability of the art, breadth of the claims.

[364] USPTO Written Description Guidelines – 706.03(c) Rejections Under 35 USC 112(a) or Pre-AIA 35 USC 112, First Paragraph [R-07.2015]- 7.31.01 Rejection, 35 USC 112(a) or pre-AIA 35 USC 112, 1st Paragraph, Description Requirement, Including New Matter Situations.

[365] Case 984 F.2d 1164 (Fed. Cir. 1993) Fiers v. Revel.

[366] Case 489 U.S. 141 (1989) Bonito Boats Inc. v. Thunder Craft Boats Inc.

[367] Case 935 F.2d 1555 (Fed. Cir. 1991) Vas-Cath Inc. v. Mahurkar.

[368] Case 19 F3d 1559 (Fed. Cir. 1997) Regents of the Univ. of California v. Eli Lilly & Co.

It was also ruled in the Fiers v. Revel Case[369] that the inventor was not entitled a patent due to inadequate written description for the claim. The three foreign inventors, namely Fiers, Revel and Sugano filed at different times US patent application and claimed (at the time of their foreign application date) to be the first one that have isolated a DNA sequence for beta – interferon (B-IF). The claim made by Revel was rejected by the Court on the grounds that he had not listed the actual human DNA sequence in the application.

> "An adequate written description of a DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself. Revel's specification does not do that. Revel's application does not even demonstrate that the disclosed method actually leads to the DNA, and thus that he had possession of the invention, since it only discloses a clone that might be used to obtain mRNA coding for B-IF.[370] A bare reference to a DNA with a statement that it can be obtained by reverse transcription is not a description; it does not indicate that Revel was in possession of the DNA. Revel's argument that correspondence between the language of the count and language in the specification is sufficient to satisfy the written description requirement is unpersuasive when none of that language particularly describes the DNA... Such a disclosure just represents a wish, or arguably a plan, for obtaining the DNA."

The best mode requirement sets forth the best process for obtaining the invention. In Amgen v. Chugai Case[371] it was stated that

> "The best mode requirement thus is intended to ensure that a patent applicant plays "fair and square" with the patent system. It is a requirement that the quid pro quo of the patent grant be satisfied. One must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him of carrying out his invention. Our case law has interpreted the best mode requirement to mean that there

[369] See Case at supra note 365.

[370] Interferon's are proteins released by the immune system against pathogens such as tumor cells and/ or bacteria, viruses.

[371] Case 927 F.2d 1200, (Fed. Cir. 1991) Amgen v. Chugai

> must be no concealment of a mode known by the inventor to be better than that which is disclosed."

This requirement does not have a corresponding concept in the "European patent law" at the EPO practice.[372] But there is still possibility to apply it under Article 29 of the TRIPS.

The America Invents Act of 2013 made the insufficient disclosure of best mode requirement an invalid defense in patent infringement cases. Although the law still formally requires the best mode, by eliminating its failure to disclosure from invalidation of the patent, this requirement becomes unenforceable. In effect, it was expected that this provision would eliminate the direct defense as previously seen in some litigation cases, that a patent failed to comply with the statutory "best mode" requirement.[373] Best mode requirement has had its critics, as well. As noted by McClain (2014) for inquiries into best mode violations the courts had limited their check to examining only the claims on the patent application. However, in some cases the requirement extended beyond the claims section. By this kind of uncertainty, the applicant was encouraged to disclose more than is necessary and this resulted in increased costs and a lower return for patent since the inventor might be disclosing more information that might otherwise not be required. Besides the opponents also stressed the fact that this requirement was applicable only in few other countries. Foreign applicants needed to update and modify their applications in order to be able to file in the United States. This resulted in increased costs and inconveniences for foreign patent applicants. It was argued that elimination of best mode requirement would harmonize America's patent system with the rest of the world.[374]

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[372] See T 412/93 Erythropoietin / KIRIN – AMGEN, EPO Decision of 21 November 1994 at reason 7.

[373] OHLY, D.C. (2011). The America Invents Act of 2011. *Intellectual Property & Technology Law Journal*, Volume 23, Issue 6, pp. 3-8 at p.6.

[374] MCCLAIN, M. A. (2014). Who Are the New "Best Mode" Police? An Analysis of Proposed New Methods of Enforcement of the Best Mode requirement after The Leahy-Smith America Invents Act. *University of Toledo Law Review*, Volume 46, Issue 1, pp 191-219 at p.200.

Although AIA did not remove the best mode requirement, the failure to disclose is no longer a basis for litigation.[375] Litigation in this regard concerned mainly invalidation of the granted patent, and although AIA § 112 still dictates this requirement, AIA § 119 excludes it from priority claims.[376] The aim of the best mode requirement was to ensure that the invention ended in public domain soon after the patent expiry.[377] Since the enactment of AIA, legitimate alternatives to the best mode requirement have been discussed. The term "public disclosure" under AIA § 102(b)(1)(b) is assumed to be a "disclosure that was made by the inventor" under §102(b)(1)(a) being a subset of "disclosures," so that some information that was not public will be disclosed.[378] These are relevant for priority claims. Other alternatives include increasing USPTO's use of the "requirements for information" and "duty of candor" (duty of disclosure in good faith), ethical violations as stated by American Bar Association, federal fraud and false statement statue (threat of federal prosecution) and inequitable conduct doctrine (breach of good faith, in which all patents by the same inventor may be invalidated by the court).[379]

3.4.4 Nonobviousness Requirement

Pre-AIA nonobviousness is defined as " the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains".[380] Gene claims deemed unpatentable when

[375] Ibid p.201

[376] AIA § 119 on Benefit of earlier filing date; right of priority (e)(1) explicitly states "….an invention disclosed in the manner provided by section 112(a) (other than the requirement to disclose the best mode)…"

[377] See McClain at supra note 374 pp 193-194.

[378] MERGES R. P. (2012). Priority and Novelty Under the AIA, *Berkeley Technology Law Journal*, Volume 27 pp.1023 – 1046 at p. 1039.

[379] See McClain at supra note 374 pp 202-206.

[380] Pre AIA - 35 USC § 103 (a). Today AIA - 35 USC § 103 continues to be the legal base for the nonobviousness requirement of patentability with similar wording, but the time referring to effective filing

they were found to be obvious where the disclosure of the prior art motivates and enables a person with ordinary skills with a reasonable expectation of success.[381] But the motivation from possible commercial use and further study were deemed nonobvious.[382] Nonobviousness requirement can be used to determine whether the claimed invention is obvious, especially in cases where the inventor of the prior art has had the intention to do what the later inventor has achieved, whether there has been some kind of anticipation for the claimed results. The patent cannot be granted if there are only obvious differences to prior art references. So, for instance if the claim is generation of amino acid A from amino acid B, it can be rejected on the basis of being obvious, unless a new method of generation is presented.

There are some important changes to nonobviousness requirement for patentability and to the definition of prior art after America Invents Act as explained in the USPTO manual of patent examining procedure (MPEP). Firstly, the effectiveness does not concern when the invention was made but starts with the filing date.[383] Secondly, the new act necessitates "consideration of the difference between the claimed invention and the prior art, whereas pre- AIA requirement referred to the difference between the subject matter sought to be patented and the prior art".[384] Still MPEP emphasizes that the difference in terms "claimed invention" and "subject matter sought to be patented" is not expected to bring a major difference in examining the obviousness; the Courts have associated the two terms nevertheless, but it shows a shift towards equating the terms with

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date of invention.

[381] Case 947 F2d 488 (Fed. Cir. 1991) In re Vaeck

[382] Case 51 F.3d 1552 (Fe. Cir. 1995) In re Thomas Deuel

[383] See USPTO Manual of Patent Examining Procedure, Section 2141 "this …section is applicable to applications subject to the first inventor to file (FITF) provisions of the AIA except that the relevant date is the "effective filing date" of the claimed invention instead of the "time of the invention," which is only applicable to applications subject to pre-AIA (provisions)."

[384] See USPTO Manual of Patent Examining Procedure, Section 2158 quoting Federal Circuit, "the term 'claims' has been used in patent legislation since the Patent Act of 1836 to define the invention that an applicant believes is patentable. Case 109 F.3d 756, (1997) Hoechst-Roussel Pharms., Inc. v. Lehman (citing Act of July 4, 1836, ch. 357, § 6, 5 Stat. 117)."

the writings of the applications.

Thirdly, under the old regime pre-AIA §103(c) referred to the common ownership. If the references to prior art were considered to be qualifying as prior art and constituted a rejection to obviousness, then patentability was not precluded if the subject matter and the claimed invention were, at the time the claimed invention was made, owned by the same person or subject to an obligation of assignment to the same person.[385] So, prior art did not qualify as prior art of the claimed invention, if at the time invention was made the subject matter and the claimed invention were owned by the same person or the assigned person(s). This would include also joint research agreements if the claimed invention was made by or on behalf of the parties to the agreement effective on or before the invention date, or it was made as a result of the activities within the scope of this agreement or when the application disclosed the names of the parties to these agreements.[386] Hence, this common ownership could be used to indicate the obviousness of the claimed invention so that the exception in pre – AIA §103 (c) could be used for obviousness rejections for prior art under pre- AIA § 102 (e) , (f), (g).[387] The new (post) AIA 35 §103 eliminates the pre – AIA §103 (c), however similar provisions are found in AIA § 102 (b) (2) and AIA § 102 (c) but the joint research agreements or the common ownership must now exist before the effective filing date and not before the invention date. Hence when the invention and the prior art references are commonly owned at the effective filing date, the prior art is disqualified as prior art and does not impede patentability. Taking into account the fact that patent publications take up to 18 months from the date of filing, [388]

[385] Pre- AIA 103 (c) (1) MPEP Section 7000.

[386] Pre- AIA 103 (c) (2).

[387] Pre – AIA § 102 precludes patent grant if according to; § 102 (e) the invention was described in another patent application or filed before the date of invention, § 102 (f) (the person) did not himself invent the subject matter sought to be patented, § 102 (g) (the invention) was made in the US by another inventor who had not abandoned, concealed, or surpassed the invention before the (applicant) inventor's date of invention. These three provisions were to indicate who was actually the first to invent.

[388] Both at EPO and USPTO; see EPO Guide applying for a patent Chapter 5.3 "Publication of the European patent application" available at https://www.epo.org/applying/european/Guide-for-applicants/html/e/ga_c5_3.html and USPTO Manual of Patent Examining Procedure Section 1120 "Eighteen-Month Publication of Patent Applications [R-07.2015]" available at https://www.uspto.gov/web/offices/pac/mpep/s1120.html last visit 30.04.2020. Before the publication, the

in case there is an earlier patent application which has not yet been published, the inventors from different institutes may establish a common ownership before filing a patent application together, provided that the invention took place as a result of the activities within the scope of a joint research agreement. In such a way they would be able to overcome the prior art rejection by the patent office.

Moreover, moving prior art exception from § 103 (Conditions for patentability; non-obvious subject matter) to § 102 (Conditions for patentability; novelty) may show a shift from USPTO rejections based on lack of nonobviousness towards those based on lack of novelty. Indeed, in pre-AIA, § 102 was called "Conditions for Patentability; Novelty and Loss of Right to Patent" and there were seven requirements to be met for patentability. In the new AIA § 102, these requirements have been comprised into two main novelty / prior art conditions, but the scope of prior art has been increased so as to include not only previous publications, but also any description in a printed publication, in public use, on sale, or otherwise available to the public comprehending any form of public disclosure [389] and a US patent application or a PCT application effectively filed.[390] So in AIA a foreign priority date can be invoked as prior art.

For the last but not the least, the new law does not include the provision in the former law applying nonobviousness only to biotechnological inventions invoked. The biological inventions that met the requirements under pre-AIA §103(b) were not considered obvious under pre-AIA §103(a). These requirements were that the composition of matter from a biological process should be novel under pre-AIA §102 and nonobvious under pre-AIA §103 (a) and certain claims as defined in pre-AIA §103(b) to this process could not be rejected by the USPTO on the grounds of obviousness.[391] In the new law this exception given solely to certain biological process claims is no longer

applications are kept confidential.

[389] AIA § 102 (a) (1).

[390] AIA § 102 (a) (2).

[391] The definitions for the accepted biological process claims can be found in pre-AIA 103 (b) (3) such as processes genetically altering the organisms, cell fusion procedures or a method of using a product produced by these two mentioned processes.

present. This shows some sort of widening of the provision.[392] The reason might be that the pre-AIA provisions on biotechnological inventions were rarely applied, where a biotechnological process using or producing compositions of matter that were novel under 35 US § 102 and nonobvious under § 103(a)and that § 103(b) needed to be invoked so that the claimed invention was to be considered nonobvious.[393] In short biotechnological process claims that involved nonobvious provisions under § 103(a) could not be rejected. Biotechnological patent applications that are still subject to pre-AIA 35 USC §102 provisions are subject to pre-AIA 35 USC § 103(b), as well. In Cases In re Ochiai,[394] and in re Brouwer,[395] the Federal Circuit analyzed whether a biotechnological process that is obvious in light of the prior art can be patented for using novel and nonobvious materials and whether the claim produced could be regarded as novel and nonobvious.

Indeed, before these two cases, there was a famous in re Durden[396] Decision of the Federal Circuit in 1985 stating that a chemical process is obvious, if prior art refers to processes with similar starting material, and it does not automatically become nonobvious when the "specific starting material employed, and the product obtained are novel and nonobvious". Although this was not a per se rule to be applied to all patent claims, it must have raised concerns, especially in the biotechnological industry. It was reported by the Congress that there were complaints from various industry groups that the USPTO was automatically rejecting process claims under circumstances similar to In re Durden

[392] AIA 35 USC §103 reads as "A patent for a claimed invention may not be obtained, notwithstanding that the claimed invention is not identically disclosed as set forth in section 102, if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. Patentability shall not be negated by the manner in which the invention was made."

[393] See MPEP section 2158.

[394] Case 71 F.3d 1565 (Fed. Cir.1995) In re Ochiai

[395] Case 77 F.3d 422 (Fed. Cir. 1996) In re Brouwer

[396] Case 763 F.2d 1406 (Fed. Cir. 1985) In re Durden

case.[397] Biotechnology processes often use genetically altered bacteria and other organisms, that can be patentable, but some end products, which may be for instance diagnostic, therapeutic and surgical methods may not be patentable. The rationale behind such unpatentability is to grant access for all persons to such methods, and not deny treatment / surgery / diagnostics due to IPR protection.[398] Hence although the method can be conventional, the starting material can still be nonobvious and patentable. The rejection of or the delay in patent grants of these biotechnological processes have then caused substantial costs to innovators and investors in the US and end products, which were developed by the not patented processes in the US, but which had received patent protection in third countries were being imported to the US.[399] The discussions around re Durden criteria with the controversy in broad interpretation of these criteria plus the economic losses of the US biotechnology sector required some clarification and certainty

[397] DRATLER J. & MCJOHN S. M. (2006). *Intellectual Property Law: Commercial, Creative and Industrial Property*, Volume 1, New York: Law Journal Press, at p. 201. In re Durden the Federal Circuit affirmed the USPTO rejection of a biotechnology process claim due to failure to meet nonobviousness criteria.

[398] In the EU treatment, surgical and diagnostics methods are not patentable under EPC Art. 53(c) which reads as "European patents shall not be granted in respect of … methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body…". But the same article continues "…this provision shall not apply to products, in particular substances or compositions, for use in any of these methods." Besides, Art. 54(5) also gives flexibility in patenting of substances or compositions "for any specific use in a method referred to in Article 53(c), provided that such use is not comprised in the state of the art". So, if the substance is claimed as purpose-limited, for a specific use in a surgical, therapeutical, or diagnostic method, it can be patented. See for instance G2/08 decision of EPO from 19.02.2010, where the patentability was granted for a medicament known to be used for an illness can be used in a different treatment by therapy of the same illness. In the US these methods are not excluded from patentability in the statutory law, however in the case law we see limitations such as the US Supreme Court decision Mayo v. Prometheus (566 US 66 (2012)) – where the Supreme Court stated that a specific application of a law of nature could be patentable, but this was not the case with Prometheus patents. As a result, these patents claiming pure diagnostics methods were found to be invalid.

[399] See Case 902 F.2d 1532 (Fed. Cir. 1990) Amgen v. United States International Trade Commission. Amgen had a patent on a gene on human EPO (erythropoietin – a kidney secreted protein; stimulates the production of red blood cells and is a useful therapeutic agent for the treatment of some blood disorders characterized by low or defective bone marrow of red blood cells, such as anemia), however the biotechnological processes using this gene and host cells to produce recombinant EPO were rejected by the USPTO due to In *re Durden* criteria. Meanwhile a Japanese company Chugai Pharmaceuticals Co. produced recombinant EPO using Amgen's patented genes and started exporting them to the US. Though Amgen filed a complaint against Chugai Pharmaceuticals at the United States International Trade Commission, the Judge ruled that Amgen's patent on the gene on EPO did not cover the process of making recombinant EPO, and that imports of Chugai Pharmaceuticals were assured. So, Amgen appealed to the Federal Circuit, which again ruled that the import of the products could not be prevented due to the scope of the patent of Amgen, excluding the process to produce recombinant EPO.

regarding patentability of biotechnological processes. Finally, the lobbying efforts of the US biotechnology sector opened the way to the enactment of the Biotechnological Process Patent Act of 1995, amending Title 35, Section 103 of the USC adding the new subsection 103(a) and making an exemption for biotechnology processes for the nonobviousness requirement provided that they use or result in novel and nonobvious compositions of matter by subsection 103(b).[400]

The cases In re Ochiai, and In re Brouwer were heard by the Federal Circuit after the 1995 amendment in law.

3.4.4.1 In re Ochiai

Ochiai had applied to USPTO for a biotechnological process of using a particular type of new and nonobvious organic acid to make a novel and nonobvious compound with antibiotic properties. USPTO rejected the claims for failure to meet nonobviousness criteria stating that a standard, conventional process is being claimed and that there is a slight difference between the claimed invention and prior art and resulted in a slightly different product. Ochiai appealed to USPTO Board of Appeals and Interference arguing that the starting material, the process of using this material and the final product were novel and nonobvious.[401]

In reviewing the appeal, the Board referred to another case In re Pleuddemann[402], which had somehow softened the In re Durden criteria by differentiating between the

[400] Public Law No. 104-41. See BEIER D.& BENSON R. H. (1991). Biotechnology Patent Process Act. *Denver University Law Review*, Volume 68, pp 173 -190 for a discussion of calling on the Congress to act upon unfair foreign competition and to support development of pharmaceutical products derived from biotechnological processes.

[401] Ochiai stated that "neither the final product nor the method of introducing the particular [acid] component were known, obvious or even remotely suggested in the prior art should be dispositive of the obviousness of the invention".

[402] Case 910 F.2d 823 (Fed.Cir.1990) In re Pleuddemann.

method of using and method of making. However, Ochiai's application was for a claim on a process of making a particular compound. The Board stated

> "We have reviewed the Federal Circuit's decisions in In re Pleuddemann, 910 F.2d 823, 15 USPQ2d 1738 (Fed.Cir.1990) and Durden, supra, and the CCPA decisions in In re Mancy, 499 F.2d 1289, 182 USPQ 303 (CCPA 1974) and In re Kuehl, 475 F.2d 658, 177 USPQ 250 (CCPA 1973) for guidance. We note that prior to resolving the patentability question in each case, the court first reviewed all the facts of the case, including arguments of counsel, and determined whether the claims were directed to a "method of making" or a "method of using". When the process claimed was considered to be one of "using" a novel material, patentability of the process was linked to the patentability of the material used. However, when the process claimed was considered to be directed to a "method of making" a novel material, patentability of the process was determined based on the inventiveness of the process steps themselves. Selection of a novel starting material was not considered dispositive of patentability if, indeed, an element of the process."

Indeed, the Board was aware of the dilemma stemming from the "using" and "making" distinction to consider the patentability of the claims and further stated that:

> "The chicken/egg conundrum discussed by appellants … presents a real-world dilemma to a patent examiner trying to balance the "invention as a whole" concept with the rationale of the … Durden line of cases. Faced with the use of a novel and unobvious material to make a novel and unobvious product, it is difficult to determine whether the invention is patentable as a "use" of the new starting material or unpatentable as a "method of making" the final product. Moreover, it is difficult to divorce from the patentability consideration the novelty and unobviousness of starting materials and final products when one is constantly advised to consider the invention

> as a whole when reaching the ultimate conclusion of patentability."

Hence the Board of Appeal concluded that there was nothing unobvious in the particular process chosen, rejected the claims of Ochiai affirming the rejection of the examiner.

Ochiai then appealed to the Federal Circuit arguing that the examining division and the Board of Appeal of the USPTO both failed to apply the nonobviousness test established by Graham v. John Deere Co.[403] This test has three elements: the content and scope of the prior art, the difference between the prior art and the claimed invention, and the level of ordinary skill in the art. In addition to these three elements, secondary considerations such as commercial success, long felt but unsolved needs and failure of others can also be included to enlighten the circumstances, all to be examined on a case-by-case basis.

Ochiai also argued that the Examining Division and the Board of Appeal failed to apply the so-called "second Graham factor" weighing "the specific differences between the claimed invention-with all its limitations-and the prior art references".

The Federal Circuit began examining the case in order to see whether the Board of Appeal erred in upholding the examiner's rejecting of the claim of Ochiai. In doing so the Federal Circuit held that test of obviousness is statutory and requires a comparison of the prior art with the claim's subject matter as a whole. Hence it was approved once again that applying per se rules for obviousness is not the right way of testing and should be done by trying to establish a "prima facie case of obviousness". Applying this statutory test, the Court concluded that Ochiai's process invention as claimed is not prima facie obvious. This process requires use of new, nonobvious acid as one of the starting materials, the particular acid chosen is part of this process.[404] The Court continued to state that:

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[403] US Supreme Court decision 383 U.S. 1 (1966) Graham v. John Deere Co.

[404] The Court stated "…it would not have been obvious to those of ordinary skill in the art to choose the particular acid of claim 6 as an acylating agent for the known amine for the simple reason that the particular

> "The Board noted that Ochiai's specifically claimed acid is "similar" to the acids used in the prior art. Likewise, the examiner asserted that the claimed acid was "slightly different" from those taught in the cited references. Neither characterization, however, can establish the obviousness of the use of a starting material that is new and nonobvious, both in general and in the claimed process. The mere chemical possibility that one of those prior art acids could be modified such that its use would lead to the particular cephem recited in claim 6 does not make the process recited in claim 6 obvious "unless the prior art suggested the desirability of [such a] modification."

Therefore, it was concluded by the Federal Circuit that the process claimed by Ochiai was nonobvious clarifying how both the USPTO examiner and the Board erred. First, the examiner concluded that Ochiai's new and nonobvious starting material was part of the prior art so that use of a nonobvious starting material to make a nonobvious product appears to be obvious. Second, "the examiner incorrectly drew from Durden a per se obviousness rule: namely, that a process claim is obvious if the prior art references disclose the same general process using "similar" starting materials." In the end the Board repeated the examiner's error by applying per se rules "sidestepping fact-intensive inquiry" required by §103.[405]

As a result, the Court stated that similarity is not necessarily obviousness and reversed the rejection of the claim as an "incorrect conclusion reached by an incorrect methodology."

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acid was unknown but for Ochiai's disclosure in the (patent) application. As one of our predecessor courts had occasion to observe, in a case involving a highly analogous set of facts, "one cannot choose from the unknown."

[405] The Board had particularized the inquiry by §103 in such a way that it had referred to court cases where claims on "process of making" were rejected and claims on "process for using" were accepted. Since Ochiai's claim was directed to "process of making", the rejection of the examiner was affirmed.

3.4.4.2 In re Brouwer

Indeed, the same judges at Ochiai case heard the Brouwer case. Brouwer's claim consisted of "a process for the preparation of a catalyst comprising an aryl group having a functional substituent group of general formula". This was a process of preparing novel resins. The claim used the so-called ""Michael addition" reaction, which was named after chemist Arthur Michael (1854-1942), and which is known as a standard technique in organic chemistry for reacting a material having an α,β-unsaturated carbonyl group with a material having an active methylene group".[406] This was regarded by the examiner as prior art, however the prior art references indeed did not involve the specific process claims of Brouwer. After the examining division rejected the claim on obviousness reasons, the Board of Appeal also affirmed the rejection with the reasoning that one having ordinary skills in the art that had used "Michael addition" reaction would have found it obvious to make the catalyst.

When appealing the Board's decision to Federal Circuit, Brouwer argued that the examiner and the Board had failed to apply a proper test for obviousness established by the Graham v. John Deere Co. case[407] and erred by presuming his claim to be prior art. The Court agreed with Brouwer stating:

> "Applying this statutory test to the art of record, we conclude that Brouwer's process invention was not prima facie obvious. Although the prior art references the examiner cited teach a generic chemical reaction of a compound containing an active methylene group with an ester of vinylsulfonic acid, we have made clear that "[t]he mere fact that a device or process utilizes a known scientific principle does not alone make that device or process obvious."

The Court also cited In re Ochiai stating:

> "[T]here are not 'Durden obviousness rejections' … but rather only section 103 obviousness rejections."

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[406] See Case footnote 3.

[407] Supra note 403.

Thus, the Court reversed the rejection of the claim.

3.5 Concluding Remarks

The enactment of American Invents Act can be regarded as an attempt to harmonize the US patent system with the rest of the world. The shift from first to invent system to first inventor to file system in the US is similar to the European first to file system. However, in the US the first to invent system will continue to be applicable for applications filed before the effective date of AIA on March 16, 2013. The applications made before this date will operate under first to invent system till their terms expire after twenty years after the date of filing. Besides follow-up applications to the current patents, which are filed before this date shall also be subject to first to invent system. Therefore, although the AIA creates real changes in the system, it will take years till the effects of these changes can really be evaluated. Hence the comparison in this dissertation especially regarding the case law is mainly between the pre- AIA US system with the EU system.

Making a comparison between the US Code Section 35 (USC 35) and European Patent Convention (EPC) would at first sight hint similar patentability requirements. Whereas the EPC sets requirements on novelty, inventive step, sufficient disclosure and industrial applicability excluding treatment methods of human/animal body by surgery/therapy and diagnostic methods practiced on human/animal body; USC 35 requirements include novelty, non-obviousness, written description, enabling and best mode. However, the way these requirements for biotechnological inventions are examined at EPO and USPTO differ.

As explained in Chapter 3.4.4, the US Federal Circuit concluded that there is not a per se rule of obviousness, each case should be reviewed by a fact-intensive inquiry. Although such a rule could have been very suitable for the patent examiners from an administrative point of view, per se rules would be harming the biotechnology sector in the US. It can be wise to expect that he administrative burden of patent examiners must have risen after the In re Ochiai and In re Brouwer decisions.

Before continuing with examination differences in the two patent offices it is essential to note that Article 53 of EPC strictly forbids the patentability of surgery, treatment, and diagnostic methods on animal/human body. The rationale behind this is that medical law has its origins in the Hippocratic Oath and medical practitioners should not be limited by patents when preserving human life.[408] In the US treatment methods may be patentable, but diagnostic methods per se cannot according to the Supreme Court ruling. There is a protection in USC 35 for medical practitioners and health care entities with respect to patent infringement in performing a medical activity that penalties for such an infringement shall not apply.[409] These differences and comparison are better explained in the case law examples in the next chapter.

[408] MARTIN, T. (2000). Patentability of Methods of Medical Treatment: A Comparative Study. *Journal of Patent & Trademark Office Society*, Volume 82, pp. 381 -423 pp.381-382.

[409] USC 35 287 (c).

4. CASE LAW IN THE EU AND THE US

In this chapter some examples of EU and US case law are introduced with direct comparisons of the two legal systems within the same sub-chapter on cases such as orphan drugs development, human embryonic stem cell patents, as well as accompanying differentiation around the different sub-chapters on treatment, diagnostics methods, CRISPR implementations, the patents of Myriad Genetics and anticommons problems.

As seen in the previous chapter although patent law has a statutory nature both in EU and US (and even has a base in the US constitution) these statutory laws are of general nature and leave room to jurisprudence for their application. Judges have applied statutes different across EU and US jurisdictions and as such have contributed to significant differences.

The law especially in the field of biotechnology has evolved over time through specific court cases and patent office decisions. Shaping of the law through court cases is a feature to be seen in case law, i.e. common law as explained by Posner it refers to "body of principles created by royal courts of England, the fields of law that have been created largely by judges as the by-product of deciding cases, rather than by legislatures and any field of law shaped largely by judicial precedents".[410] He continues to explain positive and normative aspects of economic analysis of law which deal with the law as it is and what it ought to be and argues that common law rules induce efficiency by maximizing the wealth of the society. It cannot be easily argued that each and every court or patent office decision has so far been successful in maximizing the wealth of the society. However, inquiry into cases may show whether the law has been evolving in terms of economic efficiency, which may lead to gains in social benefit. For instance, concerning patent exhaustion, in its Lexmark decision the Supreme Court of the US[411] reversed the

[410] POSNER, R. A. (2014). *Economic Analysis of Law*, Ninth Edition, New York: Wolters Kluwer at p. 39 Posner gives the in-text mentioned definitions of common law although his analysis in the book mainly concerns the law created by judges as by-products.

[411] 581 US_(2017) Impression Products Inc. v. Lexmark International, Inc: The Case involved sales of products abroad that were patented in the US. Lexmark owned several patents over toner cartridges for its printers and all domestic sales and some international sales were concluded with a single-use / no-resale restriction. (For the US customers there were two possibilities of buying: from the Return Program, which entailed US buyers agreeing to return the cartridge to Lexmark for a 20% discount in price or buying a regular cartridge at full price.) Impression Products acquired the used cartridges, refilled them and placed

decision of the Federal Circuit,[412] which had firstly addressed the question whether the exhaustion doctrine is based on statutory law or a judge made case law and stated that the "Congress defines the existence and scope of patent rights….the task of the federal courts is to interpret and apply statutory law, not to create common law". By looking at the Statue 35 USC §271(a)[413] the Federal Circuit stated that "If ordinary congressional supremacy is to be respected, exhaustion doctrine in the Patent Act must be understood as an interpretation of § 271(a)'s "without authority" language." As such when a patentee sells an article subject to single-use / no- resale restriction that is clearly communicated and lawful to a 3rd. party, it cannot grant the 3rdparty a resale / reuse option that has been clearly and lawfully denied. For the sales outside the US the Federal Circuit held that these sales do not automatically exhaust US patent rights, and the Lexmark patents were infringed for products resold in the US by return program or cartridges sold abroad. Since Lexmark patents were not exhausted in either case, it was decided that Impression Products had infringed.

The Supreme Court reversed the Federal Circuit decision stating that authorized sale made by the patentee or licensee in the US or abroad exhausts all the rights to a patent regardless of any post-sale restrictions. According to the Supreme Court, the Federal

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a microchip on them to enable re-use and re-sell in the US. Besides, Impression also bought some Lexmark cartridges abroad and imported them to the US. Lexmark started an infringement lawsuit against Impression products. Impression Products had one single defense argument that Lexmark's initial sales both abroad and, in the US, had exhausted patent rights in the cartridges; hence the single use/ no-resale restriction should not apply to remanufacturers /downstream purchasers. The District Court reviewed several cases including those ones decided by the Supreme Court which found exhaustion for sale of "licensed products without restrictions or conditions". Still the District Court dismissed the infringement claim for products sold in the US stating that "post-sale use restrictions do not prevent patent rights from being exhausted given that the initial sales were authorized and unrestricted". For products sold abroad the Court stated that "exhaustion did not apply and did not render imports and domestic resales of (Impression) non-infringing". The district court stated that "[t]he Supreme Court's decision was rooted in interpretation of a statutory provision of Copyright Act, but "[n]noticeably absent from patent law is a codification of the exhaustion doctrine," concluding: "the core statutory text that weighed in favor of a non-geographical interpretation is non-existent in the context of patent law." (See case background in Federal Circuit decision Lexmark Int. Inc. v. Impression Prod., Inc., 816 F.3d 721 (Fed. Cir. 2016)) Federal Circuit held in both cases of Return Program cartridges and regular cartridge imports from abroad that Lexmark could file infringement because Impression was aware of the restrictions on the products.

[412] Case 816 F.3d 721 (Fed. Cir. 2016) Lexmark International Inc. v. Impression Products Inc.

[413] 35 USC §271(a) refers to patent infringement in the US or for imports into the US for making, using, offering for sale without authority.

Circuit reached a different result because it recognized the exhaustion doctrine as “an interpretation of the patent infringement statute, which prohibits anyone from using or selling a patented article “without authority” from the patentee””. The Supreme Court concluded that the exhaustion doctrine is a “limit on the ‘the scope of the patentee’s rights”. The purchaser has the right to use, sell and import the product, not because it purchased an authority from the patentee to do so, but these are rights that come along with ownership. The Patent Act gives the patentees a limited exclusionary power. An authorized sale in the US and outside of US exhausts all rights under Patent Act.

The Supreme Court still left room for contractual enforcement of post-sale restrictions, but the issue cannot be dealt under patent infringement.

This decision has a significant impact also on biotechnology companies. Patent protection for biotechnological products will not quite mean the same as before. Patent infringement lawsuits for post-sale infringement activities should be replaced by claims due to breach of a contract. Authorized sale by a licensee would exhaust the patent rights. Infringement claims can still be placed for activities outside of the scope of the license; however, it may be difficult to assess what constitutes an authorized sale. The Supreme Court decision clearly identified that the sale by a licensee within the scope of the license is affirmed to be authorized by the patent holder. On the other hand, the third-party purchaser may have good faith about being the authorized purchasers, even in cases where they are not. An authorized foreign sale may also exhaust the domestic patent rights. The Lexmark decision does not address all these questions. However, it is obvious that the patent holders will need to make clear term distribution agreements especially with their foreign distributors, if they want their products to be prevented from being resold in the US, and also want to apply some restrictions towards use by 3rd. parties. In cases where biopharmaceutical companies are delivering the active pharmaceutical ingredients instead of a finished product especially through a distribution chain involving several agents, these restrictions would be more difficult to enforce.

For both the US and the EU jurisdictions one cannot think that case law and the statutory law exist independent of each-other. The statues or the legislation is inscribed on the case law and both are an integral part of the legal system. The legislation is

interpreted with common law principles by the Courts, and this forms a legal precedent for future cases. A difference between the jurisdictions is that the US patent system is unitary compared to the EU. In the US the USPTO grants patents, which are subject to the oversight of the district courts, the Federal Circuit and the Supreme Court. In the EU the patent system is more complex. The EPO grants European patents, which need to be validated in each EPC signatory country where protection is required. Each EPC signatory country is also responsible for the enforcement of patents and litigation of disputes with their national patent offices and national courts. The European Court of Justice (ECJ) rarely rules especially in biotechnological inventions on the patentability of certain claims.[414] Although, ECJ involvement cannot be compared to that of the Federal Circuit in terms of frequency of the decisions, the rulings are very import for the evolvement of biotechnological patenting. For instance, in the Case Monsanto v. Cefetra[415] the ECJ ruling limited the scope of the EU Biotech Directive so that patents

[414] See the judgement in Case 528/16 on 25.07.2019 which is explained in detail in Chapter CRISPR implementations in the EU. Also, the EU Directive on biotechnological inventions was challenged before the ECJ, which is explained in detail in Chapter 4.1.1.

[415] Case C-428/08 Monsanto Technology LLC v Cefetra BV and Others of 06.07.2010. Monsanto sued the Dutch importer of soy meal, Cefetra Company and some other importers for infringing its European patent on soybeans, which were resistant to herbicide glyphosate due to a gene alteration. Monsanto claimed to have found traces of the DNA of its patented genes in the soy meals imported from Argentina to the Netherlands. Since Monsanto did not have patent protection in Argentina, it sued in the Netherlands. Article 53a(3) of the Dutch patent law states

"In respect of a patent on a product containing or consisting of genetic information, the exclusive right shall extend to all material in which the product is incorporated and in which the genetic information is contained and performs its function."

The Dutch Court ruled that the DNA found in the soy meal is not an isolated organism, it is incorporated into the soy meal and cannot function as a herbicide resistant in the soy meal, which is dead material and not a living organism. Yet it referred the case to the ECJ and asked among others whether Article 9 of the European Biotech Directive would apply, which states

"The protection conferred by a patent on a product containing or consisting of genetic information shall extend to all material, save as provided in Article 5(1), in which the product is incorporated and in which the genetic information is contained and performs its function."

Because Monsanto had argued that this article should not apply here under Article 27 of the TRIPS Agreement, since the case concerns the protection of a DNA sequence as such, which is not linked to a function, and such protection is absolute under applicable national law under Article 1(1) of the European Directive which states:

"Member States shall protect biotechnological inventions under national patent law. They shall, if necessary, adjust their national patent law to take account of the provisions of this Directive."

ECJ did not accept the argument of Monsanto, since the Directive makes the patentability of a DNA

could only be enforced for their patented function. This decision has shown that biotechnological patents are not treated in the EU like other patents, which are based on the product and are given per se protection.

Actually, the parties had settled out of the court before the announcement of the ECJ ruling.[416] By this ruling patent rights were rendered enforceable depending on their functions. Biotechnology companies having patent protection in the EU needed to go through a detailed review of the functionality of their claims. The ruling does not only effect agricultural biotechnology, but also claims in diagnostic methods, and other medical applications of biotechnology where the claimed genetic material needs to perform its function.

This decision might have put the biomedical diagnostic companies in Europe at risk of patent enforcement of isolated nucleotides used as reagents, since these nucleotides do not perform their function in a reagent vial or kit. Genes do not mostly perform their functions in all tissues and at all times.[417]

One more point to note is that before the ECJ ruling there were also different outcomes at the Spanish, UK and the Dutch courts as to the applicability of EU Biotech Directive and the decisions given on the infringement of the Monsanto patent. The Spanish court had concluded that the EU Directive was applicable and there was no infringement. The UK Court on the other hand had concluded that the Directive was not applicable, the imported soy meals were indeed infringing the Monsanto patents, since in the UK the Directive only applied to patents filed after July 28, 2000 and the Monsanto

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sequence subject to indication of the performed function and ruled that this interpretation is indeed supported by the Article 9 of the Directive. An interpretation to grant patent protection to a DNA sequence irrespective of its function would deprive this provision of its effectiveness. So, the patent right should be conferred to the gene functioning in the soy plant, of which the soy meal is derived from. In addition, the ECJ also ruled that the TRIPS do not affect the interpretation of Article 9 of the Directive.

[416] Reuters – news "Monsanto settles Argentine soy import case", 5 July 2010 available at https://www.reuters.com/article/eu-monsanto-idUKLDE6641RB20100705 last visit 30.04.2020.

[417] MOHAN-RAM V., PEET R., VLAEMMINCK P. (2011). Biotech Patent Infringement in Europe: The "Functionality" Gatekeeper. *The John Marshall Review of Intellectual Property Law*, Volume 10, pp. 540-552.

had filed its application before this date.[418] The Dutch court, although in line with the Spanish ruling, referred the case to the ECJ with questions on applicability of the Directive and TRIPS. With the upcoming "unitary patents" within the EU and the Unified Patent Court (UPC), harmonization will be achieved in appeals, at least in the EU member states, that have signed (and ratified) the UPC Agreement.

4.1 Practice in the EU and at the European Patent Office

4.1.1 The Directive Approach

The Directive was published in 1998 after long discussions, rejections and amendments. Critics on the issue came not only from lobbies and NGOs but also from the governments of the non-ratifying member states.

Though the member states have meanwhile all implemented the Directive, it must be mentioned that the Directive had been challenged before the ECJ for an annulment by the Netherlands.[419] Italy and Norway (being a member of EEA) had supported the Dutch government in the case. Before mentioning the patentability of biotechnological inventions under the Directive, it is important to have a look at this case.

The case filed by the Netherlands was an objection to the Directive in its ends and in its means. The Netherlands considered that patentability of biotechnological material should be limited to the biotechnological process and not extended to the products deriving from them: that is to say, neither plants nor animals, including genetically modified plants and animals, nor human biological material should be patentable.[420] Mentioning the pleas briefly, the Netherlands considered that the Directive was:

1. incorrectly based on Article 100(a) of the EC Treaty, which aims to ensure

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[418] Ibid pp 544-545

[419] Case C-377/98 Kingdom of the Netherlands v European Parliament and Council of the European Union judgement of the Court of 9.10.2001 available at http://curia.europa.eu/juris/liste.jsf?language=en&num=C-377/98# last visit 30.04.2020

[420] See Opinion of the Advocate General on Case C-377 /98.

the approximation of laws among member states.

2. contrary to the principle of subsidiary as laid down by Article 3(b) of the EC Treaty.

3. contrary to the principle of legal certainty as such the Directive was worsening the legal ambiguities discussed in the recitals instead of clarifying them.

4. incompatible with international obligations by breaking the agreement on TRIPS and Convention on Biotechnological Diversity (CBD).

5. not in line with fundamental rights to respect human dignity as an element isolated from the human body is considered to be patentable according to Article 5(2) Besides the importance of consent of the donor or recipient of products obtained by biotechnological means and the absence of a special provision in this regard was argued to be undermining the right to self-determination.

6. not properly adapted by the Parliament and the Council due to some procedural failures.

The ECJ delivered its decision by rejecting all of the six pleas. One may conclude that the pleas 1, 2, and 6 are related to the formality of the Directive, however, the other pleas should be of specific interest for patenting biotechnological matter when regarded from law and economics point of view.

With respect to plea 3 the Netherlands firstly argued that, "the Directive gives the national authorities discretion in applying concepts expressed in general and ambiguous terms, such as order public and morality, which appear in Article 6." Secondly, it was stated that "there are unclear provisions in the Directive, particularly as regards the patentability of plant varieties[421], mentioned in Article 4(1) and (2), in Articles 8 and 9, and in the 31st. and 32nd. recitals of the preamble to the Directive."

[421] Although variety is a taxonomic rank in botany below species, what is meant by plant variety is a non-taxonomic, legal term. Likewise, the term "animal variety" caused a lot of discussions in EPO patents as explained in Chapter 4.1.2 on EPO Decisions

The ECJ stated firstly that "Article 6 rules out the patentability of inventions whose commercial exploitation would be contrary to ordre public or morality, …allows the administrative authorities and courts of the Member States a wide scope for maneuver in applying this exclusion…. The scope for maneuver left to Member States is not discretionary, because the Directive limits these concepts , in two ways: By stating that commercial exploitation is not to be deemed to be contrary to ordre public or morality merely because it is prohibited by law or regulation, and by giving four examples of processes or uses which are not patentable." (cloning humans, modifying humans' genetics, commercial /industrial use of human embryos, causing animals suffering in modifying their genetics without any substantial medical benefit). As a result, ECJ ruled that these concepts which do not exist in general patent law, are clarified by the Community legislature.

Therefore, the Court concluded that the Directive does not worsen legal uncertainty, on the contrary legal uncertainty is lessened through the Directive.

With regards to the patentability of plant varieties ECJ found no inconsistency: Article 4 of the Directive excludes plant variety from patenting but if the technical feasibility of an invention is not limited to a particular plant variety, it can be patented. It was stated:

> "That distinction is made clear by the 29th. to 32nd. recitals of the preamble to the Directive, which indicates that plant varieties as such are covered by the legislation on protection of new plant varieties, but that the protection of new varieties applies only to varieties which are defined by their whole genome. For plant groupings of a higher taxonomic level than the variety, defined by a single gene and not by the whole genome, there is no risk of conflict between the legislation on new varieties and the legislation on patents. Thus, inventions which incorporate only one gene and concern a grouping wider than a single plant variety may be patented.…, a genetic modification of a specific plant variety is not patentable but a modification of wider scope, concerning, for example, a species may be."

Therefore, patent claims can be made in respect of plant groupings.

On scope of protection as brought in Articles 8 and 9 the Court concluded that these articles "do not concern the principle of patentability but the scope of the protection conferred by the patent." These provisions allow for protection to biological material derived from that material through propagation or multiplication. Hence, "the protection conferred by the patent may therefore cover a plant variety, without that variety being patentable in itself."

Therefore plea 3 of the Netherlands was rejected.

With respect to plea 4 the Netherlands argued that "the Directive breaches the TRIPS Agreement of the WTO, Technical Barriers to Trade Agreement (TBT), European Patent Convention (EPC), and Convention on Biological Diversity (CBD)"; in particular where TRIPS Article 27(3)(b) allows Member States to exclude plants and animals other than micro-organisms from patentability but "the Directive does not allow Member States that possibility." The ECJ ruled out that "the option taken in Article 4 of the Directive is in itself compatible with TRIPS, which, moreover, does not prevent certain party States adopting a common position with a view to its application. The joint selection of an option offered by an international instrument to which the Member States are parties is an act that falls within the approximation of laws provided for by Article 100A of the Treaty".[422] Hence the Directive is not found to have affected international obligations. Indeed Article 1(2) of the Directive indicates clearly that it is without prejudice to the Member States' international obligations in particular the TRIPS and the CBD.

Regarding the EPC, the ECJ ruled that the EPC does not create obligations for the Community, as it is not a party to it.

On the TBT Agreement, the ECJ ruled that the "Directive does not contain any technical regulations within the meaning of the TBT Agreement". Such a regulation which describes "product characteristics or their related processes and production

[422] Currently Article 114 TFEU – after the Treaty of Lisbon.

methods" is defined in WTO Agreement. Hence a ruling on the issue was found unnecessary.

Regarding CBD the plaintiffs argued that one of the objectives of the CBD is the "principle of equitable sharing of the benefits arising out of the utilization of genetic resources" and making biotech inventions patentable is contrary to this. ECJ ruled that the "risks are expressed in hypothetical terms and are not derived directly from the provisions of the Directive 98/44/EC but, at the very most, from the use of them". The ECJ also emphasized CBD does not make granting of biotech patents conditional on the "consideration of the interests of the country from which the genetic resource originates or the existence of measures for transferring technology" and referred to Article 1(2) of the Directive on international obligations.

As it is seen by this ruling, the ECJ did not rule the enforceability of a WTO Agreement, but ruled that the courts should review the compliance with the obligations from the CBD agreement.

With regards to plea 5 the ECJ ruled since Article 5(1) excludes "the human body at the various stages of its formation and development" from patentability, human dignity is indeed safeguarded. Regarding work on the "sequence or partial sequence of human genes", the patentability is only possible if application discloses "the original method of sequencing, which led to the invention" and provides the industrial application.

As a result, it was verified once again by the decision of the ECJ that patent claims can only be made for inventive work and can be "extended to biological data existing in their natural state in humans only …(with) particular industrial application". The four examples in Article 6 (cloning human beings, modifying humans' genetics, commercial /industrial use of human embryos, causing animals suffering in modifying their genetics without any substantial medical benefit) that were deemed unpatentable for being contrary to ordre public, and which do constitute not an exhaustive list of exceptions according to Recital 38, were also found to be providing additional security in this regard.

Human dignity is thus found to be safeguarded according to the provisions of the

Directive.

With regards to second part of the fifth plea the ECJ actually recognized that not to obtain free and informed consent from the donor and recipient for all potential uses of biological material is actually a violation of fundamental rights. However, by stating that the scope of the Directive does not extend to activities before and after the patent grant, the ECJ considered these ethical concerns to be beyond the scope of the Directive. Besides a patent grant shall not impede legal limitations on research into patentable products or their commercialization as stated in Recital 14. The issue is transferred to national law under Recital 26 of the Directive.[423] As a result the Directive does not bring any sanctions in case of non-compliance with expression of free and informed consent. Although this ruling seems to be sustainable in itself, there is a discrepancy regarding the Article 6(1) of the Directive, which considers the inventions non-patentable where their commercial exploitation would be contrary to morality.[424] Accordingly if the commercial exploitation violates the fundamental rights by not obtaining free and informed consent of the donor, then it should be considered as immoral. But according to Article 6(1), the granting of the patent cannot be considered immoral, only the commercial exploitation. Moreover, the Recital 26 foresees the consent of the donor at the time of filing of the patent application. Therefore, the ambiguity in the Directive regarding the consent of donor remains. This issue has been a considerable point at the discussions around human embryonic stem cell patents in the EU as explained in Chapter 4.5

Accordingly, although Netherlands based its challenges on technical grounds, the concerns of unethical consequences of biotechnological research are obvious. There are many outcomes of the decision of the ECJ on the issues of limitations of the EC Treaty

[423] Recital 26: "Whereas if an invention is based on biological material of human origin or if it uses such material, where a patent application is filed, the person from whose body the material is taken must have had an opportunity of expressing free and informed consent thereto, in accordance with national law."

[424] Under plea 4 the Netherlands had emphasized the wording of Article 6(1) (inventions whose commercial exploitation would be contrary to ordre public or morality) with respect to Article 53 of the EPC (inventions the publication or exploitation of which would be contrary to ordre public or morality). The ECJ ruled that "… it seems reasonable to suppose that a breach of ordre public and morality as regards a specific invention could be equally well established by reference to its publication, exploitation or commercial exploitation."

and principles of harmonization and subsidiarity. The non-grant of the pleas can also be interpreted as an ECJ response that provisions of the Directive concerning patentability of isolated parts of body respect human integrity and dignity fully. However, although ECJ gave this response and upheld the conformity of the Directive with the EU law, the Directive caused so much resistance and opposition that the deadline of 30 July 2000 to transpose it into national law was respected only by few member states. By 2003 eight of the fifteen EU member states (Germany, Austria, Belgium, France, Italy, Luxembourg, the Netherlands and Sweden) had failed to harmonize their national laws with the Directive.[425] The Commission referred these states to the ECJ and started infringement proceedings. The ECJ convicted Belgium[426], France[427], Luxembourg[428], Italy[429], Germany[430] and Austria[431] for failure to implement the Directive. By June 2006 all 27 member states of the EU have implemented the Directive and latest member to the EU, Croatia had also adopted the legislation before joining the Union in 2013 as its 28th member state.[432]

In order to understand why this was the case, it is better to look at the process of adoption of the Directive. The motivation for the adoption of the Directive was to "establish a sound legal framework, which allowed European businesses to develop and

[425] See the press release of the Commission dated 10.07.2003 "Eight Member States referred to Court for failure to implement Directive on legal protection of biotechnological inventions" available at https://ec.europa.eu/commission/presscorner/detail/en/IP_03_991. Report from the Commission to the EP, the Council, the CoR and the EESC - Life sciences and biotechnology - A strategy for Europe - Third progress report and future orientations dated 29.06.2005 {SEC(2005)850} /* COM/2005/0286 final */ available at https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52005DC0286&from=EN last visit 30.04.2020.

[426] Case C-454/03.

[427] Case C-448/03.

[428] Case C-450/03.

[429] Case C-456/03.

[430] Case C-5/04.

[431] Case C-4/04.

[432] See the press release of the Commission dated 30.06.2006 "Commission acts to ensure 14 Member States implement EU laws" available at https://ec.europa.eu/commission/presscorner/detail/en/IP_06_900 last visit 30.04.2020.

market the products and processes derived from genetic engineering".[433] The European Parliament had initially vetoed the Directive in 1995, but in a later draft in 1996, the Commission introduced some changes especially to address the ethical concerns of the Parliament. Critics of the Directive claimed that these changes were minor, and the Parliament had actually foregone its concerns due to pressure from patient interest groups sponsored by the biotechnology industry.[434] On July 6th of 1998, the final version of the Directive was adopted. Hence it can be said that although some ethical and social aspects were introduced to the Directive, the main concerns in adopting the Directive were to assure adequate legal protection for high-risk investments in the field of biotechnology and to assure harmonization among member states.[435] It was the biotechnology industry in Europe that was being protected. The exceptions to patenting due to "ordre public" do not change this fundamental characteristic of the Directive. The ECJ also recognized this fundamental characteristic; it has approached patenting of biotechnological inventions as an industrial issue, and not as a social or moral issue per se. It upheld in its decision that the protection of biotechnological inventions was appropriate under the existing patenting regime provided that the applications fulfill the requirements of patentable subject matter. The Court did not address the issue to what extend the patenting of biotechnological inventions is a matter of the existing patent regime and biotechnological inventions can be regarded like any other inventions. If this consideration was taken into account, alternative protection mechanisms could also be discussed in the EU.

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[433] "Development and implications of patent law in the field of biotechnology and genetic engineering" Report from the Commission to the European Parliament and the Council COM (2002) 545 Final Brussels, Belgium 07.10.2002 p. 4, available at http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52002DC0545&from=EN last visit 30.04.2020.

[434] Corporate Europe Observer, Quarterly Newsletter, Issue 1, May 1998, *"Industry and the EU Life Patent Directive";* available at http://archive.corporateeurope.org/observer1/patents.html#note8; last visit 30.04.2020.

[435] Recitals 1-3 of the Directive read as follows: "(1) Whereas biotechnology and genetic engineering are playing an increasingly important role in a broad range of industries and the protection of biotechnological inventions will certainly be of fundamental importance for the Community's industrial development; (2) Whereas, in particular 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; (3) Whereas effective and harmonized protection throughout the Member States is essential in order to maintain and encourage investment in the field of biotechnology."

The ECJ also stated that the Community is competent under Article 100A[436] to harmonize intellectual property laws. And this again fits to the motivation of the Directive; harmonization of patent laws for the well-functioning of the internal market and increased competitiveness of European biotechnology industry against foreign competitors.[437] If, however, a socially efficient approach would be taken into consideration alternatively, the validity of the Directive would be questionable.

The effect of the EU Biotech Directive on EPO proceedings is huge in the interpretation of law. For instance, the legal provisions of EPC have been changed to align with the Directive so that animals and plants obtained by essentially biological processes cannot be patentable subject matter (explained in detail in Chapter 6) and also by Brüstle Decision of the CJEU in 2011 defining the term "human embryo" and excluding from patentability (explained in detail in Chapter 4.5). As a result, the EPO revised its examination guidelines, although it is not bound by CJEU decisions.

4.1.2 EPO Decisions

4.1.2.1 Transgenic Animals

With regards to discussions concerning patentability of transgenic animals and of life we must address the famous Onco-Mouse decision of the EPO for a genetically altered mouse by the Harvard University to be used in cancer research. The inventors had developed a method to add a gene susceptible to cancer into DNA of the animal, so that development of animal models could be used in testing progress of the chosen chemical compounds. The examining division refused the patent among others pursuant to EPC Article 53(b) which excludes animal varieties from patenting (citing also French and

[436] Currently Article 114 TFEU – after the Treaty of Lisbon.

[437] Recital 7 of the Directive reads as follows: "Whereas uncoordinated development of national laws on the legal protection of biotechnological inventions in the Community 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;"

German texts with different "animal variety" terminology). When deciding on the patentability of the Onco-Mouse in Europe, the EPO Board of Appeal concluded that the legislators' intention had not been to exclude animals generally from patenting. Otherwise, they would have stated this in "unambiguous terms". Article 53(b) excludes "certain groups of animals from patentability, but not animals as such.[438] The case was remitted to examining division, adding order public and morality considerations into account to weigh the suffering of animals and environmental risks against the usefulness to mankind. On appeal the examining division concluded three different interests needed to be balanced:[439]

> "…there is a basic interest of mankind to remedy widespread and dangerous diseases, on the other hand the environment has to be protected against the uncontrolled dissemination of unwanted genes and, moreover, cruelty to animals has to be avoided. The latter two aspects may well justify regarding an invention as immoral and therefore unacceptable unless the advantages, i.e. the benefit to mankind, outweigh the negative aspects ... The present invention's usefulness to mankind cannot be denied. Cancer is one of the most frequent causes of death in many countries of the world and also causes severe suffering. Any contribution to the development of new and improved human anti-cancer treatments is therefore a benefit to mankind and must be regarded as valuable and highly welcome by everybody. Legislation in Contracting States allows animal testing under certain restrictions and subject to administrative approval … The mere fact that uncontrolled acts (release into environment) are conceivable cannot be a major determinant on patent grant."

Regarding Article 53(b) exceptions to patentability, the Division concluded that patent claims on non-human mammals and rodents are not covered in this exception that a claim to a transgenic mammal/rodent does not mean a claim on an individual animal

[438] T 19/90 Onco-Mouse of 03.10.1990

[439] Decision of the opposition division Grant of European patent No. EP 0 169 672 (Onco-mouse/ Harvard) OJ EPO 1992 /10 pp.591-593.

variety.

Hence the first patent on Onco-Mouse by EPO was granted in 1992.[440]

The patent was originally applied to all transgenic mammals having Onco-Mouse engineering technology. When many parties appealed the EPO decision, it was restricted in 2001 to cover rodents only.[441]

In 2003 there were additional oppositions. The Ground for appeals based on wrong interpretation of EPC Articles 53 (a) and (b). In 2004 the Board of Appeal further restricted the patent to mice only.[442] The revocation of the patent was finally published in 2006.[443]Although the case was resolved in 2006, it has been a lengthy and complex one. According to EPC Article 53 (a) the patents are not granted to inventions contrary to ordre public or morality. And as explained above according to Article 53 (b) patents are not granted for "animal varieties or essentially biological processes for the production of animals". The EPO had concluded that Onco-Mouse was not an animal variety and claims were directed to non-human mammals and rodents, so that they were not covered by Article 53 (b).

For the exclusion on grounds of ordre public and morality under Article 53 (a), EPO made a utility test, weighing the suffering of the animal with the potential benefit to mankind. It was presumed that since animal testing in cancer research was essential in general, and the number of animals required in the claimed method was less than the number in conventional testing, ordre public/ morality clause of the EPC did not prevent the patenting of Onco-Mouse.

On the other hand, patentability of a mouse for experimental purposes of hair

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[440] Patent No: EP 0 169 672

[441] EPO Decision of the Opposition Division dated 7 November 2001, OJ10/2003 pp. 473-506.

[442] T 0315/03 (Transgenic animals/HARVARD) of 6.7.2004

[443] See European Patent Bulletin (33/2006) of 16.08.2006 Part II.7(3) Revocation of the European Patent 0 169 672 at p.761.

growth was rejected by the EPO, with the reasoning that the suffering of the animal, and the possible danger to the environment, does not outweigh the benefit of the invention for mankind.[444]

As it may be seen from the practice, the EPO had a utilitarian approach on the issue. The exceptions to patentability of invention with regard to biotechnological inventions were evaluated with the possible harms and benefits of the invention. How the exception to the patentability of invention with regards to ordre public and morality would apply to biotechnology seems to be well determined in the above-mentioned practices. Still there is a huge time between the first application of the inventor done in 1985, and the finalization of the case in 2006. On contrast, the patentability of the Onco-mouse was rather a smooth case in the US. USPTO granted the patent in 1988 with a broad scope[445] and the patent was not challenged at all till its expiry in 2005. There were even two following patents granted to Harvard University for a method of providing a cell culture from a transgenic non-human mammal[446] and testing methods for a material suspected of being a carcinogen using transgenic mice containing an oncogene sequence.[447]

4.1.2.2 Transgenic Plants

Plants into which a foreign plant, animal or human gene is incorporated by biotechnological methods are called transgenic plants. Transgenic plants are used in medical biotechnology to produce human and animal vaccines.[448] The efficacy of these

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[444] HO, C. (1992), Building a Better Mousetrap: Patenting Biotechnology in the European Community, *Duke Journal of Comparative and International Law*, Volume 3, pp. 173-201.

[445] US Patent No: 4,736,866 with claims on nonhuman mammals.

[446] US Patent No: 5,087,571

[447] US Patent No: 5,925,803

[448] A vaccine from trans-genetic tobacco plant is found to be safe on humans against non-Hodgkin's lymphoma cancer; see MCCORMICK, A.A et al. (2008). Plant-produced idiotype vaccines for the treatment of non-Hodgkin's lymphoma: Safety and immunogenicity in a phase I clinical study. *Proceedings of the National Academy of Sciences*, Volume, 105, Issue 29, pp 10131-10136.

Similarly, the use of a transgenic tobacco variety is found to be safe and effective in producing vaccines

vaccines in human use still needs to be researched further, but the vaccines have found to be safe and effective in animal use. Edible vaccines produced with the help of transgenic plants are considered to reduce the cost of administering (transport, storing, distribution and other logistics) of vaccination especially in the developing countries.[449]

With regards to patentability of transgenic plants there are different decisions of the EPO. A patent shall not be granted for a single plant variety but can be granted if varieties are not individually claimed.[450]

Conflicts arose as regards patentability of plants due to "product of nature" doctrine which considers the new plants as manifestation of nature, hence the longstanding tradition against patenting of laws of the nature.[451] As explained by Van Overwalle (1999) one objection against patenting of plants was that breeders' products could not comply with novelty requirement. Another objection to plant patenting arose as the subject matter of plant inventions are living organisms and patents are tailored to be granted to inanimate techniques. Hence, breeders' products should be excluded not "because they lack a creative step, but because of the special nature of the inventive subject, a position which reflects an inveterate distrust of techniques affecting living nature".[452]

Here the decision G 1/98 of the EPO[453] can be examined. Main points that led to

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against pig diarrhea. See BAE et al. (2003). Induction of antigen-specific systemic and mucosal immune responses by feeding animals transgenic plants expressing the antigen, *Vaccine*, Volume: 21, Issue: 25-26, pp 4052-4058.

[449] By incorporating genes into plants vaccines could be produced against various diseases such as respiratory problems, diarrhea, tetanus, cholera and hepatitis. So far lettuce, tomato, potato, papaya, carrot, quinoa and tobacco have been converted into vaccines. See KURUP, V. M. & THOMAS J. (2020). Edible Vaccines: Promises and Challenges. *Molecular biotechnology*, Volume 6, Issue 2, pp 79-90.

[450] EPC Art. 53(b) excludes plant varieties from patentability. However, in Decision G 1/98 the EPO Enlarged Board of Appeals concluded that a claim where specific plant varieties are not individually claimed does not fall under the Art. 53(b) exception, even if one or more plant varieties are embraced by this claim.

[451] DAVIS, M.D. (1995). The Patenting of Products of Nature. *Rutgers Computer & Technology Law Journal*, Volume 21, pp.293-349.

[452] VAN OVERWALLE, G. (1999). Patent Protection for Plants: a Comparison of American and European Approaches. *IDEA-Journal of Law and Technology,* Volume 39, pp. 143-194.

[453] Decision G 1/98 Transgenic plant/NOVARTIS II of 20.12.1999 upon the referring decision of the Technical Board of Appeal T 1054/96 (Transgenic plant/NOVARTIS, OJ EPO 1998, 511)

this decision was the question referred in the Technical Board of Appeals Decision were

- whether a claim which relates to plants but wherein specific plant varieties are not individually claimed automatically avoids the prohibition on patenting in Article 53(b) EPC even though it embraces plant varieties,
- whether the provisions of Article 64(2) EPC [454] should be taken into account when deciding on acceptable claims,
- whether plant varieties were patentable if each individual plant of that variety is produced by recombinant gene technology or by a microbiological process, which is outside the scope of Article 53(b) (which cites essentially biological processes).

The argument of Novartis (the applicant) was that claims where particular plant varieties are not individually embraced do not fall under exclusion under Article 53 (b) EPC. This view is also in line with Article 4(2) of the Directive 98/44/EC.[455]

The main conclusions of the decision G 1/98 are:

- "A claim wherein specific plant varieties are not individually claimed is not excluded from patentability under Article 53(b) EPC even though it may embrace plant varieties.
- When a claim to a process for the production of a plant variety is examined, Article 64(2) EPC is not to be taken into consideration.
- The exception to patentability in Article 53(b), EPC applies to plant varieties irrespective of the way in which they were produced. Therefore, plant varieties containing genes introduced into an ancestral plant by recombinant gene technology are excluded from patentability." Besides genetic engineering processes were not deemed

[454] Article 64 (2) EPC reads as "If the subject-matter of the European patent is a process, the protection conferred by the patent shall extend to the products directly obtained by such process."

[455] The article reads as "Inventions which concern plants or animals shall be patentable if the technical feasibility of the invention is not confined to a particular plant or animal variety."

microbiological processes.

Hence it may be noticed that the EPO decision was in accordance with the Directive 98/44/EC. Indeed, the EC Directive only foresees harmonization of national patent laws of the EU Member states, but not an approximation of the EPC, since the Directive is not binding on non-EU contracting states. On the other hand, the Directive was adopted by the EPO into its implementing regulations in 2001 (the Rules 23 b-e of the implementing regulations to the EPC were adopted from the Directive 98/44/EC).[456] As a result although the Directive does not have a direct effect on the EPC, the approximation of national laws of the EU member states has come to affect the Convention.

4.1.2.3 Human DNA

With regards to patentability of human DNA and issue of consent, Relaxin[457] decision of the European Patent Office can be mentioned. The patent was granted to "molecular cloning and characterization of a further gene sequence coding for human relaxin".[458] Relaxin is a hormone produced in the placenta of a pregnant woman that relaxes the uterus and thereby assists in labor. Outside of pregnancy, relaxin is also produced during the formation of new blood vessels, during wound healing, as a result of which, it is considered to be an ideal candidate for production of medications. The decision of the EPO was appealed by the Greens of the European Parliament with 2 pleas:

- subject matter having lack of novelty and inventive-step, since the gene sequence of a human hormone had to be regarded as a discovery.
- and contrary to ordre public and morality, since the samples had to be taken from

[456] Rule 23b (1) of the Implementing Regulations reads as "For European patent applications and patents concerning biotechnological inventions, the relevant provisions of the Convention shall be applied and interpreted in accordance with the provisions of this chapter. Directive 98/44/EC of 6 July 1998 on the legal protection of biotechnological inventions shall be used as a supplementary means of interpretation."

[457] T_0272/95 Howard Florey Institute / Fraktion der Grünen im EP of 23.10.2002

[458] European Patent No EP 0303033B1

a pregnant woman.

The appeal was rejected by the decision of the Technical Board of Appeal of October 23rd of 2002 as stated:

> "In its decision (OJ EPO, 1995, 388), the Opposition Division concluded under Article 53(a) EPC that an invention concerning a human gene was not an exception to patentability because it would not be universally regarded as outrageous: it did not amount to patenting life because DNA as such was not life but one of the many chemical entities participating in biological processes, no offence to human dignity had occurred, as the woman who donated tissue was asked for her consent and her self-determination was not affected by the exploitation of the claimed molecules. Under Article 52(2)(a) EPC, it was decided that in accordance with the long-standing EPO practice the claimed DNA fragments which were new in the sense of having no previously recognized existence were not to be considered as discoveries and, therefore, did not fall within the category of unpatentable inventions. The existence of the claimed DNA fragments was not known or even hinted at before the priority date of the patent in suit. The requirements of novelty and inventive step were fulfilled."

The decision emphasizes long-standing EPO Practice in granting patents to DNA fragments that have no previous recognized existence. As a result, a biological material from humans does not lack novelty and inventive step simply by being a part of human body. It is interesting to note that the EPO differs from the ECJ's decision on human embryonic stem cell patents (explained in Chapter 4.5) as the EPO decision implies human dignity is not offended, since the woman, who donated the tissue samples had given her consent. Otherwise, the invention would be excluded from patentability.

Besides the Relaxin case, the Alpha-Interferon[459] case can also be mentioned with regards to the novelty criterion. EPO concluded that a DNA sequence reserved in a well-known gene bank was not found to be in breach of novelty criterion, since the full

[459] T_0301/87 BIOGEN /Alpha-Interferon 16.2.1989.

characteristics of its isolation were not disclosed.

> "…the mere existence of a DNA sequence within ..gene bank cannot automatically mean that the chemical compound .. concerned does become part of the state of the art. The latter would only then be the case if the existence of the compound concerned had recognisably been made publicly available."

Hence the mere existence was regarded insufficient to challenge the novelty criterion and the claims were found to be novel. In a follow-up decision Biogen.[460] the appellants called for the revocation of the patent given to Biogen on recombinant DNA molecules comprising Hepatitis B virus[461] arguing that the claimed DNA sequences lacked novelty, since they were not substantially different from those disclosed in the prior art and could be anticipated thereof. . However, EPO concluded that:

> "…it is well known that even a change in one amino acid can dramatically change the properties of a protein molecule."

As a result, the arguments stated by the appellants and the intervener to challenge novelty on the grounds of having solely small differences was not accepted by the Board. Moreover, the Board found that a comparison between the claimed sequence and the known sequence would be theoretical since discrete fragments were not disclosed and made available to the public as required by EPC Art. 54(2). Hence the claims were found to be novel.

The description of the DNA Sequences must be done in accordance with Article 83 of the EPC.[462] In the Case Erythropoietin / KIRIN – AMGEN[463] the Board of Appeal of the EPO concluded that:

> "Whether this product claim can stand for the purposes of

[460] T 0886/91 Hepatitis B virus/ BIOGEN INC. of 16.6.1994

[461] European Patent No 0 013 828.

[462] Article 83 reads as: The European patent application must disclose the invention in a manner sufficiently clear and complete for it to be carried out by a person skilled in the art.

[463] T 412/93 of 21.11.1994

> Article 83 depends on whether what is claimed can be identified, and whether a reliable method existed for making it, using the teaching of the patent and common general knowledge available at the priority. For a cDNA the identification need not consist in a definition of the base sequence, provided either explicitly or implicitly a method for making the cDNA is made available by the patent application."

The disclosure requirement in the EU system does not necessitate the disclosure of the base sequence definition. It is even possible to make a claim by disclosure of the method for making the substance, i.e., without making the substance. This point of view is very much different than the US system, as will be examined in Chapter 4.2.

4.1.3 Patenting of diagnostic methods; the Myriad Genetics case

There have been numerous controversies of gene patenting, but Myriad case must be one of the most referred ones in literature. The case raised concerns as described in "tragedy of anticommons", as well as concerns over patentee's monopoly rights allowing him to exercise excessive pricing and to exclude others from accessing the innovation.

In general, the European Court of Justice allows IPR holders to extract monopoly returns. According to EC Competition Legislation, it is acceptable for an undertaking to hold a dominant position, yet the abuse of dominant position and any conduct that prohibits competitive behavior is forbidden.[464] Hence the problem with Myriad patents in the EU was not that the company had acquired a monopoly power and demanded excessive prices on its test, but it had abused this power by refusing to grant full sequence screening licenses. The company required that the samples had to be sent to its laboratory in the US.[465]

Certain mutations of BRCA1 and BRCA2 genes have been found to be linked to

[464] Joined Cases C-241/91 P and C-242/91 P "RTE and ITP v EC Commission" (Magill Case) - of 6.4.1995.

[465] See Gold & Carbone at supra note 177.

breast and ovarian cancer. Myriad Genetics Inc. together with University of Utah Research Foundation was the first one to sequence BRCA1 gene and was granted patent protection over the sequenced gene with several mutations of the gene and their related diagnostic test in the US throughout 1997 and 1998.[466] In 1998 and 2000 the company was granted patent protection by USPTO on BRCA2 gene, as well.[467]

The company received three European Patents on BRCA1 gene in 2001.[468] In 2003 a patent was also granted for the mutations of the BRCA2 gene and its diagnostic testing.[469] Having those patents Myriad received control over diagnostic testing of these gene mutations and started to offer 3 different types of diagnostic testing: comprehensive testing (for full sequencing of both genes), single site test, multisite 3 test (for 3 mutations of the genes, which are found to be frequent especially among Ashkenazi (Eastern and Central European Jewish women) at quite a high price. Moreover, acquiring genetic data for testing would render the company to work on further diagnostic and treatment methods.[470]

Due to controversies explained in Chapter 2.5, and also the fact that the cheaper methods of testing have become available in Europe, but their use was obstructed by the Myriad patents, European Parliament issued a resolution, expressing its disappointment at the possible consequences of the granting by the European Patent Office of a patent on a human gene and calling on the European Patent Office "to ensure that all ... patent applications in Europe do not violate the principle of non-patentability of humans, their genes or cells in their natural environment…"[471]

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[466] US Patents No: 5,693,473; 5,709,999; 5,710,001; 5,747,282; 5,753,441; 6,162,897

[467] US Patents No: 5,837,492 and 6,033,857

[468] European Patents No: 699 754; 705 902 and 705 903

[469] European Patent No 785 216

[470] See Gold & Carbone at supra note 177.

[471] European Parliament resolution on the patenting of BRCA1 and BRCA2 genes, 03.10.2001 available at http://www.europarl.europa.eu/sides/getDoc.do?pubRef=-//EP//TEXT+MOTION+P5-RC-2001-0633+0+DOC+XML+V0//EN last visit 30.04.2020.

Curie Institute of France (supported by some other research institutions, as well as individuals in Europe and Greenpeace) challenged in 2002 European Patent BRCA1 of the Myriad Genetics on three grounds: [472]

- lack of novelty (with the argument that methods for breast cancer tests were available long before the Myriad patent),
- lack of inventive step (with the argument that the sequence patented by Myriad was partially developed from public database),
- inadequate description (with the argument that the sequence published by Myriad was not disclosed fully for a person skilled in the art to carry out).

In its ruling on 18 May 2004 EPO revoked the BRCA1 patent of Myriad announcing its claims invalid due to a few minor errors in the gene's sequence in its US application leading to EPO gene patents losing their priority dates.[473]

Although the BRCA2 patent was granted by EPO in January 2003, in December 2003 and in the upcoming years Curie Institute (again supported by various other institutes such as the Belgian Society of Human Genetics) also challenged several Myriad patents and filed opposition proceedings at EPO and succeeded in limiting the scope of the patents.[474]

The case on Myriad emerged not only from the abuse of monopoly power, that the company was asserting for the tests to be carried on in its own laboratories, but also from concerns about the limitations of patenting on further research, such as development of new diagnostic methods, as well as limitations on access to testing.

During the proceedings for the Patent No 699,754 on BRCA1 it was revealed that

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[472] For BRCA1 gene patents EP 705 902: 17q-Linked breast and ovarian cancer susceptibility gene and EP 705 903: In vivo mutations and polymorphisms in the 17q-linked breast and ovarian cancer susceptibility gene.

[473] Patent EP 699 754 Method for diagnosing a predisposition for breast and ovarian cancer.

[474] See EPO Board of Appeal Decision T 0666/05 Mutation/UNIVERSITY OF UTAH of 13.11.2008

there were in fact errors in the first patent application, i.e., the claim was not fully disclosed, and by the time it was fully disclosed in the amended application, it was not novel anymore.[475] Hence the First Instance decision of EPO in May 2004 revoked the patent No 699,754. The other two patents were also limited in scope in such a way that the diagnostic testing was excluded. Meanwhile in November 2004 Myriad transferred all its rights over the patents to University of Utah Research Foundation, hence it was no longer the owner of the genes, but retained the license for their use.[476]

But after the appeal of University of Utah Research Foundation, on 19 November 2008 the Technical Board of Appeal of EPO overruled the first decision for the Patent No 699,754 and decided that the patent may be maintained in its amended and limited form so that the patent would now cover methods for diagnosing a predisposition resulting in breast and ovarian cancers caused by mutations of the BRCA1 gene.[477] The patent would not cover claims to the BRCA1 gene itself, or for all of the mutations of the gene. On 29 June 2005 EPO also ruled that the patent No 785216 on BRCA2 gene could be upheld in its amended, limited form, so as to cover only the mutation in Ashkenazi women. Obviously, EPO had to give its decision within the limits of patent law, as regards what could be deemed novel, inventive, and industrially applicable and the claim for the Ashkenazi women seemed to meet these criteria. However, separating one ethnic group from the others also raised concerns as regards access to diagnostic methods. Women, who were not of Ashkenazi origin or who were not aware of their ethnic origin would be entitled to a diagnostic test free of charge, but health care providers treating women of Ashkenazi origin would have to pay a license fee for this test. It is not hard to imagine that women of this origin would have to pay higher health insurance premiums. In October 2007 EPO Board of Appeal rejected the appeal of the University of Utah Research Foundation/Myriad Genetics and remained partial revocation of the patent No 705902 related to BRCA1 gene. Later in January 2011 EPO Board of Appeal rejected the

[475] WIPO Magazine (2006), *Bioethics and Patent Law: The Case of Myriad*, Issue 4, pp.8-9.

[476] See Gold and Carbone at supra note 177.

[477] T 0666/05 - Mutation/UNIVERSITY OF UTAH of 13.11.2008

appeal of University of Utah Research Foundation/Myriad Genetics for the refusal of the patent application over BRCA2 gene on the grounds that subject matter of the claims even in the amended form was not novel.[478]

The Myriad Case created discussions not only on validity of gene patents (and that the original BRCA1 and BRCA2 patents were all wrongfully granted), but also on the licensing practices for such patents. In 2006 OECD issued "Guidelines for the Licensing of Genetic Inventions", which encouraged the rapid dissemination of information especially as regards to diagnostic methods in human genetic testing.[479] Similarly, National Institute of Health of the US also issued guidelines.[480]

It must also be noted that the European Parliament, who had supported the European Biotechnology Directive, indeed conflicted with itself by calling European Patent Office not to grant patents to Myriad over human genes.

4.1.4 Patenting of treatment methods

Treatment methods practiced on human / animal body are not patentable according to Article 52(4) of the EPC 1973 as not having industrial applicability.[481] Article 53(c) of EPC 2000 confirmed this provision.[482] This provision allows savings in time and efforts during the treatment of a patient. However according to Article 52(4) of EPC 1973

[478] T 0156/08 - BRCA2/UNIVERSITY OF UTAH of 14.1.2011

[479] See infra note 710.

[480] NIH Guide of 07.05.2004 - NIH Policy on Sharing of Model Organisms for Biomedical Research. The policy document supports the timely sharing and distribution of resources in biomedical research.

[481] Former Article 52(4) reads as "Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body shall not be regarded as inventions which are susceptible of industrial application within the meaning of paragraph 1. This provision shall not apply to products, in particular substances or compositions, for use in any of these methods."

[482] Article 53(c) reads as "Methods for treatment of the human or animal body by surgery or therapy and diagnostic methods practiced on the human or animal body; this provision shall not apply to products, in particular substances or compositions, for use in any of these methods."

inventions in which products, substances or compositions used in therapeutic or diagnostic methods are not exempted from having industrial application and may be patentable.

Similarly, according to Articles 54(4) and 54(5) of EPC 2000, any substance or composition, for use in a (treatment) method provided that this use is not comprised in the state of the art shall be patentable.[483] Article 54(5) EPC 1973 also allowed for an exception to the novelty rule for clinical products. It is stated that even if such a product is not novel itself, but its use in a treatment method is novel, it may be patentable.

These provisions allowing flexibility in the novelty criteria for the use of a known substance or compound were applied by EPO for the first use of products in clinical / therapeutic methods. However, this rule was allowed in the first use and once a medical use of a known substance was also known, so it lacked novelty under provisions of Article 54. By the time it became apparent to consider the subsequent uses and EPO started to recognize the novelty of the claims by the so-called "Swiss" type of claims with the "Eisai" decision so that the claims refer to the manufacturing process, when they are part of a non-patentable subject matter.[484]

When EPC 2000 came into force, it brought some changes in this regard. First of all, when talking about non-patentability of treatment methods, Art. 53(c) removed the part about industrial applicability in Art. 52(4) EPC 1973. Secondly, in terms of novelty Art. 54(4) and Art. 54(5) EPC 1973 are similar, but EPC 2000 emphasizes more specifically any "such" method (of treatment), besides in Art. 54(5) "such" use. Thirdly according to the new Art. 54(3) early dates of filing for late publishing of applications are considered state of the art in all countries. In EPC 1973 Art. 54(4) allowed for having

[483] Article 54 (4) and 54(5) bring the legal criteria that even the substance or composition were compromised in the art, meaning they were not novel, if they are claimed for a new use that Article 53(c) exceptions apply.

[484] See EPO Decision No: G 5/83 of 5.12.1984 for second medical indication and Swiss type of "use claim" for the appellant Eisai Co. Ltd.

priority in the designated Contracting States where the two applications were filed. This is a significant difference in the evaluation of novelty requirement. Fourthly, Article Art 54(5) EPC 2000 provides scope for the second or subsequent medical use. In Article 54(5) of EPC 1973 this scope was not clear for the subsequent uses after the first use. The ambiguity had been solved by the case law of the EPO – Enlarged Board of Appeals, with Eisai decision, by a formula applied by the Swiss Federal Intellectual Property Office. It is stated in this decision that "Claims directed to the use of a substance or composition for the preparation of a pharmaceutical product are equally *clearly directed to inventions which are susceptible of industrial application*(emphasis added), within the meaning of Article 57 EPC"[485] It is further noted that the Enlarged Board has carefully analyzed protection of second and subsequent medical indications by the use of a substance/ composition for the manufacture of a medicament for a new therapeutic application and concluded that "such claims do not conflict with Article 52(4) EPC or Article 57 EPC but there may be a problem concerning the novelty of the invention".[486] If the medicament has novel features, such as new dosage, formulation, patentability requirements will be met and the novelty will not be challenged regardless of the fact whether the claims are directed to the medicament or to the use of the active ingredient in preparation of the medicament.

In short EPO -Enlarged Board of Appeals concluded that claims having industrial application under Article 57 EPC 1973 did not conflict with Article 52(4) EPC 1973 on patentability exceptions to treatment methods practiced on human body; since these are deemed not susceptible of industrial applications. However, problems concerning novelty of these claims were recognized. Because the medicament itself was evidently not novel, hence the innovators were not subject to novelty exception, as set out in Article 54(5) EPC. To solve this problem EPO concluded that the novelty requirement necessary for the concerned medicament will be derived from the new pharmaceutical use and this shall apply "irrespective of the fact whether a pharmaceutical use of the medicament was

[485] Ibid reasons point 16.

[486] Ibid reasons point 19.

already known or not".[487] Consequently "Swiss" types of claims were enabled for the first and the subsequent pharmaceutical uses. It was also emphasized that "the application of this special approach to the derivation of novelty can only be applied to claims for substances or compositions intended for use in methods referred to in Article 52(4) EPC."[488] It was also asserted that "the intention of Article 52(4) EPC was only to free from restraint non-commercial and non-industrial medical and veterinary activities."[489] It was further considered "legitimate in principle to allow claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application, even in a case in which the process of manufacture as such does not differ from known processes using the same active ingredient".[490]

Similar reasoning was applied also using the equivalent provisions of EPC 2000.[491] Boards of Appeal cited the Eisai decision concluded that Article 54(5) EPC 1973 did not intend to "exclude second (and further) medical indications from patent protection other than by a purpose-limited product claim".[492] It also seemed not likely in terms of EPC or legislative history "to exclude second (and further) medical indications generally from patent protection".[493] Hence revised EPC Art. 54 (5) was interpreted for having the intention to allow for purpose-related patent protection for each new medical use of an already known substance or composition.

To summarize, the Enlarged Board of Appeal ordered in the Eisai decision that "a European patent may be granted with claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive

[487] Ibid reasons point 21.

[488] Ibid reasons point 21.

[489] Ibid reasons point 22.

[490] Ibid. reasons point 23.

[491] See for instance T 2369/10 Cranial nerve stimulation for treatment of substance addiction of 13.11.2015

[492] Ibid reasons point 4.

[493] Ibid reasons point 4.

therapeutic application."[494] Nonetheless patent protection for the use of a substance/composition for the therapeutic treatment of human / animal body was not permitted.

After the Eisai decision, the EPO Technical Boards of Appeal concluded in 2004 that patent protection by means of second medical use is not limited to novel medical conditions and it can be granted for substances for use in novel ways of drug administration on well- known indications and former case law extended the second medical use to cover such cases where "the treatment of the same disease with the same compound could also represent a novel therapeutic application, when it is carried out on a new group of subjects which is distinguished from the former group".[495] This may relate to for instance specification of a new dosage regimen for basically known medical treatments in order to lessen the toxicity and/or side effects of medicaments. It was also indicated in the 2004 decision that the Eisai decision had a "certain logical discomfort …treating as the basis for novelty under Article 54(5) EPC, the very feature which Article 52(4) EPC specifies not to be an invention capable of industrial application"[496]. This logical discomfort was "assuaged by treating this as a pure fiction to ensure the freedom of physicians (but not the freedom of suppliers)"[497], and the hope was expressed that with the new EPC 2000 this would be removed for all countries. The legal fiction on lack of industrial applicability to ensure freedom of physicians was developed due to public health considerations so that the physicians should not be obstructed by patents in treating a disease.[498]

In short if any known substance was found to have a new therapeutic application, the invention was protected by the "Swiss" type of claim, for the use of this substance in

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[494] G 5/83 Order 1.

[495] T 1020/03 Method of administration of IGF-I/GENENTECH INC. of 29.10.2004 reasons point 29.

[496] Ibid reasons point 73.

[497] Ibid.

[498] BROWN, J. (2008). Medical use patents in Europe – EPO and UK approaches, paper submitted to the 16th Annual Fordham IP Conference, available at http://fordhamipconference.com/wp-content/uploads/2010/08/Medical-Method-Patents-in-Europe-EPO-and-UK.pdf last visit 30.04.2020.

the preparation of a medicament. With the enforcement of EPC 2000, the part about industrial applicability was removed by Article 53(c). Article 53(c) EPC 2000 assures that medical methods are not patentable, excluding products, especially substances/ compositions, for use in these methods.

In terms of novelty Article 54(4) EPC 2000 is similar to Article 54(5) EPC 1973, but it refers more specifically to any "such" method. Priority dates for earlier filings and later applications are valid for all contracting countries in the revised EPC.

Article 54(5) EPC 2000 provides scope for the second or subsequent medical use and allows the patenting of substances/ compositions use in a (pharmaceutical) method, provided that such use is not included in the state of the art. Hence, by allowing explicitly claims related to further uses of a known substance, there is no more need for a case law.

The implications of these amendments should be seen in the medical use claims in patent applications. The claims for the second or subsequent use should be formulated in such a way that they are related to the use, such as "the use of Substance A in the treatment of Disease C", whereas the Swiss type of claim was formulated in the following way "the use of Substance A for the manufacture of Medicament B in the treatment of Disease C". Hence, Swiss type of claims were expected to be less often after the enforcement of EPC 2000. Indeed in 2010 EPO ruled the abolition of Swiss type of claims for the second or subsequent medical use with the justification that Swiss type of claims were objected as not having legal clarity due to the "absence of any functional relationship of the features (belonging to therapy) conferring novelty and inventiveness, if any, and the claimed manufacturing process".[499] Because although Swiss type of claims described a method for the manufacturing of a medicament, the invention was indeed related to the use of the medicament. Therefore, "where the subject matter of a claim is considered novel only by a new therapeutic use of a medicament, such claim was no longer allowed to have the format of a so called Swiss-type claim" introduced by Eisai Decision.[500]

[499] Decision G 2/08 Dosage regime/ABBOTT RESPIRATORY of 19.02.2010. reasons point 7.1.3.

[500] Supplementary publication 4/2016 - Official Journal EPO on Further medical use dated 20.09.2010 OJ

4.2 Practice in the US

Before the implementation of the Bayh-Dole Act in 1980 in the US,[501] most academic scientists did not seek patent protection for their research, the universities could still patent and did to some extend so, but the rules and procedures for applications varied considerably among government agencies involved in the funding. As a result, the scientists avoided patenting and licensing activities for they were not willing to compromise on their R&D activities.[502] The rights for inventions made by federal funding had to be granted to the federal government. At the time, less than 5 % of the 28,000 patents held by federal agencies had been licensed, compared with 25 % to 30 % of the small number of federal patents for which the government had allowed companies to retain title to the invention.[503] The Bayh-Dole Act enabled the private ownership of inventions made with federal funding for universities, small businesses, and non-profit institutions.

Although the aim of the Act was to encourage universities as a source of technology development to transform patent rights into commercial products and promote entrepreneurial activity, the result of the Act was not only stimulation of technology commercialization at research universities but also an exploitation of markets for knowledge. As a result, the universities shifted their patenting to those fields where licensing is an effective mechanism to acquire new technical knowledge.[504] The rise of the patenting and licensing activities after the implementation of the Act was noted in various research.[505]

EPO 2010, 514.

[501] The Bayh–Dole Act or Patent and Trademark Law Amendments Act (Pub. L. 96-517, December 12, 1980).

[502] SAMPAT, B.N. (2006). Patenting and US Academic Research in the 20th Century: The World before and after Bayh-Dole. *Research Policy*, Volume 35, Issue 6 (2006) pp. 772-89.

[503] U.S. Government Accounting Office (GAO) Report to Congressional Committees. at supra note 337 p. 3.

[504] SHANE S. (2004). Encouraging university entrepreneurship? The effect of the Bayh-Dole Act on university patenting in the United States. *Journal of Business Venturing*, Volume 19, Issue 1, pp 127–151.

[505] See MOWERY D. C et al. (2001) The growth of patenting and licensing by U.S. universities: an assessment of the effects of the Bayh–Dole act of 1980. *Research Policy*, Volume 30, Issue 1, pp 99–119

Patenting of genes created controversies also in the US, especially when NIH started to seek patent protection for over 8000 expressed sequence tags (EST) between 1991-1993.[506] All applications were rejected by the USPTO between 1992-1993 for lack of utility. NIH had chosen not to fight after the rejection from USPTO and dropped its applications in February 1994.[507] While NIH did not continue to support immense sequencing activity, interest had risen among businesses, and the private sector took on the task.[508] By September 1995 some 50,000 ESTs had been identified.[509] Now private companies were flooding the USPTO with EST patent applications, where thousands of ESTs could be filed in a single application. The EST controversy increased, as academic institutions could not mostly gain access to privately - held databases.[510] Later, there were some initiatives by the public and private sector to create some sort of public domain, which the scientific community benefits from.[511] Although the knowledge in the public

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and TSENG A. A & RAUDENSKY M. (2015). Performances of Technology Transfer Activities of US Universities after Bayh-Dole Act. *Journal of Economics, Business and Management*, Volume 3, Issue 6, pp. 661-667 where authors found that the patenting and licensing activities in US universities slow down considerably after 2000 (less than 60 % compared to 1991-1999) and remain flat until 2010. There is no evidence to relate this to housing or dot.com bubbles. On the other hand, the number of university start-up companies from 2010 to 2012 increased more and they were more active in licensing compared to the level in the period before 2000 and after the enactment of the Act. See also AUDRETSCH, D.B. (2014). From the entrepreneurial university to the university for the entrepreneurial society. *The Journal of Technology Transfer*, Volume 39, Issue 3, pp 313–321 for a critical review of role of the university in society where the entrepreneurial university was a policy response to generate innovative activity and economic growth via technology transfer and knowledge-based startups. However, the role of the university has evolved over the time from the purity of Humbolt University model of scholarly freedom and independence to enhance entrepreneurship capital and society.

[506] US National Research Council (NRC) Committee on Federal Policy for Access to Research Resources. Finding the Path: Issues of Access to Research Resources, (1999), Washington (DC): National Academies Press (US) at p.13 available at: https://www.ncbi.nlm.nih.gov/books/NBK208765/ last visit 30.04.2020. The cost of the sequences was estimated to be roughly USD 20 each. See KIGHT, A. T. (1998). Pregnant with Ambiguity: Credibility and the PTO Utility Guidelines in Light of Brenner. *Indiana Law Journal*, Volume 73, Issue 3, Article 6, pp 997- 1024 at p. 1003.

[507] See Kight at supra note 506 p. 999.

[508] EISENBERG, R. S. (1996). Intellectual Property at the Public-Private Divide: The Case of Large-Scale cDNA Sequencing. *University of Chicago Law School Roundtable*, Volume 3, Issue 2, pp. 557-73 at pp 561- 563.

[509] See Kight at supra note 506 at p. 1004.

[510] See Eisenberg at supra note 173.

[511] For instance, the pharmaceutical company Merck funded an EST-sequencing center at Washington University, where the sequences were not patented and put into public domain. See Eisenberg at supra note 508 at p.561 for a discussion of how Merck took on a quasi-governmental role, while the NIH refused to

domain increased over the time, differences on the kind of information available from the public and private sources made the commercial firms continue to sign up for private databases and the private databases remained larger.[512] The issue for opponents of EST patenting was that granting patents on uncharacterized cDNA sequences would reward those making "routine discoveries" and impede the development of diagnostics and therapeutics, which was clearly not in the public interest.[513]

In the 1995 utility examination guidelines of USPTO, the interpretation of "specific utility" requirement of § 101 was clarified and required that the applicant should make it immediately apparent why the invention was useful. Applications that were failing to do so would be rejected. [514] In the guidelines some legal analysis was given to demonstrate the rejections by USPTO for failing to comply with the utility requirement, and how "specific utility" is interpreted by the appeal courts as having "practical utility" with "real world value" and being "credible".[515] It must be noted that biotechnology patent applications were receiving an increasing strictness from USPTO in its application of the utility requirement in line with the rulings of the Federal Circuit and the Supreme Court that supported disclosure of practical utility.[516]

Having an ever increasing number of patent applications, the USPTO changed its

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fund these efforts and favored a rather aggressive position in patenting. The arguments were so heated that the Nobel prize winning scientist and the former director of US human genome project at NIH, James Watson, who himself was opposed to patenting of EST sequences without a known function, resigned from his post at NIH in 1992. See News, Watson resigns, genome project open to change (1992), *Nature*, Volume 356 p. 549.

[512] See Eisenberg at supra note 508 at pp. 563-564.

[513] HUGO (Human Genome Organization) 1995 statement on the patenting of DNA sequences available in CLAGUE, J. (2003). Beyond Beneficence: The Emergence of Genomorality and the Common Good, in *Brave new world? Theology, ethics and the human genome,* Deane-Drummond C. (ed.) T&T Clark Ltd. at p. 215

[514] [BILLING CODE 3510-16] [Docket No. 950706172-5172-01] pp 3-11.

[515] Such as Case 626 F.2d 853, 856, 206 USPQ 881, 883 (CCPA 1980) (CCPA-the Court of Customs and Patent Appeals) Nelson v. Bowler, Case 383 U.S. 519, 148 USPQ 689 (1966), Brenner v. Manson, Case 992 F.2d 1197, 26 USPQ2d 1600 (Fed. Cir. 1993) re Ziegler.

[516] EISENBERG, R. S. & MERGES, R.P. (1995). Opinion Letter as to the Patentability of Certain Inventions Associated with the Identification of Partial cDNA Sequences. *AIPLA Quarterly Journal*, Volume 23, No 1 pp. 1-52.

view by the end of 1990s, articulating that the ESTs can be patented by meeting the utility requirement as probes, i.e., research tools and argued that without patent incentives, there would be less investment in DNA research and less dissemination of knowledge.[517] In October 1998, the first EST patent was granted to a private company on human kinase homologues.[518] In its revised utility examination guidelines in 2001, the USPTO started asking for credible, substantial, well-established and specific utility, and the ESTs were deemed patentable subject matter, if they meet the patentability requirements (not only on utility, but also on others such as novelty, nonobviousness and disclosure).

A more detailed case law analysis will be given in Chapter 4.2.3.3 regarding the Federal Circuit's In re Fisher Case on utility criteria of ESTs.

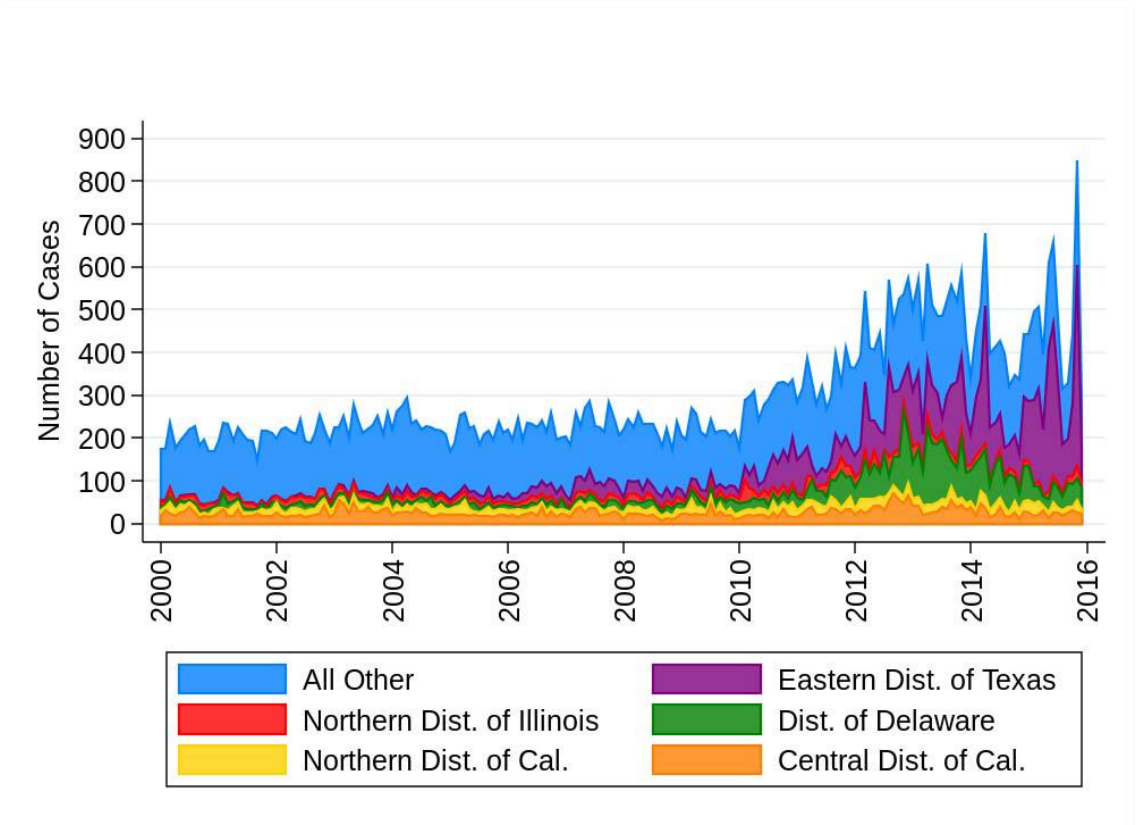
In a survey among clinical laboratory directors in the US, respondents generally reported that their perception over the effects of patents on benefit sharing, access and development of genetic tests is negative and patents have an adverse effect on their research. 53% reported that they decided not to develop a clinical genetic test due to a patent or a license. 25% reported that they had stopped carrying out a genetic test due to a patent or a license.[519] Therefore broadening and strengthening of patent protection cannot always result in more innovation. If the patent rights on a pioneer invention impede follow-up inventions, the overall innovation is actually reduced. And indeed, the increase in patent litigation coming along with the increase in the number of patents also hint to a strategic patenting of companies, not necessarily aiming at innovation per se, but at financial gains. The below chart shows patent litigation data from US district courts:

[517] See the former USPTO Biotechnology Examination Director Doll's article at supra note 16.

[518] US Patent no. 5,817,479 to Incyte Pharmaceuticals Inc.

[519] CHO, M.K. et al. (2003). Effects of patents and licenses on the provision of clinical genetic testing services. *Journal of Molecular Diagnostics*, Volume 5, Issue 1, pp. 3-8.

Chart 3: Patent Litigation by Month and Courts Years 2000-2015



Source: Marco et al.[520]

[520] MARCO, A. C., TESFAYESUS, A. & TOOLE, A. A. (2017). Patent Litigation Data from US District Court Electronic Records (1963-2015). *USPTO Economic Working Paper No. 2017-06*. available at SSRN: https://ssrn.com/abstract=2942295 last visit 30.04.2020.

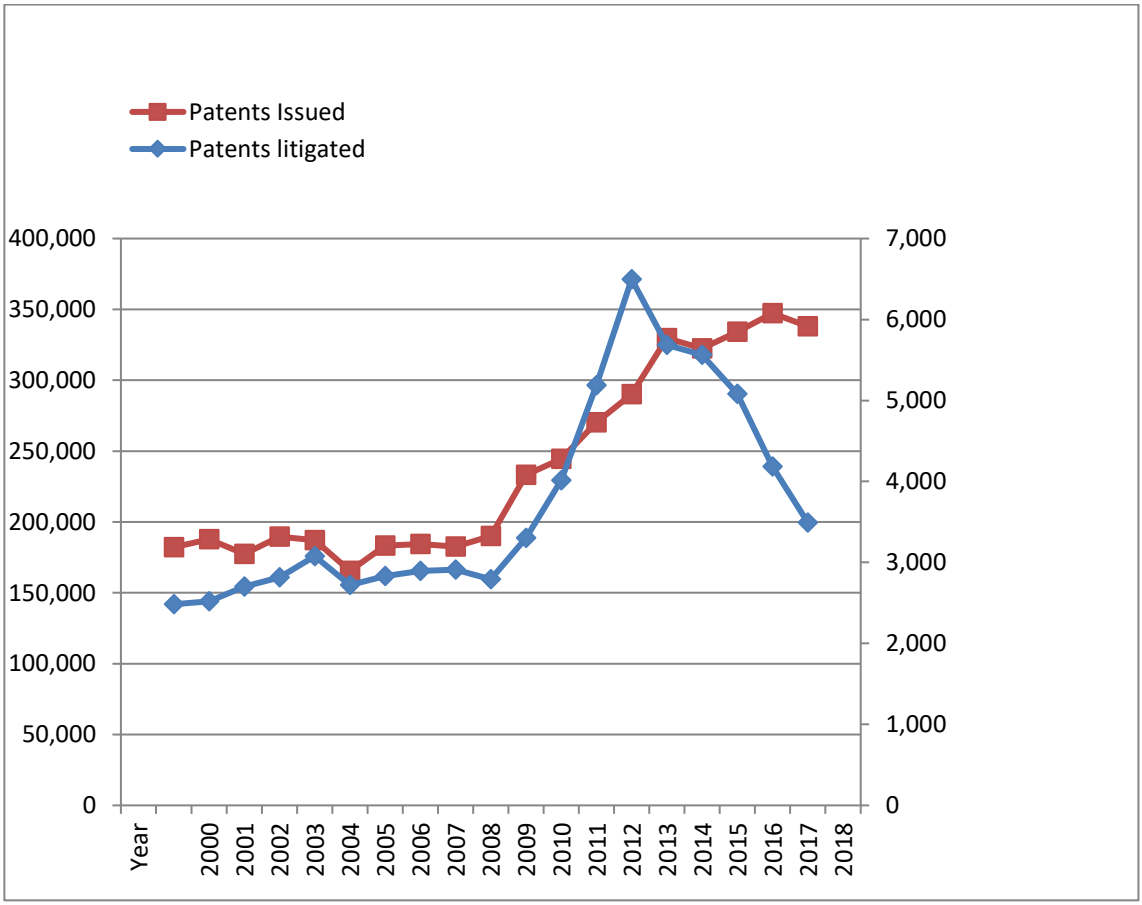
Another issue has been the choice of location where litigation suits were filed. Until a recent decision of the Supreme Court, the plaintiffs were allowed to file in judicial districts believed to be patent-owner friendly and this gave a competitive advantage especially to patent trolls or non-practicing entities. Particularly before the establishment of the Federal Circuit, there was significant non-uniformity in the outcomes across US circuits. After the establishment of the Federal Circuit, this non-uniformity remained, but became less.[521] With the Supreme Court decision in Case Heartland v. Kraft Foods [522], patent owner's personal choice over jurisdiction venue is no longer allowed. Lawsuits can only be filed to the district where alleged infringements took place or in the state where the accused infringer is established.

[521]ATKINSON, S. E, MARCO, A. C. & TURNER, J. L. (2009). The Economics of a Centralized Judiciary: Uniformity, Forum Shopping, and the Federal Circuit. *The Journal of Law & Economics*, Volume 52, No. 3, pp. 411-443.

[522] US Supreme Court Case 581 U.S. ___ 137 S. Ct. 1514; 197 L. Ed. 2d 816; 122 U.S.P.Q.2d 1553 (2017), TC Heartland LLC v. Kraft Foods Group Brands LLC.

The below chart shows patents granted versus patents litigated during 2010-2018:

Chart 4: Patent Grants and District Court Litigations 2000-2018



Source: US Courts Judicial Facts and Figures, U.S. District Courts— Patent Cases Filed During the 12-Month Periods Ending June 30, 1990, and September 30, 1995 Through 2018 available at www.uscourts.gov, USPTO 2018 Performance and Accountability Report

The decrease in patent litigation after 2012 can mainly be attributed to the Supreme Court decisions regarding therapeutic /diagnostic method patents in biotechnology in Case Mayo v. Prometheus (March 2012), Case Association for Molecular Pathology v. Myriad Genetics (June 2013) and regarding business method patents in software in Case Alice Corp. v. CLS Bank (June 2014). These decisions are discussed in detail in the upcoming sections of the dissertation, but in a nutshell: These three decisions have raised the bar for the patent eligibility of method claims and invalidated (some of) the patents in dispute or narrowed down their claims. As a result, several district courts and the Federal

Circuit further invalidated several patents in biotechnology[523] and software sectors.[524] An analysis carried out for software patents only two years after the Alice decision concluded that of 568 litigated patent cases examined till mid-June 2016, 66.5% of the decisions on average resulted in patents' invalidation. Concerning Federal Circuit decisions in 37 cases, the invalidation ratio was 91.9%.[525] In such a legal environment where the disputed patents are mostly invalidated, the patent holders especially patent trolls and non-practicing entities (NPE) are expected to be less willing to go for a litigation. For once they would not only lose a case and let go of some royalties; going for infringement litigation would also mean for them losing their patents.

There are some major differences between the US and EU legal orders concerning biotech patents. In patenting of biotechnological material morality does not seem to play an immense role in the US as in the EU. For instance, in the Chakrabarty ruling the US Supreme Court stated that ethical matters should not be addressed by the courts, but by

[523] For instance, Myriad tried to fight over the BCRA patents for those ones that had not been invalidated by the Supreme Court decision and continued to sue companies / laboratories that were offering the gene mutation tests at lower costs. In 2014 the company finally lost all its patents, as the Federal Circuit upheld Myriad's claims for being patent- ineligible relying on the Supreme Court decision. See the Federal Circuit Decision Myriad v. Ambry No. 2014-1361,1366 (decided on December 17, 2014). Similarly, Federal Circuit ruled in 2015 Ariosa v. Sequenom (788 F.3d 1371) that Sequenom patents for prenatal fetal screening methods were invalid for they were claiming a method of natural phenomena (referring to Mayo decision). In 2016 in Decision Genetic Technologies v. Merial / Bristol- Myers Squibb No: 2015-1202,1203 (decided on April 8, 2016) patent claims on methods of analyzing sequences of DNA were found to be invalid under § 101 (on inventions patentable) for claiming a law of nature (applying Alice steps and citing Ariosa, Mayo and Myriad decisions. These Mayo / Alice steps are explained throughout this chapter). In 2017 in Decision Cleveland v. True Health No:2016-1766 (decided on June 16,2017), the Federal Circuit invalidated three patents with claims on testing methods for MPO (an enzyme in humans the increase of which is found by independent studies to be correlated with cardiovascular diseases) to and a fourth patent that claims a method for treating a patient with cardiovascular disease. The patents were found to be patent ineligible under § 101 for being a law of nature, The Court stated that "….the inventions are "based on the **discovery** (emphasis added) that patients with cardiovascular disease have significantly greater levels of … [MPO]," and that "…..patents' … claims were focused on a patent-ineligible law of nature because, inter alia, they "involve[d] no creation or alteration of DNA sequences"….Because the testing patents are based on "the relation [between cardiovascular disease and heightened MPO levels that] exists in principle apart from human action," they are directed to a patent-ineligible law of nature."

[524] Some famous examples include in re TLI Communications 823 F.3d 607 (2016), Ultramercial Inc. v Hulu LLC 772 F.3d 709 (2014) where patent claims were found to be directed to abstract ideas; hence patent ineligible.

[525] TRAN, J.L. (2016), Two Years After Alice v. CLS Bank, *Journal of Patent & Trademark Office Society*, Volume 98, No 3, pp 3-18.

the Executive.[526] In the EU moral concerns over gene patents have always been an issue.

In patenting of surgical, therapeutical, and diagnostic methods there are also differences between the two legal orders. EPC Art. 53 (c) precludes patents for methods for treatment of the human / animal body by surgery or therapy and diagnostic methods practiced on the human / animal body, excluding products for use in these methods. Although these methods may contain a novel step, the exclusion from patentability is brought for ensuring that the medical treatment of patients are not retrained by patents and also that such treatments even when applied by health professionals shall not entail a substantial health risk for the patient. EPO sets out the patentability exclusion criteria of such methods narrowly and has a substantial framework to identify these criteria. In Decision G1/07 of the Enlarged Board of Appeals it is stated that the imaging method, which necessitated the injection of contrast matter into the heart, "represents a substantial physical intervention on the body, which entails a health risk and required professional medical expertise to be carried out" [527]. Such an injection was "regarded as a method for treatment of the human or animal body by surgery (*and was excluded from patentability*-emphasis added) although, in the context of the claimed imaging methods, the physical intervention on the body did not aim in itself at maintaining life and health but constituted a prerequisite for the collection of data in the course of an examination phase of a medical diagnosis."[528] In the narrower Decision of G1/04 the Enlarged Board of Appeal clarified the technical steps practiced on human or animal body, which would exclude a claimed diagnostic method from patentability.[529]

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[526] The decision reads as "The Court refers to the logic employed by Congress in choosing not to perpetuate the "dichotomy" suggested by Secretary Hyde. *Ante* at 447 U. S. 313. But by this logic, the bacteria at issue here are distinguishable from a "mineral . . . created wholly by nature" in exactly the same way as were the new varieties of plants. If a new Act was needed to provide patent protection for the plants, it was equally necessary for bacteria. Yet Congress provided for patents on plants, but not on these bacteria. In short, Congress decided to make only a subset of animate "human-made inventions" *ibid.,* patentable...even though Congress plainly has legislated in the belief that § 101 does not encompass living organisms. It is the role of Congress, not this Court, to broaden or narrow the reach of the patent laws. This is especially true where, as here, the composition sought to be patented uniquely implicates matters of public concern."

[527] G 1/07 Treatment by surgery/MEDI-PHYSICS of 15.2.2010 the referring decision point 3

[528] Ibid.

[529] G 1/04 Diagnostizierverfahren of 16.12.2005. Among others see conclusion no.3 where these technical

Initially in the 19th century US Patent Act there was not a provision prohibiting the patenting of medical methods, but the granting of such patents was banned with the so-called Morton Doctrine.[530] However the decisions given were not very well expressed. For instance, the 1883 Decision of Ex parte Brinkenhoff[531] shows the patentability of medical methods till the patents at issue were invalidated. Later in the 1954 Case of Ex parte Scherer[532] this decision was overruled. Diagnostic methods were however regarded as patentable till Supreme Court's Mayo v. Prometheus decision.

The revision of the Patent Act in 1996 brought exceptions to infringement of patents by use of medical practitioners. Although the revised act does not prohibit the patenting of medical methods, the medical practitioners who may infringe such patents have a liability exemption. The objective of this provision was to prevent civil actions and injunctive reliefs for the infringement of patents.[533]

Unlike the first to file patent system of the EU, in the US the patents have been granted to those that are first to invent. Although the AIA will bring a similar first-inventor to file system, the application made before the enactment of AIA on March 16, 2013 and the continued applications to existing patents filed before this date shall still be subject to first to invent system. Accordingly, a disclosure or any kind of previous claim means termination of any rights to a later patent in the EU legal order. In this sense the

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procedural steps were found to be constitutive in the strict sense and must fulfil the criterion "performed on the human or animal body" for the diagnostic method to be under the patent prohibition pursuant to Art. 52(4) EPC.

[530] From the Case 17 F. Cas 879 Morton vs. New York Eye Infarmary from the year 1862. The case referred to natural functions of an animal, hence helped the medical methods used to treat human body be excluded from patentability.

[531] From 24 Commission Manuscript Decision 349 (1883) in 27 Journal of Patent of Society 797 (1945). The Patent Bord of Appeals rejected the patent since the result of a method of treatment was deemed uncertain. But patents continued to be granted for medical processes. See US Supreme Court Bilski & Warsaw v. USPTO – On Writ of Certiorari – Brief of Pharmaceutical Research and Manufacturers of America as Amicus Curiae in Support of Neither Party, No:08-864 at pp.9-10.

[532]103 USPQ 107 (1954). It was ruled that Ex Parte Brinkerhoff decision shall not categorically exclude medical method patents, the usefulness of a claim dependent on the reaction of human body was irrelevant and claims on medical processes involving treatment of human body are patentable. Ibid pp.9-11.

[533] SIRJANI, F. & KEYHANI, D. (2005). 35 USC § 287(c): Language Slightly Beyond Intent. *Buffalo Intellectual Property Law Journal*, Volume 3, Issue 1. pp 13-45.

EU system gives more incentives to disclose the information than the US system whereas in the US system there has been no pressure on the inventors with regards to date of filing till AIA.

The clause of ordre public does not exist in the US system as opposed to the EU system. In the US system there are also no restrictions regarding therapeutic or diagnostic use.

In the US the patent applicants must show utility, instead of industrial application. This means that there is room for a broader legal interpretation in the US system. The industrial application standard of the EU brings a more precise criterion.

With regards to the patentability of animal and plant varieties, the EU and the US have different approaches as well. In the EU animal / plant varieties cannot be patented as the process of production by crossing and selection is considered to be essentially biological, even if this process is supported by technical means and as such excluded from patentability under EPC [534], as well as in the Directive 98/44/EC.[535] With regards to animals that are produced under technical intervention by non-biological steps, patentability is possible under both jurisdictions, provided that the subject matter meets the criteria of patentability. For instance, the "Harvard Onco-mouse" was granted patent in both legal systems.[536] However, the breadth of the claim was much larger in the US. The first claim in the US patent application read as "A transgenic non-human mammal all of whose germ cells and somatic cells contain a recombinant activated oncogene sequence introduced into said animal, or an ancestor of said mammal, at an embryonic stage." This is the broadest claim in the application for the US patent. Claim no 11 reads as "The mammal of claim 1, said mammal being a rodent". Claim no 12 reads as "The mammal of claim 1, said rodent being a mouse." And this last claim had been the basis for the EPO decisions for granting a narrower European patent protection to the Onco-

[534] See Article 53(b).

[535] See Article 4(1).

[536] US Patent 4,736,866, EP Patent 169 672.

mouse before it was revoked.

Although TRIPS Art. 27(3)(b) allows member states to exclude from patentability animals and essentially biological processes for the production of animals, the US chose to grant patent protection to animals.[537] There have been debates in the US in the mid-80s concerning patenting of animals[538], but today it is an essentially accepted issue, which presents a clear difference to the European case.

Patentability of plant varieties is possible in the US only for asexually reproduced crops, except species with edible tuber.[539] Patentability of transgenic plants, i.e., plants that are produced as a result of a technical process is assured in both US and EU legislations.

The US legal system explicitly excludes laws of nature, natural phenomena, and abstract ideas from patentable subject matter.[540] The patentability of biotechnological inventions gained recognition in the US as early as 1980 by the Diamond v. Chakrabarty

[537] By its Diamond v. Chakrabarty decision, the Supreme Court held that micro-organisms produced by genetic engineering are not excluded from patent protection granted by 35 USC 101, which reads as "Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title." By contrast to the Funk Seed Co. & Kalo Co., 333 U.S.127 (1948) decision, where the patent protection was not granted on combination of bacteria, as they were regarded as laws of nature, the Diamond v. Chakrabarty decision points out that " … the patentee has produced a new bacterium with markedly different characteristics from any found in nature and one having the potential for significant utility. His discovery is not nature's handiwork, but his own; accordingly, it is patentable subject matter under § 101." Later the USPTO granted patent protection for oysters in Ex parte Allen, 2 USPQ2d (BNA) 1425 (Bd. Pat. App. & Int. 1987) decision. Shortly after this decision, USPTO issued a notice (Animals - Patentability, 1077 O.G. 24, April 7, 1987) that "the office now considers non-naturally occurring, nonhuman multi-cellular living organisms, including animals, to be patentable subject matter" excluding claims on human beings. See the Notice at https://www.uspto.gov/web/offices/com/sol/og/2011/week52/TOCCN/item-125.htm#cli125, last visit 30.04.2020.

[538] DRESSER, R.S. (1988). Ethical and legal issues in patenting new animal life. *Jurimetrics*, Volume 28, Issue 4, pp. 399-435.

[539] Title 35 USC § 161 which states: "Whoever invents or discovers and asexually reproduces any distinct and new variety of plant, including cultivated sports, mutants, hybrids, and newly found seedlings, other than a tuber propagated plant or a plant found in an uncultivated state, may obtain a patent therefore, subject to the conditions and requirements of title."

[540] USC 35 & 101, also mentioned in US Supreme Court Decision Gottschalk v. Benson 409 US 63 (1972).

case.[541] In 1974 Chakrabarty made a patent application for a genetically engineered bacterium capable of degrading crude oil. The application was rejected by the USPTO on the grounds that micro-organisms, as living things are "products of nature" and are not patentable. The decision of the US Supreme Court on the issue in 1980 was that the discovery of Chakrabarty was his own work not that of the nature, the bacterium in question was a new one with distinctly new features that are different from the ones found in nature and showed significant utility. As a result, it became a patentable subject matter.

4.2.1 Standards of conception and reduction to practice

Standard of conception and the reduction to practice have been the two steps in the US patent system to define an invention especially under the first to file system. The conception standard sets forth that the claimed process or item can be conceived, i.e. there is a detailed description and disclosure of it. In biotechnological claims the DNA sequences, proteins and enzymes must all be chemically and physically well-defined with their unique characteristics.[542] Moreover, the making of these inventions must be well defined as well so that someone enabled in the art can reduce it to practice easily.[543]

The standard of conception requires "corroborating evidence, which shows that the inventor disclosed to others his complete thought expressed in such clear terms to as to enable those skilled in the art to make the invention."[544] It is also described as the "formation in the mind of the inventor, of a definite and permanent idea of the complete

[541] US Supreme Court Decision 447 US 303 (1980)

[542] See Case 119 F.3d 1559 (Fed. Cir. 1997); Regents of the University of California v. Eli Lilly and Co.; Regents of the University of California v. Eli Lilly, Case 927 F.2d 1200, (1991) Amgen, Inc. v. Chugai Pharmaceutical Co., "one must define a compound by "whatever characteristics sufficiently distinguish it."

[543] See 179 USPQ 757, 763 (Bd. Pat. Inter. 1973) Hiatt v. Ziegler, "Conception is established when the invention is made sufficiently clear to enable one skilled in the art to reduce it to practice without the exercise of extensive experimentation or the exercise of inventive skill."

[544] See 754 F.2d 353, (Fed. Cir. 1985) Coleman v. Dines, "… in establishing conception a party must show possession of every feature recited in the count…conception must be proved by corroborating evidence."

and operative invention, as it is hereafter to be applied in practice".[545]

The next standard is the reduction to practice. A functioning example of the claimed invention must be available, and the invention must ensure that it functions in the intended way and achieves the aim that it was developed for.[546] The concept refers to the real embodiment of the invention. The embodiment can be done in actual or constructive reduction to practice.

Actual reduction to practice means that the actual production of the invention in its physical state is required so that a working example of the invention will demonstrate that the invention delivers its intended purposes.[547] Constructive reduction could be done upon the filing of a patent application on the claimed invention.[548] Hence someone skilled in the art can make and use the invention without undue efforts in terms of experimentation and R&D. Especially under the first-to-invent system these standards were essential in interference proceedings of the US Board of Patent Appeals and Interferences[549] for setting the date in priority contests where multiple patent applications for the same claim were proceeding to challenge the others.[550] In short the first inventor of a claim has been

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[545] See Ibid and 802 F. 2d 1367 (Fed. Cir. 1986) Hybritech Inc. v. Monoclonal Antibodies Inc.

[546] See 285 F.3d. 1029 (Fed. Cir. 2002) Griffin v. Bertina 129 F.3d 588 (Fed. Cir.1997) Estee Lauder Inc. v. L'Oreal S.A. "[A] reduction to practice does not occur until the inventor has determined that the invention will work for its intended purpose."

[547] See Case Hybritech v. Monoclonal at supra note 545 and Case 204 F.3d 1094 (Fed. Cir. 2000) Eaton v. Evans, in order to satisfy the actual reduction to practice the party (must have) "constructed an embodiment or performed a process that met every element of the interference count, and the embodiment or process operated for its intended purpose."

[548] See Case Hybritech v. Monoclonal at supra note 545 , also MERANI, S. (1999). Hyatt v. Boone. *Berkeley Technology Law Journal*, Volume 14, Issue 1 pp 137-151 for a review of the Decision 146 F.3d 1348 (Fed. Cir. 1998) Hyatt v. Boone at p. 139 "The filing of a patent application has the legal effect of constructively serving as both conception and reduction to practice of the subject matter described in the application. Therefore, the inventor does not have to provide proof of either conception or actual reduction to practice when relying on the content of the patent application, unless a date earlier than the filing date is sought to be established."

[549] Board of Patent Appeals and Interferences was replaced with Patent Trial and Appeal Board with the America Invents Act.

[550] Pre-AIS 35 U.S.C Section 102 set the conditions for patentability, novelty, and loss of right to patent. Section 102(g) of pre- AIA USC 35 reads as "(1) during the course of an interference conducted under section 135 or section 291, another inventor involved therein establishes, to the extent permitted in section 104, that before such person's invention thereof the invention was made by such other inventor and not

the one, who reduced the invention to practice as the first, or the one, who reduced the invention to practice as the second / third, but conceived the invention first and showed reasonable diligence in later reducing the invention to practice. Diligence needed to be demonstrated from the date of actual reduction of practice to the filing date of a patent application.[551] The date of conception needed to be tied to the date of reduction to practice by demonstrated diligence.

Under the first to invent system a panel of judges at the USPTO (Board of Patent Appeals and Interferences) needed to conduct an interference proceeding (or a so-called priority contest) and review the evidence of conception, reduction to practice and diligence to define an invention and to decide to which party the patent must be granted. These proceedings have been lengthy and costly processes, however the supporters of the system argued that the system protected small inventors, who invented first, but who could not have filed in time because they lacked the resources to file quick applications, and thus in return would lose a patent to a large company who invented after they did, but filed first.[552]

Since the effective date of the America Invents Act (AIA) of March 16, 2013, the first applicant to file has the right for the grant of a patent. Since then, interference

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abandoned, suppressed, or concealed, or (2) before such person's invention thereof, the invention was made in this country by another inventor who had not abandoned, suppressed, or concealed it. In determining priority of invention under this subsection, there shall be considered not only the respective dates of conception and reduction to practice of the invention, but also the reasonable diligence of one who was first to conceive and last to reduce to practice, from a time prior to conception by the other." With the AIA the new law says in 35 U.S.C 100 on first inventor to file provisions that these provisions will apply to any application for patent containing a claim that has an effective filing date after March 16, 2013.

[551] See 79 F. 3d 1572 (Fed. Cir. 1996) Mahurkar v. CR Bard, Inc. also Amgen, Inc. v. Chugai Pharmaceutical Co., Ltd. 927 F. 2d 1200 (Fed. Cir. 1991) quoting 35 U.S.C Section 102(g) of pre-AIA.

[552] LEMLEY, M. A., & CHIEN, C. V. (2002). Are the US patent priority rules really necessary? *Hastings Law Journal*, Volume 54, pp. 1299-1334. Indeed, Canada switched to first-to-file system from first-to-invent system in 1989. A study in 2009 shows that the switch may harm Canada's innovative activities as it has a small negative impact on Canadian patents. The first to file system is unfavorable for SMEs and individual inventors but serves to larger corporations. The ownership structure of patents changed from SMEs to large businesses. See LO, S. and SUTTHIPHISAL, D. (2009), Does it Matter Who Has the Right to Patent: First-to-Invent or First-to-File? Lessons from Canada, *NBER Working Paper* No. w14926. pp.5-6.

proceedings have been eliminated from the patent law.[553] However it is still of interest to show how the patentability of claims and priority date were decided at the USPTO Board of Patent Appeals and Interferences for pre- AIA cases and also very recently a decision by the USPTO Patent Trial and Appeal Board on an interference case with regards to CRISPR/Cas9 gene editing technology.[554]

4.2.1.1 Kridl vs. McCormick

In case Kridl vs. McCormick[555] the claims involved the use of antisense recombinant DNA technology to develop a plant cell resistant against viruses. McCormick filed the patent application at USPTO on 16.10.1985. Kridl applied for an interference proceeding on 28.03.1986 arguing for prior conception of the claims. Based on testimonies and some laboratory notes from 1984, the USPTO Board of Appeals concluded that McCormick demonstrated corroborating evidence that the conception of the invention dated back to 1984 and McCormick was the first to conceive and also the first one to reduce to practice by filing a patent application. Kridl filed at the Board a request for the re-consideration of the decision arguing that the Board improperly used a rule of reason analysis to substitute for testimony, which corroborates conception of a utility.[556] The request of Kridl for reconsideration was rejected by the Board stating that "the "rule of reason" in its evaluation of the evidence does not require that conception be

[553] Under the new law AIA an applicant with an effective filing date of March 16, 2013 (enactment of the law), is not allowed to initiate an interference proceeding. There are still derivation proceedings under the new law to determine whether an earlier application claiming the same invention was wrongly granted a patent protection and whether the inventor in the earlier application derived the claimed invention from the petitioner's application. See 77 Fed. Reg. 56068 of 11.09.2012 on USPTO Changes to Implement Derivation Proceedings.

[554] The CRISPR/Cas9 dispute between University of California Berkeley (UC Berkeley) and Broad Institute of MIT and Harvard University dates back to 2012, hence the appellant (UC Berkeley) was able to ask for an interference proceeding. See Chapter 4.2.1.3 for a detailed analysis.

[555] Case105 F.3d 1446 (1997) Kridl v. McCormick.

[556] A "rule of reason" analysis is carried out to identify whether the inventor's prior conception claim has been corroborated. In order to be able to conclude the credibility of inventor's conception claim, the judges carry out a thorough evaluation of all pertinent evidence. See Price v. Symsek, 988 F.2d 1187 (1993)

proved in detail by an unbroken chain of corroboration but rather that a reasoned determination be made as to the credibility of the inventor's story". It was found that the inventor's story was credible in concluding utility to confer viral resistance via the construct of the count since the "laboratory notes included each feature of the count except for utility and is consistent with the other evidence".

Kridl then appealed to Federal Circuit, contesting the Board's decision regarding priority. The Court also stated that the inventor must disclose everything clearly to enable those skilled in the art to make the invention (i.e., conception must be proved by corroborating evidence) and that there was "adequate proof of McCormick's conception of utility because the Board found the (expert) testimony credible… no other relevant evidence contradicts or conflicts with the testimony". Taking these corroborated evidences, especially the corroborated laboratory notes into account, it is stated by the Court that the Board correctly found "no reason to doubt the testimony". In its appeal to Federal Circuit Kridl also argued "McCormick may have intended to use the antisense constructs described laboratory notes as experimental controls or may have designed the experiments as a means for producing DNA constructs in the sense orientation". Here the Court also concluded that, "antisense constructs in plants were not known; only sense constructs were known" at the time of the conception. "It would have been illogical to use novel constructs as experimental controls; controls are usually known and established materials". The Court further noted that "it would also have been wasteful to attempt to generate sense constructs by a process that also generated antisense constructs because it was well-known how to make sense constructs alone".

In addition, the Court also stated that "contrary to Kridl's argument, the antisense constructs do "speak for themselves" in as much as use to confer viral resistance was their only tenable utility and the conception of that utility was consistent with all of the other corroborated evidence". Accordingly, the Board's conclusion was correct in "approving McCormick's evidence as sufficient to prove conception of the invention, even though that evidence lacked explicit corroboration of the conception of antiviral utility". Hence the Court ruled that McCormick conceived the invention before Kridl.

In brief: The case is important because the Federal Circuit reviewed the Board decision addressing the utility requirement during a patent interference proceeding and applied a rule of reason i.e., an analysis whether the prior conception claim can be verified. The Court affirmed the Board decision under this analysis and held that although "explicit corroboration of the conception of antiviral utility" lacks in this case, "McCormick's evidence was sufficient to prove conception of the invention". Kridl had argued that the evidence (laboratory notes and testimonies of laboratory experts) was insufficient to support the decision of the Board, since the invention "had more than one substantial use" and McCormick may have intended to use the antisense constructs as experimental controls or as means of producing DNA constructs in the sense orientation. The Court disagreed with this view and held that it would be wasteful to generate these "constructs as experimental controls", since "controls are usually known and established materials". It would also be "wasteful to use them for sense constructs, because it was well-known at the time how to make sense constructs alone". Rule of reason analysis applied by the Court in this case gave a new aspect to law and economics approach applied in patent law. By finding Kridl's arguments wasteful in an alleged attempt to generate sense constructs or experimental controls, the Court acknowledged that the utility may sometimes be contained in the given evidence and that is adequate for proving conception: The explicit corroboration of inventor's conception of utility need not always to be sought.

4.2.1.2 Invitrogen v. Clontech Laboratories

In case Invitrogen v. Clontech Laboratories[557] there was an appeal to a District Court decision which annulled the claims in three Invitrogen patents for being anticipated with the novelty requirement under 35 USC § 102(g)(2). The Federal Circuit revoked the District Court's annulment decision stating that the "District Court misapplied the law of appreciation and erred in the calculation of conception date of Columbia University

[557] 429 F.3d 1052 (2005) Invitrogen Corp. v. Clontech Laboratories Inc.

researchers". Thus, the Federal Court removed the invalidity judgment and the district court's conception ruling and remanded for further proceedings. However, the District Court's decisions on enablement, written description, and infringement were affirmed by the Federal Circuit.

The novelty requirement under pre- AIA 35 USC § 102(g)(2) was sometimes referred as secret prior art, where "prior art" is undiscoverable to the patent applicant since it hasn't been made public or published before. Under the first to invent doctrine an inventor would do a careful search of prior art before making a patent application. Such a search was especially problematic for provisional patents that are not published and thus their prior art references remain secret. [558]

The Federal Circuit considered secret prior art to be prior art also through different cases. For instance in Tyco v. Ethicon case,[559] Ethicon was found by the District Court to be infringing several claims of Tyco patents on ultrasonic surgery devices and the District Court had ordered Ethicon to pay damages to Tyco. In the Federal Circuit case Ethicon appealed that certain claims of Tyco patents would not meet the nonobviousness requirement. The Federal Circuit upheld the district court decision that Ethicon's prototype, which anticipated several Tyco claims constituted prior art under 35 USC § 102(g) due to its earlier date of conception. However, is stated that "a prior invention under § 102(g) does not need to be "known to the art" or to the patentee at the time of invention to constitute prior art under § 103" i.e., nonobviousness requirement and that the District Court erred in refusing the Ethicon prototype to be prior art under §103 because of its later reduction to practice. The significance of this case is that according to Federal Circuit prior reduction to practice did not necessarily mean prior art under § 103 with prior conception.

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[558] GATTUSO K., (2011). Secret Prior Art: Does Prior Art in a Provisional Patent Application Bar Future Patents, *Missouri Law Review*, Volume 76, Issue 3 pp 934-938. In the study of CHEN, C.T., CHEN, D.Z., (2016), Who files provisional applications in the United States?, *Scientometrics*, Volume 107, Issue 2, pp 555–568 the authors went through the US Patent Application database and found that category of Drugs and Medical have the highest provisional applications. The authors relate the factors encouraging filing provisional applications to the possibility of obtaining an earlier filing date, a longer patent term, and an earlier promoting opportunity at p. 556.

[559] 774 F.3d 968 (Fed. Cir. 2014) Tyco Healthcare Group LP v. Ethicon Endo-Surgery, Inc.

In case Invitrogen v. Clontech Laboratories the patents owned by Invitrogen related to the genetically modified enzyme reverse transcriptase (an enzyme used in order to generate complementary DNA (cDNA) from an RNA template[560]). Naturally-occurring enzyme reverse transcriptases possess RNase H activities, degrading only the RNA in a double-stranded RNA-DNA hybrid.[561] Genetically modified enzyme reverse transcriptases do not possess RNase H activities, hence cannot degrade the mRNA template after the cDNA synthesis. So, the genetic modification enables the reverse transcriptase as a template to obtain additional cDNA.

RNase H activity is essential for viral proliferation. It is used to develop antiretroviral drugs used for the treatment of diseases caused by retroviruses.[562] The degradation of the mRNA undermines the capacity of reverse transcriptase enzyme to make cDNA.

Inactivation of the RNase H activity means on one hand a higher yield of full - length cDNA products, on the other hand the ability for researchers to reuse the mRNA in reverse transcriptase to generate further cDNA.

The legal dispute arose as Invitrogen filed an infringement suit against Clontech, and in return Clontech responded by invalidity, unenforceability, and non-infringement claims. In arguing invalidity, the claim of Clontech was that there was a prior conception by Columbia University researchers before the patented invention by Invitrogen. Indeed, the researchers had begun their work in conceiving the reverse transcriptase enzyme in 1984. However due to certain restrictions in their testing, they were not able at that time to show whether the modified reverse transcriptase lacked RNase H activity. Later in 1986 they were able to sequence the reverse transcriptase genes in these modifications.

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[560] Reverse transcriptase can be regarded as the enzyme which makes DNA from RNA. It is used to create cDNA libraries from mRNA. Some viruses use reverse transcriptase to copy its genetic material and create new viruses. Hence several drugs can be developed to suppress this activity.

[561] RNase H activity means degrading of mRNA. When the mRNA is destroyed, it cannot be used as template to create cDNA.

[562] A retrovirus is a single-stranded RNA virus. It contains its own enzyme reverse transcriptase to produce DNA from its RNA. Normally in viruses, the usual process is the other way round; the DNA is transcribed into RNA.

Invitrogen reduced this invention to practice in 1987. This reduction to practice was not disputed by Clontech at the District Court. The District Court also ruled among others that the Columbia University researchers had conceived of a "genetically modified reverse transcriptase with no RNase H activity" either in 1984 by isolating modified reverse transcriptase, or in 1986 by sequencing the reverse transcriptase genes. However, the District Court also ruled that the work of Columbia University researchers did not anticipate Invitrogen's patents under § 102(g)(2), since such anticipation would require a "resolution on a claim-by-claim basis".

In analyzing prior conception, the Federal Court stated that indeed Columbia University researchers´ findings did not constitute prior art, and that the District Court erred by establishing an earlier date of conception and reduction to practice for Columbia University researchers and by granting partial summary judgment in favor of Clontech. The Federal Circuit believed that this case "fits squarely within the unrecognized, accidental duplication cases". It was further stated that "conception requires that the inventor "be able to define" the compound "so as to distinguish it from other materials, and to describe how to obtain it" and "….that the inventor appreciate that which he has invented". The Federal Circuit vacated the District Court's invalidity judgment and District Court's partial summary judgment on Columbia University researcher's conception remanded the case for further proceedings.

This problem of secret prior art was eliminated by America Invent Act of 2013, since the act eliminated prior knowledge of the patent applicant derived from someone else under pre-AIA § 102(f) and the necessity to determine priority to determine who was the first to conceive in case of prior invention by another inventor under pre-AIA § 102(g).[563] However secret sale activity and commercial uses may still create prior art that can invalidate a patent on grounds of novelty and obviousness.[564]

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[563] Pre- AIA 35 U.S.C §102 (Conditions for patentability; novelty and loss of right to patent) Provision (f) required that a patent could only be given to the person, who himself invented the subject matter.§ 102 (g) required proof of earlier conception to determine priority regarding who was first to invent.

[564] 35 USC § 102(a)(1) (post-AIA) states that any kind of public disclosure of the claimed invention by means of description in a printed publication, public use, sale, or other availabilities to the public before

In brief: The Federal Circuit acknowledged that "conception requires that the inventor appreciate that which he has invented, … requires more than unrecognized accidental creation." The researcher from Columbia University had testified that he had thought about the invention, but his notebook entries from different years did not support his suspicion. The conception has to be corroborated by objective evidence and expert testimonies alone would not be adequate to demonstrate conception. From law and economics point of view, this case is significant because it attained an analysis of the invention activities; it required the inventor to be aware of the novelty of his invention and also recognized the importance of keeping detailed laboratory notes.

4.2.1.3 UC Berkeley v. Broad Institute of MIT and Harvard University

The CRISPR-Cas9 dispute between University of California, Berkeley (UC Berkeley) and Broad Institute of MIT and Harvard University began in 2012 when researchers from UC Berkeley published in June 2012 a paper on CRISPR [565] and showed in bacterial cells that the technology can be used to cut DNA and highlighted the potential of the technology for RNA-programmable genome editing.[566] Later, one of the researchers filed a patent application at the USPTO for CRISPR.

In parallel, in January 2013 researchers from the Broad Institute published a similar paper where they showed that they engineered two different type CRISPR-Cas systems that edited the genomes in human and mouse cells.[567] Shortly after they also applied for

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the effective filing date of the claimed invention would constitute prior art.

[565] JINEK, M. et al. (2012). A Programmable Dual-RNA–Guided DNA Endonuclease in Adaptive Bacterial Immunity. *Science*, Volume 337, Issue 6096, pp. 816-821.

[566] CRISPR (Clustered regularly interspaced short palindromic repeats) are segments of DNA with short repetitive sequences. The gene editing technology CRISPR-Cas9 can be used to edit genomes and is used as a tool for permanant modification within organisms. The technology has many potential applications in medical biotechnology. See SMITH, C. et al. (2014), Whole-Genome Sequencing Analysis Reveals High Specificity of CRISPR/Cas9 and TALEN-Based Genome Editing in Human iPSCs, *Cell Stem Cell*, Volume 15, Issue 1, pp 12 – 15.

[567] CONG, L. et al (2013), Multiplex Genome Engineering Using CRISPR/Cas Systems, *Science*, Vol. 339, Issue 6121, pp. 819-823.

a patent, and although UC Berkeley had filed first, USPTO granted the patent to the Broad Institute in April 2014.[568]

What is notable in the patent applications of UC Berkeley and Broad Institute was that the claims were actually not identical. UC Berkeley researchers had found the CRISPR-Cas systems working in simple bacterial cells and claimed the patent more broadly to cover all cell types. Broad Institute on the other hand had applied the system to more complex mice and human cells and claimed the patent only on such kind of cells, called indeed as eukaryotic cells. However, the argument of UC Berkeley was that any ordinary person skilled in the art after having seen the demonstration by UC Berkeley research would anticipate that the system working in simple (prokaryotic) cells would also work for eukaryotic cells, hence the technology would be obvious. Besides the UC Berkeley researchers had also shown later in January 2013 that the mechanism was working in human cells, as well.[569] As a result UC Berkeley asked for an interference proceeding at the USPTO - Patent Trial and Appeals Board (PTAB) in January 2016 to determine who was the first to invent the DNA-cutting / gene- editing CRISPR-Cas9 mechanism.[570]

PTAB announced its decision in February 2017 stating that there is in fact no interference, hence both parties can be granted patents. In the summary PTAB stated that Broad Institute has persuaded the judges that the parties claim different subject matter, Broad's claims being "limited to CRISPR-Cas9 systems in a eukaryotic environment", whereas UC Berkeley's claims are "all directed to CRISPR-Cas9 systems not restricted to any environment". Broad evidence showed that the "invention of CRISPR-Cas9 systems in eukaryotic cells would not have been obvious over the invention of such systems in any environment, including in prokaryotic cells or in vitro, because one of

[568] USPTO Patent Number US 8,697,359 B1

[569] JINEK, M. et al. (2013), RNA-programmed genome editing in human cells, *E-Life Sciences* research article available at http://dx.doi.org/10.7554/eLife.00471.001last visit 30.04.2020.

[570] In this case the patent rights could still be determined by interference proceeding and first -to-invent system, since the applications were filed before the Leahy-Smith America Invents Act took effect in March 2013 and the shift to the first-to-file took place.

ordinary skill in the art would not have reasonably expected a CRISPR-Cas9 system to be successful in a eukaryotic environment."[571]

A difference in the method of the two teams was that UC Berkeley researchers used a single-molecule guide DNA-targeting RNA in their work with prokaryotic cells, whereas Broad Institute researchers used two-molecule guide RNA to complete CRISPR-Cas9 gene editing task in eukaryotic cells.

This decision means that existing patents of Broad Institute in eukaryotic cells would remain and UC Berkeley could still be granted patent protection. Broad Institute was granted 12 patents for applications that were filed between 2013 till 2014; UC Berkeley's application from March 2013 was still pending as the Decision of USPTO – PTAB decision was announced on 15 February 2017.[572] With this decision the pending application of UC Berkeley could be returned to the patent examiner, thus the patent protection can be granted to UC Berkeley for CRISPR-Cas9 in all types of cells.

UC Berkeley announced on 13 April 2017 that it will appeal to Federal Circuit to reverse the PTAB's decision stating that their research team "was the first to engineer CRISPR-Cas9 for use in all types of environments, including in non-cellular settings and within plant, animal and even human cells" and their earliest patent application with description and use of CRISPR-Cas9 was filed on May 25, 2012, while that of Broad was filed on December 12, 2012.[573]

It is important to stress once again that PTAB decision allows both UC Berkeley and Broad Institute to be granted different patent protection. It may seem at first confusing that claims of UC Berkeley and Broad were found not to interfere, although Broad's claims fall within the territory of UC Berkeley's claims. UC Berkeley can pursue its

[571] See USPTO Decision of Motions at infra note 572, p. 2.

[572] See USPTO – PTAB Patent Interference No. 106,048 (DK) Decision available at https://e-foia.uspto.gov/Foia/RetrievePdf?system=BPAI&flNm=fd106048-02-15-2017-1 last visit 30.04.2020.

[573] UC Berkeley Announcement available at http://news.berkeley.edu/2017/04/13/uc-appeals-u-s-patent-board-decision-on-crispr-cas9/ last visit 30.04.2020.

original patent applications in all types of cells; however Broad Institute will still be left with valuable patents in prokaryotic cells. Due to different embodiments, two different applications can be argued to be relying on the same invention. It is a fact concerning biotechnological patents that the inventor can be granted patent protection on a very broad scope of claims than the actual embodiments provided that these broad scopes meet non-obviousness criteria and other patenting criteria for further advances in the technology. The appeal of UC Berkeley at the Federal Circuit would be to argue that Broad Institute patents would not have been granted at first place and hence to ask PTAB to reverse its decision. Given the fact that Federal Circuit judges will not re-examine the factual interpretation concluded by PTAB[574], time will show if UC Berkeley can effectively argue at the Court that PTAB did a reversible error of law such as negligence, misfeasance or malfeasance resulting in an unfair trial.

In May 2017 the EPO granted a broad single-guide CRISPR patent protection to UC Berkeley, in its original claims covering all cell types.[575]An opposition has already been filed to EPO regarding the patent in June 2017, and the Broad Institute also has 9 months' time after the issuance of the patent to file its opposition to the EPO. Depending on review proceedings EPO may maintain, adjust or revoke the patent.

Meanwhile the Broad Institute has eight granted European CRISPR patents at EPO.[576] A settlement between UC Berkeley and the Broad Institute could have been possible before the PTAB Interference Proceeding, if both parties had willingness to do so. The case is a good example of how important collaboration among scientist can be in order to avoid lengthy and costly litigation. However, both parties must have seen the potential in commercializing the gene editing technology. For instance, Caribou

[574] Federal Circuit Appeal No:2017-1907 on p. 5 where the Court states that "UC improperly asks the Court to redo the PTAB's fact finding rather than to judge whether substantial evidence supported this finding" and concludes that the Court cannot reweigh the evidence.

[575] See EPO File EP 2800811 for application no 13793997.1 filed on 15.03.2013 available at https://register.epo.org/application?number=EP13793997&lng=en&tab=main last visit 30.04.2020.

[576] See Broad Institute Announcement on number of CRISPR patents at the USPTO and EPO available at https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-patents-and-licensing-information last visit 30.04.2020.

Biosciences Inc., founded by the researchers of UC Berkeley holding exclusive licenses from UC Berkeley on CRISPR-Cas9 technology has raised USD 41 million itself in 2015 and 2016[577], in addition to USD100 million its joint venture Intellia received in funding in 2014 and 2015 alone[578], and declared in 2016 having signed a further licensing and collaboration agreement with NASDAQ- listed Regeneron Pharmaceuticals Inc. where Intellia would receive a USD 75 million upfront payment and would be eligible to receive significant milestone and royalty payments on potential Regeneron products. In this deal Regeneron Pharmaceuticals, Inc had also agreed to invest up to USD 50 million in Intellia's next equity financing.[579] Intellia announced in June 2017 that the Company will be granted patent protection in China for CRISPR-Cas9 gene editing methods and compositions for use in all cell types including human and other eukaryotic cells.[580] Intellia has obtained the IP rights of CRISPR-Cas9 gene editing technology through its mother company Caribou Biosciences Inc. In June 2017 the shares of Intellia Therapeutics Inc. were traded around USD 16,00 giving the Company a market capitalization of nearly USD 630 million.

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[577] See the press releases of the Company at http://caribioubio.com/in-the-news/press-releases/caribou-biosciences-raises-11-million-in-series-funding, last visit 30.04.2020.

http://www.fiercebiotech.com/groundbreaking-gene-editing-player-caribou-raises-30m-b-round last visit 30.04.2020.

[578] See the press releases of the Company at http://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-15-million-funding-develop last visit 30.04.2020.

http://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-reports-financial-results-third-quarter last visit 30.04.2020.

And some market news at http://www.marketwatch.com/story/intellia-therapeutics-announces-15-million-in-funding-to-develop-therapeutic-products-utilizing-crispr-cas9-gene-editing-technology-2014-11-18 last visit 30.04.2020.

[579] See the press release of the Company at https://www.prnewswire.com/news-releases/regeneron-and-intellia-therapeutics-announce-collaboration-to-discover-and-develop-crisprcas-therapeutics-300249375.html last visit 30.04.2020.

[580] See the press release of the Company at https://ir.intelliatx.com/news-releases/news-release-details/intellia-therapeutics-announces-patent-crisprcas-genome-editing last visit 30.04.2020.

Chart 5: Share price of Intellia Therapeutics Inc. 2016-2017

The share prices are affected by many factors such as macro-economic developments, general market trends, sectoral evolution, and so on. The demand for the shares in the market is also shaped by the investors' anticipation of future gains and is very much dependent on company news. In Chart 5 we see a sharp decline on share prices of Intellia Therapeutics (which uses CRISPR licenses from UC Berkeley spin-off company - Caribou Biosciences) during 15 – 19 February 2017 around USPTO -PTAB announcement of no interference and that both UC Berkeley and Broad Institute can be granted patent protection. Because UC Berkeley was hoping to get the patent protection for its own claims only. Then we see some increase during 13- 23 April 2017 where UC Berkeley announces to issue an appeal with the Federal Circuit. The bigger increase comes after 11 June 2017 after EPO patent grants in May 2017, raising funds worth of millions of USD with partnership agreements especially in spring 2016 and securing very broad patent protection in China as announced in June 2016.

Meanwhile the Broad researchers founded in 2013 Editas Medicine and the Company had raised US $ 163 million by 2015.[581] In 2016 the Company raised on the NASDAQ exchange nearly US $ 109 million by an initial public offering per share price at $16.00 for 6,785,000 shares.[582] In June 2017 the shares were traded at USD 17,80 level after having seen a huge decline from USD 40,45 levels, still bringing the Company to a market capitalization of US $ 780 million. Indeed, the Editas shares have seen the decline in January 2016 after Patent and Trial Board of USPTO announced that they will begin an interference proceeding on CRISPR patent dispute between UC Berkeley and Broad Institute, and again in April 2016 probably after the good-faith discussions of both parties did not reach a settlement.[583] We see increasing share price after the IPO announcement in February 2016; hitting highest level in April 2016. Afterwards there is a decline till 24 October 2016. From there on a gradual increase till 15 February 2017, where USPTO announced that there is no interference in the claims of the parties and both Broad and Berkeley can be granted patent protection. Although there are some fluctuations in the share price after this date, it can be seen from Chart 6 that there is an upwards trend.

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[581] See the press releases of the Company at http://ir.editasmedicine.com/phoenix.zhtml?c=254265&p=irol-newsArticle&ID=2125226 http://ir.editasmedicine.com/phoenix.zhtml?c=254265&p=irol-newsArticle&ID=2125221 last visit 30.04.2020.

[582] See the press release of the Company at http://ir.editasmedicine.com/phoenix.zhtml?c=254265&p=irol-newsArticle&ID=2136486. The Company closed the offering by 5,900,000 shares in addition granted the underwriters a 30-day option to purchase up to an additional 885,000 shares. See the press release at http://ir.editasmedicine.com/phoenix.zhtml?c=254265&p=irol-newsArticle&ID=2135046 last visit 30.04.2020.

[583] For a timeframe of the dispute between UC Berkeley and the Broad Institute see CRISPR patent interference updates available at https://www.broadinstitute.org/what-broad/areas-focus/project-spotlight/crispr-patent-interference-updates last visit 30.04.2020.

Chart 6: Share price of Editas Medicine Inc. 2016-2017

This largely disputed grant of patents in CRISPR in the US and in the EU is a good example of how patenting of biotechnological materials can be very much difficult, where the claims of one applicant falls within the territory of the other applicant, yet still can be found not to interfere.

In brief: UC Berkeley appealed the patent office's decision of January 2016, but in February 2017 the Broad Institute won the right to keep its patent for CRISPR. The USPTO Board still had the view that the patents held by UC Berkeley and the Broad Institute were applying to different subject matters. The UC Berkeley appealed the February 2017 decision of the Board to Federal Circuit in April 2017. In September 2018, the Federal Circuit affirmed the decision of the Board on no interference and announced that the Broad Institute can keep its patents. However, the Court also announced that the ruling is not on the validity of either set of claims, but about the scope of two sets of applied-for claims and whether those claims are patentably distinct. It was also

emphasized that the Court has found the remaining arguments of UC Berkeley unpersuasive.

Both Editas and Intellia have already granted broad licenses (both exclusively and non-exclusively) to downstream companies for agricultural, and medicinal /pharmaceutical and research tool applications for commercial purposes. Broad Institute has announced that exclusivity was deemed necessary for human therapeutics, since companies involved in this area need exclusivity in order to justify their investment in expensive clinical trials. On the other hand, both UC Berkeley and the Broad Institute have kept the patent rights freely available for academic research.[584]

Although this method of licensing through private, for profit, spinoff companies is not uncommon in university technology transfer agreements, it is questionable how initially publicly-funded research may turn into a billion-Dollar business and how the assertion of exclusive patent rights can hinder further innovation in CRISPR field. A broad exclusive CRISPR license is valued somewhere between $100 million and $265 million.[585] The global CRISPR market is estimated to reach USD 5.3 billion in 2025.[586]

Despite the fact that both UC Berkeley and Broad Institute have been able to retain their patent rights in the US for now, the USPTO has announced that it will intervene in the dispute.[587] Besides, the European landscape has also been a challenging one for both. EPO Opposition Division overturned Broad Institute patents in January 2018, since their

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[584] See licensing practices of Broad Institute https://www.broadinstitute.org/partnerships/office-strategic-alliances-and-partnering/information-about-licensing-crispr-genome-edi of UC Berkeley https://news.berkeley.edu/2019/09/03/twelfth-crispr-patent-awarded-to-uc-team/ last visit 30.04.2020.

[585] SHERKOW, J.S. (2017). How Much Is a CRISPR Patent License Worth?. *Forbes*, available at https://www.forbes.com/sites/jacobsherkow/2017/02/21/how-much-is-a-crispr-patent-license-worth/ last visit 30.04.2020.

[586] Ahead Intel report (2018), CRISPR | Cas9 Tools – Global Market and Patent Landscape Report till 2025, news and headlines from the report available at https://markets.businessinsider.com/news/stocks/crispr-cas9-genome-editing-market-worth-5-3-billion-by-2025-1027738971 last visit 30.04.2020.

[587] See the USPTO declaration from 24.06.2019 available at https://www.broadinstitute.org/files/news/pdfs/106115-NoticeDeclaringInterference.pdf last visit 30.04.2020.

claims were found to be lacking priority and novelty.[588] As expected, in March 2018 the Broad Institute appealed to this decision of the Opposition Division, arguing that only national courts would have the jurisdiction to claim priority and requested the case to be referred to the Enlarged Board of Appeal. A hearing for the appeal process was decided on January 16, 2020 where the EPO Board of Appeal found Broad's priority claim by earlier US application invalid and dismissed Broad's appeal hence revoked this disputed patent.[589] The reason for dismissal was that the provisional application had named additional inventors whose names did not appear on PCT application.

To date there are still more than 80 CRISPR patents issued by USPTO and more than 20 by EPO. The institutes and the licensees will continue to do research and more patents will likely be granted in the area in the coming years. Although some patents may later be revoked, others will emerge. A patent dispute between universities and research institutions makes it harder to reach collaboration and may block the use of the technology to develop valuable applications especially in human therapeutics. Exclusive licenses should be narrowed down to the use of specific genes so that a technology that was initially publicly funded can be utilized better to create public goods. An increased competition is necessary from researchers, who now have non-exclusive license arrangements, meaning that they can make use of the tools for research, but cannot market the products they develop. Similarly, the research area now can also not benefit from the work of small biotech companies, who cannot afford the licensing fees. The legal and economic implications of CRISPR patents are enormous in the field. It is a perfect example of how patents can be powerful tools to promote innovation, but also how their overuse and their disputes create uncertainties and inefficiencies and may block further innovation.

[588] Patent EP 2 771 468.

[589] Decision T 844/18.

4.2.2 Myriad Genetics Case

It was explained in Chapter 2.5 the ethical and technical challenges that Myriad patents pose in access to testing gene mutations and that Myriad's business model has been based on offering diagnostic testing for BRCA1 and BRCA2 genes[590]. Although its patents have started expiring in 2014[591], and the last ones in 2015[592], its long-term monopoly on the testing has already been narrowed by the US Supreme Court decision of Association for Molecular Pathology (AMP) v. Myriad Genetics Inc.[593] in 2013. These claims consisted of diagnostic methods to find mutated DNA sequences and drug screening methods to isolate the DNA sequences. Before this decision the case was brought to District Court by the Public Patent Foundation and American Civil Liberties Union Foundation against Myriad Genetics Inc. and Utah Research Foundation arguing that patenting human BRCA1 and BRCA2 genes violated the Patent Act, 35 U.S.C §101, Article I(8)(8) of the US Constitution and the first and the fourteenth amendments of the Constitution,[594] as they were products of nature and therefore could not be patented. The researchers among the plaintiffs stated that Myriad's strong enforcement of patent rights against others stopped them from engaging in clinical BRCA genetic testing, although they have the willingness, expertise, staff, and the facility to do such testing and if Myriad's patents would be held invalid, they would be able to resume BRCA testing immediately.[595]

The District Court had ruled in 2010 that the challenged claims by AMP were not eligible for patents saying that:

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[590] See Gold and Carbone at supra note 177.

[591] US Patent 5,693,473

[592] US Patents 5,837,492 and 6,033,857

[593] US Supreme Court Decision 569 US 576 (2013) Association for Molecular Pathology (AMP) v. Myriad Genetics Inc. The plaintiffs beside AMP included researchers from University of Pennsylvania, Columbia, Yale, NYU, Emory, individual patients, and health advocacy organizations.

[594] See the case petition writ of certiorari p. 6. The first amendment of the US Constitution secures mainly the freedom of speech, and press, free exercise of religion. The fourteenth amendment of the US Constitution addresses citizenship and civil rights, equal protection of individuals.

[595] See Case Background 689 F.3d 1303 (2012) AMP v. USPTO.

"…The resolution of these motions is based upon long recognized principles of molecular biology and genetics: DNA represents the physical embodiment of biological information, distinct in its essential characteristics from any other chemical found in nature… DNA's existence in an "isolated" form alters neither this fundamental quality of DNA as exists in the body nor the information it encodes. Therefore, the patents at issue directed to "isolated DNA" containing sequences found in nature are unsustainable as a matter of law and are deemed unpatentable under 35 USC §101...According to Myriad, the invention claimed in its patents required the identification of the specific segments of chromosomes 17 and 13 that correlated with breast and ovarian cancer (BRCA1 and BRCA2) followed by the isolation of these sequences away from other genomic DNA and cellular components…the isolation of BRCA1 and BRCA2 DNA, while requiring technical skill and considerable labor, was simply the application of techniques well-known to those skilled in the art…the identification of the BRCA1 and BRCA2 gene sequences is unquestionably a valuable scientific achievement for which Myriad deserves recognition, but that is not the same as concluding that it is something for which they are entitled to a patent…Isolation and sequencing of DNA from a human sample, even if incorporated into the method claims-in-suit, would represent nothing more than data gathering steps to obtain the DNA sequence information on which to perform the claimed comparison or analysis. Moreover, in the absence of a specified method for isolating and sequencing DNA, "(a) requirement simply that data inputs be gathered- without specifying how-is a meaningless limit on a claim to an algorithm because every algorithm inherently requires the gathering of data inputs" (citing Bilski,[596] 545 F.3d). consequently, even if the method claims-in-suit were construed to include the physical transformations associated with isolating and sequencing DNA, they would still fail the "machine or transformation" test under §101 for subject matter patentability…Similarly, because the claimed comparisons of DNA sequences are abstract mental processes, they also constitute unpatentable subject matter under §101"[597]

[596] 545 F.3d 943 (2008) re Bilski.

[597] US District Court of the Southern District of New York Decision Association for Molecular Pathology. v. U.S. Patent and Trademark Office, 702 F. Supp. 2d 181 (S.D.N.Y. 2010)

Hence the method patent claims of Myriad for analyzing and comparing DNA sequences were found to be abstract mental processes and drug screening claims were found to be basic scientific principles; both without patent eligibility.

Upon Myriad's appeal, this decision was partially overruled by the Federal Circuit– finding still the diagnostic claims (method claims for comparing DNA sequences to detect BRCA mutations) unpatentable, but the drug screening claims (isolated cDNA sequences – meaning DNA sequences synthesized artificially from mRNA) and methods of therapeutics screening patentable.[598]An interesting aspect of this court case was that in a legal brief the US Department of Justice also suggested during the hearings that the government's long-standing tradition of granting patent genes was eroding stating that:

> "… Unlike the genetically engineered microorganism in Chakrabarty, the unique chain of chemical base pairs that induces a human cell to express a BRCA protein is not a "human-made invention…Indeed, the relationship between a naturally occurring nucleotide sequence and the molecule it expresses in a human cell — that is, the relationship between genotype and phenotype — is simply a law of nature. The chemical structure of native human genes is a product of nature, and it is no less a product of nature when that structure is "isolated" from its natural environment than are cotton fibers that have been separated from cotton seeds or coal that has been extracted from the earth…. Common sense would suggest that a product of nature is not transformed into a human-made invention merely by isolating it. The very term "isolated" suggests only that extraneous matter has been separated from the natural product of interest, not that the product itself has been transformed or altered into something man-made."[599]

[598] 653 F.3d 1329 (2011) Association of Molecular Pathology v. U.S. Patent & Trademark Office. This decision is partially reversed by the Supreme Court Decision 569 U.S. 576 (2013) Association for Molecular Pathology v. Myriad Genetics, Inc. "on remand in light of Mayo Collaborative Services v. Prometheus Laboratories, Inc., 566 U. S. 66, 132 S. Ct. 1289, 182 L. Ed. 2d 321". The Federal Court had found both isolated DNA and cDNA patent eligible. However, the Supreme Court concluded that "(A) naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but cDNA is patent eligible because it is not naturally occurring."

[599] Brief for the Federal Circuit by Department of Justice as amicus curiae in support of neither party No. 2010-1406 AMP v. Myriad Genetics Inc. pp 10-11, 22.

Although this was an important landmark in practice of granting gene patents, the legal brief was addressing the wrongdoing in the practice on granting patents for isolated gene sequences. Engineered DNA molecules including cDNAs were seen as human-made interventions that are eligible for patentability. It was further stated that until this case no other court had ever questioned whether an isolated DNA molecule is patentable. The District Court's invalidation of patents based on composition claims' being product of nature. These claims were cDNAs encoding BRCA proteins and the Supreme Court had (in its Bilski decision) set the patent-eligibility boundary on the principle that laws of nature, physical phenomena or abstract ideas are not patentable subject matter. [600]

In the amicus brief it was further stated that the District Court had erred in disputing patent-eligibility of man-made compositions of matter whose value derives from the information encoding capacity of DNA[601]. Citing the Cases Diamond v. Chakrabarty (447 U.S. 303 (1980)) and the Funk Brothers Seed Co. v. Kalo Inoculant Co. (333 U.S. 127 (1948)), it was formulated in Chakrabarty decision that the genetically modified organisms may be patented if they have "markedly different characteristics than those found in nature". Hence it was concluded that Myriad patents describing DNA sequences not found in nature (directed to cDNAs) are patentable and the District Court's invalidation of these claims was not correct.

The amicus brief also stated that the District Court "correctly held that the genomic DNA merely isolated from human body without further alteration or manipulation is not patentable because unlike the genetically engineered microorganism in Chakrabarty the chain of chemical base pairs that induce a human cell to express a BRCA protein is not a human-made invention."[602] Hence from the point of view of the Department of Justice, the invalidation of isolated DNA patents by the District Court was a too broad interpretation. Isolated and unaltered genomic DNA was not patent-eligible but those

[600] Ibid pp.7-9.

[601] Ibid p. 9.

[602] Ibid p.10.

transformed and altered should be.

In its decision the Federal Court also followed this view and held that isolated and synthesized DNAs are patentable subject matter, but "claims to methods of "comparing" or "analyzing" BRCA sequences" are abstract mental processes and cannot be patented.[603]

After this ruling, the Association of Molecular Pathology asked in December 2011 the Supreme Court to overturn the Federal Circuit decision. In March 2012, the Supreme Court, remanded the case to the Federal Circuit asking to review its decision taking into account the then recent decision of Mayo Collaborative Services v. Prometheus Laboratories, Inc.[604], in which the Supreme Court had held that claims directed to medical diagnostics were not patentable subject matter.[605]

However the Federal Circuit stated in its second Decision[606] that "the case is solely about determining whether claims to isolated BRCA DNA, to methods for comparing DNA sequences, and to a process for screening potential cancer therapeutics" are patent-eligible subject matter under 35 USC § 101 and Mayo v. Prometheus case was not relevant to this proceeding as it did not deal with patentability of gene patents.[607] As a

[603] Case 653 F.3d 1329 (2011) AMP v. USPTO

[604] Supreme Court Decision 566 US 66 (2012) Mayo Collaborative Services v. Prometheus Laboratories, Inc.

[605] The Federal Circuit judgement was vacated, and the case was remanded back to the Federal Circuit.

[606] Case 689 F.3d 1303 (2012) AMP v. USPTO

[607] Ibid stating "Before reviewing the applicability of the Supreme Court's Mayo holding to the claims of the Myriad patents, however, it is important to state what this appeal is not about. It is not about whether individuals suspected of having an in-creased risk of developing breast cancer are entitled to a second opinion. Nor is it about whether the University of Utah, the owner of the instant patents, or Myriad, the exclusive licensee, has acted improperly in its licensing or enforcement policies with respect to the patents. The question is also not whether it is desirable for one company to hold a patent or license covering a test that may save people's lives, or for other companies to be excluded from the market encompassed by such a patent—that is the basic right provided by a patent, i.e., to exclude others from practicing the patented subject matter. It is also not whether the claims at issue are novel or nonobvious or too broad. Those questions are not before us. It is solely whether the claims to isolated BRCA DNA, to methods for comparing DNA sequences, and to a process for screening potential cancer therapeutics meet the threshold test for patent-eligible subject matter under 35 USC § 101 in light of various Supreme Court holdings, particularly including Mayo. The issue is patent eligibility, not patentability…The principal claims of the

result the Federal Circuit did not change its first opinion. It held that genes found in nature are not patentable, neither are those Myriad claims directed to comparing and analyzing DNA sequences. The claims on isolated DNA molecules were again found patent eligible.

Upon this Decision of the Federal Circuit the American Civil Liberties Union and the Public Patent Foundation filed another appeal to the Supreme Court. Myriad also argued that past practice of USPTO in granting gene patents was entitled to a defense citing the Supreme Court Decision J. E. M. Ag Supply v. Pioneer Hi-Bred.[608], where the Supreme Court had held that newly developed plant breeds fall within the scope of § 101, and that neither the Plant Patent Act of 1930 nor the Plant Variety Protection Act (PVPA), 7 U. S. C. § 2321, limits the scope of § 101's coverage. A question during this hearing was whether the enactment of PVPA by the Congress had "implicitly altered the scope of patentable subject-matter under §101". It was noted by the District Court and the Federal Circuit decisions that "Congress did not implicitly repeal § 101 by passing the more specific PVPA because there was no irreconcilable conflict between the two statutes". The Supreme Court decision in J. E. M. Ag Supply v. Pioneer Hi-Bred. Case pointed to the endorsement of the US Congress to the USPTO practice of assigning utility patents for plants.

In giving its Myriad decision[609] the Supreme Court stated that there was no such endorsement in this case, pointed out to the amicus brief of Department of Justice that argued isolated DNA is not patent eligible under §101. The Supreme Court further added that "statutory patent eligibility has its limits and patent protection strikes a balance between creating incentives for creation, invention and discovery and impeding flow of information that might spur invention" and in order to determine the novelty and utility of Myriad claims this standard needed to be used emphasizing that:

> "…Myriad's DNA claim falls within the law of nature exception. Myriad's principal contribution was uncovering the

patents before us on remand relate to isolated DNA molecules. Mayo does not control the question of patent-eligibility of such claims."

[608] Case 534 U.S. 124 (2001) J. E. M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc.

[609] US 576 (2013) Association for Molecular Pathology v. Myriad Genetics, Inc.

> precise location and genetic sequence of the BRCA1 and BRCA2 genes. Diamond v. Chakrabarty, 447 U. S. 303, is central to the patent-eligibility inquiry whether such action was new "with markedly different characteristics from any found in nature," ... Myriad did not create or alter either the genetic information encoded in the BCRA1 and BCRA2 genes or the genetic structure of the DNA. It found an important and useful gene, but groundbreaking, innovative, or even brilliant discovery does not by itself satisfy the §101 inquiry."

Hence the Supreme Court concluded that there were no method claims before the Court, as they had already been invalidated by the district court and the Federal Circuit and they were not the subject of petition.[610] Hence there were no claims on "new applications of knowledge about BRCA genes." The processes used by Myriad to isolate the DNA were widely used and fairly uniform, hence "a naturally occurring DNA segment is a product of nature and not patent eligible" simply because it has been isolated from the surrounding genetic material. But cDNA claims were found to be patent eligible because this "results in an exons-only[611] molecule that is not naturally occurring."

By this ruling Myriad's broadest patent claim on "an isolated DNA coding for a specified protein" became invalid.

Although the genome DNA and cDNA distinction could already be seen in Federal Circuit's Amgen v. Chugai[612] decision and was concluded there for the claim of "purified and isolated DNA sequence consisting essentially of a DNA sequence encoding human erythropoietin" as a claim for the cDNA of the human EPO gene and granted patent protection. Afterwards until the Myriad case, the patent eligibility of cDNA was never questioned. It was also by the Myriad Case that the Supreme Court made a distinction on patentability and patent-eligibility of subject matters. The decision of the Supreme Court has had an immediate effect on the share price of the Myriad company as can be seen

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[610] See the petition p. 7.

[611] Sections of RNA transcripts. The Court referred to the reverse transcriptase process on enzymes to reproduce by copying RNA into cDNA as explained in Chapter 3.1.

[612] Case (927 F.2d 1200 (1991)

from the below chart.

Chart 7: Share price of Myriad Genetics 1995-2018

As indicated in Chapter 2.5 Myriad Genetics Inc. still has the advantage of having the database for the interpretation of VUS results, which may explain the rise in the stock price in 2014. Myriad Genetics Inc. is still a huge company with 2,300 worldwide employees and 2017 fiscal year revenues at USD 771.4 million.[613] Still there was a huge decline in stock prices again in 2016, probably due to the fact that the Company's dependence on cancer-test revenues and that these revenues from cancer testing were decreasing.[614] In 2018 we see a stock price rise again probably due to the fact that FDA

[613] Company webpage corporate fact sheet available at https://myriad.com/about-myriad/inside-myriad/myriad-fact-sheet/ last visit 30.04.2020.

[614] See Annual Report 2016 available at https://investor.myriad.com/archived-annual-reports last visit

approved the first BRCA-mutated breast cancer treatment drug on 12.01.2018.[615]

4.2.3 Anti-commons problems

Although there are several patentability requirements in the US law such as novelty, utility, nonobviousness, and disclosure, specific court cases show that to avoid the anti-commons problem specific features of the patent system needed to be addressed.

Anticommons problem leads to inefficient results in commercial products in gene patents because multiple owners hold complementary patents. In medical biotechnology the commercial product from a gene patent is a therapeutic or diagnostic product. A researcher working on a therapeutic drug by using recombinant peptides or proteins needs to have access to several genetic materials, which have been granted patent protection. But there may be high transaction costs associated with such a bargaining. In accordance with Coase Theorem, if bargaining was costless the patent would be assigned to the party that valued it the highest.[616] On the other hand, in real life situation of a genetic researcher, although bargaining is possible, it comes often at a very high cost of licensing and royalty negotiations. Part of this bargaining also includes strategic bargaining. Coase Theorem overlooks strategic behavior of companies, which itself is an important transaction cost.[617] As Scotchmer (1991) notes in cases of blocking patents on cumulative innovation, the "problem is especially acute where the initial innovation has little value of its own but is a foundation for a more valuable second -generation product. Even with licensing the

30.04.2020 share price fluctuates between USD 28 and 39 in the 4th quarter ending end of June at p.34.

[615] FDA press release 12.01.2018 FDA approves first treatment for breast cancer with a certain inherited genetic mutation available at https://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm592347.htm last visit 30.04.2020.

[616] See POSNER supra note 410 argues (along with Coase theorem) that with zero transaction costs, the ultimate use of the property is not determined by the initial assignment of the property rights, because resources shift to those who have the highest willingness to pay. As such resources are used efficiently. However, he recognizes at the same time that this is in practice difficult to apply.

[617] MERGES R. P. (1994). Intellectual Property Rights and Bargaining Breakdown: The Case of Blocking Patents. *Tennessee Law Review*, Volume 62 pp 75-106.

first innovator may not capture the full social value and have less incentives to invest."[618] If the value of the improvement product is higher than the pioneer invention, the possibility of strategic bargaining by the initial inventor is high.[619] There are significant social welfare gains from pioneer – improvement transactions and property rights must be structured to encourage improvers to approach pioneers with licensing proposals.[620]

The existence of separate patents on complementary gene fragments may make the transaction costs of assembling genetic material needed for research very high.[621] As a result these high transactions costs researchers especially from smaller research institutes and corporations may be discouraged from doing research in areas where they have got access to multiple patents. This in return may impede development of new innovative products and leaves to research environment to big institutes and / or corporations, which can afford such transaction costs in licensing, but also in litigation. Indeed, the kinds of patents that do not contribute to innovation are sometimes called as "junk" patents. They can be regarded as a fee and make the innovation more expensive, especially for end – users.

4.2.3.1 Amgen v. Chugai Pharmaceutical

Due to nonobviousness reasons explained in Chapter 3.4.4, Amgen had also filed a suit against Chugai.[622] Indeed, the patent of Chugai on human EPO[623] was issued in June 1987 a few months earlier than that of Amgen's. The claims contained among others "a homogenous EPO and a pharmaceutical composition for the treatment of anemia comprising a therapeutically effective amount of the homogeneous EPO". Amgen's patent was issued in October 1987 and the claims contained among others "a purified and

[618] See Scotchmer at supra note 142 at p.39.

[619] See Rai at supra note 67 at p. 833.

[620] See Merges supra note 617.

[621] See Landes and Posner supra note 4 at p. 319.

[622] 927 F.2d 1200 (Fed. Cir. 1991) Amgen Inc. v. Chugai Pharmaceutical Co. Ltd and Genetics Institute

[623] Erythropoietin (EPO) is a hormone produced in kidneys to induce formation of red blood cells in the bone marrow.

isolated DNA sequence consisting essentially of a DNA sequence encoding human EPO".

Amgen filed suit against Chugai and Genetics Institute (GI) on the same day as its own patent was issued alleging that the GI had infringed the Amgen patent by the production of a recombinant EPO similar to human EPO "by use of transformed mammalian host cells containing vectors with DNA coding for the production of human EPO".[624] Chugai had also allegedly contributed to this infringement by cooperating with GI. Chugai and GI answered to these allegations by counterclaiming that Amgen's patent was invalid under 35 USC patentability requirements.

The district court held that some of the claims of the Amgen patent were not valid, some were valid, but the infringement by the GI was not willful, and also that the Amgen patent did "not contain a process claim" and Chugai had not infringed any claim of this patent. Hence Amgen's complaint about Chugai was dismissed. With the same reasoning the Court held that some of the claims of the GI patent were not valid, some were valid but had not been willfully infringed by Amgen.

Both parties appealed to the Federal Court. The first issue that the Federal Court reviewed was whether there was an error in the district court's decision "in finding that the claims directed to a purified and isolated DNA sequence encoding human EPO were not invalidated by the work of GI". Chugai and GI challenged this ruling on the grounds that "as of September 1983, one of ordinary skill in the art would have had a reasonable expectation of success in screening a gDNA library by Amgen's method in order to obtain EPO". The Federal Circuit upheld the district court decision that Amgen's method of isolating the human EPO gene from a gDNA library using a fully-degenerate probes was nonobvious, because prior work practiced by defendants on cDNA from a baboon did not achieve the aimed result till Amgen isolated the EPO gene with its set of probes explaining:

> "The (district) court found that no one had successfully screened a genomic library using fully-degenerate probes of such high redundancy as the probes used by (*Amgen)- (*emphasis added*)*. In the face of this and other evidence on both sides of the

[624] Explained in procedural history of the case.

> issue, it concluded that defendants had not shown by clear and convincing evidence that the procedures used by (*Amgen)-(*emphasis added*)* would have been obvious in September 1983… While the idea of using the monkey gene to probe for a homologous human gene may have been obvious to try, the realization of that idea would not have been obvious."

As a result, the Federal Circuit concluded also depending on expert testimonies that Chugai and GI could not demonstrate that the Amgen procedures would have been obvious. The decision of the district court in this regard was found to be correct and the claims were deemed valid.

Another issue that the Federal Court examined was whether Amgen violated the best mode requirement of 35 USC § 112 by failing to show the best mode host cells. The district court had held that it was not, and Chugai and GI had appealed to this decision, as well arguing that:

> "[i]n the field of living materials such as microorganisms and cell cultures, we should require a biological deposit so that the public has access to exactly the best mode contemplated by the inventor."

It is also noted in the Federal Court ruling that it has been a routine procedure for many patent applicants to "place microorganism samples in a public depository when such a sample is necessary to carry out a claimed invention". This was found to be sufficient to meet enablement requirement by several Federal Court rulings. The District Court had held that Amgen's "use of a specific genetically-heterogeneous strain of Chinese hamster ovary (CHO) cells, which produced EPO at a rate greater than that of other cells" was the best mode. The two strains used by Amgen were disclosed in the patent application of Amgen, and at the time Amgen researcher did not know a better mode. However, Chugai argued that these strains were "not adequately disclosed so that one skilled in the art could duplicate Amgen's best mode without having first deposited a sample of the specific cells in a public depository". So, Chugai argued that in order to have adequate disclosure these CHO cells should have been placed at the public depository. The district court had concluded:

> "[o]ne must not receive the right to exclude others unless at the time of filing he has provided an adequate disclosure of the best mode known to him of carrying out his invention. Our case law has interpreted the best mode requirement to mean that there must be no concealment of a mode known by the inventor to be better than that which is disclosed."

The district court further stated that although Amgen's written description in the application was not clear enough so as to say which of the two strains is considered to be the best, since both possible strains were disclosed, the best mode requirement was met.

The Federal Circuit referred to the recently published USPTO guidelines on the deposit of biological materials so that they do not need to be deposited "if it is known and readily available to the public or can be made or isolated without undue experimentation" and further stated that it does not see any inconsistency between the District Court's decision and these guidelines. On the question of whether deposit requirement is applicable to best mode, the USPTO had responded:

> "The best mode requirement is a safeguard against the possible selfish desire on the part of some people to obtain patent protection without making a full disclosure. The requirement does not permit an inventor to disclose only what is known to be the second-best embodiment, retaining the best… The fundamental issue that should be addressed is whether there was evidence to show that the quality of an applicant's best mode disclosure is so poor as to effectively result in concealment… If a deposit is the only way to comply with the best mode requirement then the deposit must be made."

The Federal Circuit further stated that the Court found the allegation by Chugai and GI groundless that a copy / duplicate of Amgen's best mode cell strain could not be made by scientists. Because an exact duplication is not deemed necessary. The real issue is as also shown by the district court whether the disclosure is adequate so that someone "skilled in the art could produce mammalian host cell strains or lines with similar levels of production of EPO" identified in Amgen's description.

However, Amgen's original claim was very broad; wishing for entitlement for all EPO gene analogues. Besides, GI's patent claims were drafted with an expression of "at

least about".[625] The district court had found these claims to be indefinite and hence invalid because the "about" refers to an effort to reclaim an activity level between prior art and the level at which the claims were accepted in earlier rulings. When inquired, the GI scientist who had worked on the invention could not define the level in his testimony.

Here the Federal Circuit ruled that Amgen can claim only the particular analogues of the EPO gene that were disclosed stating:

> "It is well established that a patent applicant is entitled to claim his invention generically, when he describes it sufficiently … Here, however, despite extensive statements in the specification concerning all the analogs of the EPO gene that can be made, there is little enabling disclosure of particular analogs and how to make them. Details for preparing only a few EPO analog genes are disclosed. Amgen argues that this is sufficient to support its claims; we disagree. This "disclosure" might well justify a generic claim encompassing these and similar analogs, but it represents inadequate support for Amgen's desire to claim all EPO gene analogs. There may be many other genetic sequences that code for EPO-type products. Amgen has told how to make and use only a few of them and is therefore not entitled to claim all of them."

On "at least about" claims, the Federal Circuit affirmed the district court's invalidation.

With this ruling the Federal Circuit accomplished the avoidance of anticommons problems in gene patents by stating that the inventors can claim only what they have discovered and not more. Besides, it was acknowledged that adequate disclosure in gene patents would mean including the necessary number of examples, which show the structure of the subject matter, its physical, chemical properties, or other distinguishing characteristics and the best way of obtaining it without undue experimentation. Otherwise, disclosure requirement would not be met for failure to comply with written description, enablement, and best mode requirements. The Federal Circuit further

[625] The claim concerned a homogeneous EPO with a specific activity of at least about 160,000 IU (international unit of enzyme activity).

acknowledged that according to expert testimony, there had been no success in cloning the EPO gene "till the gene was in fact isolated and its sequence was known" and that the district court decision was correct that neither party had an adequate conception of the DNA sequence until Amgen researcher was the first one who successfully reduced it to practice.

Enablement requirement is especially important for gene patents due the rapidly changing industry and the uncertainty that can be brought by means of transaction costs, patent tickets and anticommons problems. The increased enablement and written description requirement standards in this case allowed the patent system to operate at a better level for gene patents as can be seen in the following case, which were heard after Amgen v. Chugai case.

In brief: Adequate disclosure requires giving sufficient examples showing the structure of the subject matter and its properties and the best way of obtaining the matter without undue experimentation. Narrowed claims can avoid the anticommons problems. Indefinite expressions, guesstimates on claims fail to satisfy the requirement.

4.2.3.2 Fiers v. Revel v. Sugano[626]

The case involves a three-face interference proceeding among three researchers on priority of their invention, which claimed to a "DNA coding for a human fibroblast beta interferon (J-IF), which is a protein that promotes viral resistance in human tissues". Sugano applied to USPTO in October 1980, Fiers in April 1981, and Revel in September 1982. The filing date for Sugano was March 1980 (in Japan), for Revel 1979 (in Israel), and for Fiers April 1980 (in the UK). Sugano's claim disclosed the "complete nucleotide sequence of the DNA that codes for J-IF, and a method for isolating the DNA". Ravel's claim disclosed "a method for isolating a fragment of the DNA that codes for J-IF", but not the complete sequence. Fiers, on the other hand claimed priority under (pre-AIA) 35 U.S.C § 102(g) for earlier conception in September 1979 or January 1980. Allegedly his

[626] Case 984 F2d 1164 (1993).

ideas were brought to the US from abroad and were given a reduction to practice in April 1980. He then filed an application in the UK "disclosing the complete nucleotide sequence of the DNA that codes for J-IF". He argued that a protocol he had given to two further scientists to bring to the US disclosed his proposed method of isolating the DNA that codes for J-IF, and this would allow someone with ordinary skills in the art to isolate the DNA without undue experiments. The availability of this protocol was confirmed by these two scientists. A draft application with the method of Fiers but without the complete sequence had also been brought to the US by his lawyer in February 1980.

It was Sugano, who was entitled to priority by USPTO Board of Appeals due to his earlier filing date and disclosure of full DNA sequence. Fiers could not prove conception of the DNA prior to his filing date. Similarly, Revel had not disclosed the complete DNA sequence at his application.

In giving this decision the Board of Appeals relied on the decision of Amgen v. Chugai in which the requirements for the conception of a DNA sequence were given, and stated the conception was not established merely because Fiers had disclosed before April 1980 only the **method** (emphasis added) of DNA isolation and had submitted expert testimony that someone skilled in the art could produce the DNA by this method. Success of the method would not have been known till the J-IF gene was actually isolated and its sequence was known. His British filing disclosed the complete DNA sequence. However, his British filing in April 1980 was after Sugano's Japanese filing in March 1980.

Fiers and Revel then appealed to the Federal Circuit. Fiers argued that the Board erred in reading the Amgen v. Chugai decision as if it established a rule that one needs to disclose the complete DNA sequence in order to show conception of a DNA coding for a protein. So, in fact Fiers argued that the written description requirement as set forth by the decision of Amgen v. Chugai would apply only to cases where disclosed method for isolating the DNA sequence could not be done by someone with ordinary skills in the art. Because his method was much easier than that of Amgen, where the researchers of Amgen had to screen a genomic library with fully degenerate probes and all he had to do was to screen a cDNA library, which is a routine screening technique for those skilled in the art. In contrast to the Amgen case, the first thirteen amino acids of the J-IF were already

known to the art. However, the Federal Circuit stated that it was held in Amgen case conception occurs when the substance can be defined by its biological activity or function and that the aim of the law is to disclose new inventions instead of research plans. It is a well-known statement of the Federal Circuit from Amgen case that conception is not deemed achieved until the reduction to practice has occurred, until after the genes / compounds have been isolated.

As a result, the Federal Circuit rejected the arguments of Fiers concluding these were related to the enablement requirement – that his method was enabling someone skilled in the art, instead of showing conception. After this case the inventors had to disclose the claimed sequence at the time of the application, and it was understood that showing workable methods for preparation of a DNA would not establish conception of that DNA.

Revel on the other hand had argued that his Israeli application had met the written description requirement, as his scope and wording in this application were similar to those in the proceeding. However, both the Board of Appeals and the Federal Circuit concluded that this application does not describe the disputed DNA sequence and is an inadequate disclosure to convey that Ravel was indeed in possession of the DNA. Again, relying on Amgen v. Chugai decision, the Board had concluded that the Israeli application would not meet enablement requirement, since "logically, one cannot enable an invention that has not been conceived."

On written description requirement the Federal Circuit concluded that "Adequate written description of DNA requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it; what is required is a description of the DNA itself." As a result, the Federal Circuit confirmed the decision of the Board of Appeals that Revel did not disclose the complete nucleotide sequence in its Israeli filing, hence could not meet the written description requirement for the DNA coding for J-IF.

Fiers had also argued that Sugano's application was not enabling, since he did not show "extrinsic evidence showing enablement". Once again, the Federal Circuit relied on

Amgen v. Chugai Decision for support that enablement review is done from the beginning (de novo):

> "Enablement requires that the application 'contain a description that enables one skilled in the art to make and use the claimed invention… Thus, once the examiner accepted the sufficiency of Sugano's specification, Sugano had no further burden to prove by extrinsic evidence that his application was enabling; the Board correctly determined that it was Fiers (or Revel) who then had to prove that Sugano's application was not enabling. Even if Fiers had no opportunity to cross-examine Sugano because Sugano elected to stand on his filing date, Fiers had other opportunities, including during the motion period, to challenge Sugano's entitlement to his Japanese application filing date. Thus, he did not lack opportunity to challenge."

The Federal Circuit confirmed the decision of the Board of Appeals and awarded Sugano priority since Sagano's Japanese application described the complete and correct sequence of the DNA coding for J-IF with the disclosure of the method to obtain it.

It can be seen how the case law in gene patents builds upon previous cases and how the legislators adapt to changes in the biotechnology inventions. It is also interesting that the applicants before this case did not see the need to show the genomic sequence of the DNA that is the subject matter of their claims. With Fiers decision it was understood that an adequate written description of the DNA requires more than showing an isolation method to obtain this DNA. The actual sequence must be shown. Because having shown a method for mRNA to be put into reverse transcription does not necessarily imply that the DNA will definitely be obtained.

In brief: Having a method or plan to develop a subject matter is not sufficient to satisfy written description requirement; full disclosure, the actual possession and conception must be demonstrated in the patent application. In this case the applicants were claiming a subject matter that was broader than what they have invented. The Court concluded that "Claiming all DNAs that achieve a result without defining the means that will do so is not in compliance with the description requirement." The description shall include "structure, formula, chemical name, or physical properties".

4.2.3.3 In re Fisher

Fisher applied in 2001 for patent protection with claims concerning compounds and compositions (purified nucleic acid sequences that encode for proteins and its fragments) derived from maize (corn) plant tissues. The claimed sequences were ESTs, the initial application included a sequence listing for partial sequences for some 32.000 nucleic acids. Claim 1 was for nucleic acid molecules, Claim 2 for proteins and Claims 3-7 for transformed plants. [627] The exact structure or function of these sequences or the encoded proteins were not known by Fisher. He had only identified some potential uses for these ESTs. The examiner required Fisher to narrow down his listing set, and Fisher selected the first five sequences. Yet USPTO examiner rejected this application due to failure to meet the utility requirement under 35 U.S.C § 101 and enablement requirement under 35 U.S.C §112. Fisher appealed first to the USPTO Board of Patent Appeals, which approved the decision of the examining board, resulting from lack of enablement due to lack of utility stating that "none of the suggested uses provided a specific or substantial benefit in currently available form"[628], quoting Case Brenner v. Manson.[629] The Board also stated that since Case Brenner v. Manson the Board and its predecessor have used the phrases substantial utility and practical utility interchangeably.[630]

Fisher then appealed to the Federal Circuit. When hearing the case, the Federal Circuit relied on the ruling from the Case re Ziegler[631] to assert enablement.

> "If the application fails as a matter of fact to satisfy 35 USC § 101, then the application also fails as a matter of law to enable one of ordinary skill in the art to use the invention under 35 USC § 112."

In other words, the Court stated that the utility requirement is a pre-requisite for

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[627] Federal Circuit Decision 421 F.3d 1365 (2005) In re Fisher, see Brief and addendum for appellee, Director of the USPTO, December 7, 2004 No: 04-1465 (Serial No. 09/619,643) p.1

[628] Ibid p.12

[629] US Supreme Court Decision 383 U.S. 519 (1966)

[630] See the Brief in supra note 627 at p.10.

[631] 992 F.2d 1197 (Fed. Cir. 1993)

the enablement requirement. And the claimed invention must show "specific and substantial utility."

Another case that was referred by the Federal Circuit was the Supreme Court's ruling in Brenner v. Manson that "…A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." It was emphasized in that the Supreme Court wanted to avoid an "unwarranted monopoly to the detriment of the public."

It was further noted in the USPTO Brief[632] to the Federal Circuit that Fisher's claims do not satisfy the utility requirement under § 101 and further experimentation will be necessary to determine the functions and properties of claimed molecules. Also, a reference was made to the problems in granting patent protection with the assumption that any pure EST is useful so that too many patents could block innovation, by referring to the Supreme Court case Sears, Roebuck & Co. v. Stiffel Co.[633]

> "…the present specification does not disclose that any specific substantial benefits are currently available. Fisher may be "on the way to discovering a practical utility," but is not there yet….methods for making cDNAs, methods for random sequencing, robots for implementing the methods, and computers for comparing the ESTs may be patentable, until a specific benefit is identified for an EST, an individual EST is not useful under § 101….It easy to see that if Fisher's EST is a random fragment of a cDNA, and another party discloses a different EST of the same cDNA, both could obtain patents covering the same cDNA, but § 101 states that only one patent can issue on an invention. For each of the genes, or fragments thereof, that is the subject of a patent claim held by someone else, a license would have to be

[632] See USPTO Brief at supra note 627

[633] Ibid pp 44-46 Sears, Roebuck & Co. v. Stiffel Co., 376 U.S. 225 (1964) where it was ruled by the Supreme Court that federal states cannot make their own legislation that give similar effects as patent protection. Stiffel Co. had some design and mechanical patents on pole lamps and Sears, Roebuck & Co put copies of lamp on the market and was sued by Stiffel Co. on patent infringement and unfair competition. Although the district court found the patents invalid, ruled and Sears, Roebuck & Co. to be guilty of unfair competition. The Appeal Court (7th. Circuit) affirmed the decision of the district court. The Supreme Court ruled that in rewarding useful invention, the rights and welfare of the community must be dealt fairly and guarded effectively. An article which is not patentable or on which the patent has expired is in the public domain and cannot be denied to anyone. Thus, the Supreme Court revised the decision of the 7thCircuit Appeal Court.

> negotiated. Each overlapping patent claim would be an extra "tollbooth" for the same cDNA. The Supreme Court has warned against allowing too many tollbooths on the road to innovation."[634]

The Federal Circuit found that "substantial evidence supports the Board's finding that the claimed compounds do not have a specific and substantial utility and are not enabled", thus, affirmed the decision of the USPTO Board of Appeals that "the proposed possible uses were so general that they did not have a specific meaning". As such the patentability of (ESTs) was rejected for lacking utility and enablement.

Although this case relates to the patentability of genes from an agricultural biotechnology point of view, it is a pioneering one in terms of increased utility requirement and shows the evolution of case law concerning gene patents. Patent grant to ESTs was rejected as ESTs were accepted as research tools. It was for instance noted that "one of the claimed ESTs, could only be used to detect the presence of genetic material having the same structure as the EST itself". Unless the claims show substantial or practical utility, a patent could not be granted. And it was noted that although the Supreme Court did not define the terms "specific" and "substantial", the Courts and the USPTO have used the terms "practical", "real world", "substantial" interchangeably meaning "immediate benefit to public". And the term "specific" refers to disclosure of a use that is "not so vague as to be meaningless".

In Brief: The Federal Circuit issued an unfavorable judgement in granting a broad patent protection to ESTs for failing to meet the substantial utility criteria adopted by the Supreme Court in Brenner v. Manson. There the Supreme Court said that "the basic (rationale of) granting a patent monopoly is the benefit derived by the public from an invention with substantial utility…A patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion… [A] patent system must be related to the world of commerce rather than to the realm of philosophy." A patentee cannot look for utility after he has gained protection, hence monopoly power. It was foreseen by the Court that granting a broad protection without utility could block further

[634] See USPTO Brief at supra note 627 pp. 24,27,45.

innovation.

If patent rights are assigned rightfully, inefficiencies such as transactions costs and anticommons problems can be eliminated even for a fast-paced developing sector such as biotechnology.

All of these cases explained above show that the patent system in the US moved towards an efficient system from law and economics point of view over time especially with Federal Circuit rulings.

In re Fisher decision of the Federal Circuit we see that the utility requirement was reinforced, and the patent protection was denied to five ESTs not showing specific, substantial utility. An anticommons problem could arise if the patents were granted to these ESTs as research tools. The exclusive rights given to an upstream technology might have hindered the downstream product development. But by requiring specific and substantial utility for the claims, the Court addressed this issue.

In Amgen v. Chugai the Federal Circuit affirmed the district court decision that Amgen's method was nonobvious and also that disclosure of cell strains would suffice for the best mode requirement. By the time this case was heard first to invent system was in applicable and Genetics Institute claimed that it was the first to conceive the probe of the DNA sequence. The Federal Circuit held that a mere DNA sequence cannot be considered as an invention until the gene with this sequence has been isolated. Hence Amgen method was found to be novel. On the other hand, the Federal Circuit found that the disclosure by Amgen on a few analogue genes would not be sufficient to claim all gene analogues. On enablement requirement the Federal Court also placed high scrutiny and found the patents of Genetic Institute to be invalid for failing to meet the enablement requirement. In short it affirmed the district court decision that the patents of Amgen were valid except for the broad claims they ask for.

In Fiers v. Revel decision the Court addressed adequate written description problem and asked for improved disclosure by requiring a description of the DNA. A mere statement referring to a "potential method of isolating it" was not found to be sufficient to meet the requirement.

In Kridl v. McCormick the Federal Circuit assessed prior art corroboration in order to determine whether the utility requirement has been fulfilled and applied rule of reason analysis to evaluate the evidence in order to decide who had conceived the invention first and ruled that in some cases the corroboration of utility may be present in the evidence put forward.

Federal Court decisions offer some guidelines on patentability requirements by not blindly applying the generalized rules but by assessing the cases with their specifics. With these decisions, utility, novelty, disclosure, written description, enablement criteria have risen, socially beneficial outcomes were preferred and some anticommons problems were addressed by applying nonobviousness criteria taking prior art with its scope and commercial viability into application. Because unlike in some other industries, defining what is obvious in biotechnology is a very complex task. For instance, in some sectors the nonobviousness criteria considers the end-product.[635] But at Federal Circuit's biotechnology decisions, consideration was also given to methods of conceiving the end-products.

As a result, broader claims needed to be narrowed down. As the biotechnological inventions increase over time, it becomes more predictable for inventors to assess what type of claims would be permissible. It will further down have a positive impact as increased certainty lowers transactions costs.

4.3 Orphan drugs and treatment of rare diseases

Orphan drugs are medicines that are used to treat rare diseases, which affect a small percentage of the population. In the US, this corresponds to less than 200.000

[635] For example, in re Durden 763 F.2d 1406 (Fed. Cir. 1985), the claims were directed to "novel oxime compounds, novel insecticidal carbamate compounds and a novel process for producing the carbamate compounds, employing the novel oxime compounds as the starting materials". USPTO rejected the process claim where "patentable starting materials" were used to form the end-product. The Court also ruled that the "process claim was obvious in light of the prior art". This decision formed a basis for biotechnology decisions as explained in Chapter 3.4.4.

individuals.[636] In the EU the definition of rare diseases is life threatening or chronically debilitating conditions whose prevalence is less than 5 per 10,000 in the Community.[637] There are over 6000 different rare diseases identified to date affecting over 60 million people in Europe and the USA alone.[638] Since 80% of the rare diseases are of genetic origin,[639] there are big opportunities for medical biotechnology companies to develop orphan drugs.

Treatment of rare diseases is seen as a public policy aim both in the EU and in the US, and incentives are given to innovators for development and marketing of medicinal products that would otherwise have lacked the necessary investment due to low levels of sales and profit return, especially with 20 years of patent term.

In the US, Orphan Drug Act of 1983 aims to increase the development of drugs for rare diseases with certain incentives such as tax incentives, R&D grants, waived fees, shorter approval terms, and seven years of market exclusivity. Indeed, the Act has been successful in creating incentives for pharmaceutical companies to develop such drugs. 20 years before the enactment of the legislation only 10 orphan drugs were developed, in 1984 alone 24 new drugs were approved.[640] Since 1983 Food and Drug Administration of the US approved more than 600 drugs and biologic products for rare diseases.[641]

In the EU, pharmaceutical innovators with an orphan medicinal product also benefit from waived fees, ten year of market exclusivity after authorization of the product, scientific assistance, and the possibility of Community authorization for such products. As of January 2014, 90 orphan drugs had been authorized by the European Commission

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[636] US Rare Diseases Act (2002) Sec. 2(a)(1)

[637] Regulation (EC) No 141/2000 on orphan medicinal products Art. 3(1)(a)

[638] See EURORDIS-Rare Diseases Europe- European Patient NGO website available at https://www.eurordis.org/about-rare-diseases last visit 30.04.2020.

[639] See Ibid.

[640] See Cooter and Ulen supra note 32 p. 125.

[641] See US Food and Drug Administration website available at https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/default.htm, last visit 30.04.2020.

and the Commission had designated more than 1000 products as orphan medicinal products.[642]

The difference in the market exclusivity term of 10 years in the EU and 7 years in the US can be attributed to the fact that there cannot be a unique tax incentive scheme in the EU, as in the US, since taxation in the EU falls under the jurisdiction of the member states. In the US there is a 50% tax credit for clinical trial costs of orphan drugs. The Congress made the tax credit permanent from May 31, 1997.[643]

The safety and the efficacy of the orphan drugs may not be as certain as other drugs at the time of market authorization due to limitations in testing and clinical trials. Economic limitations with respect to reimbursement schemes create a problem in terms of patient access to orphan drugs. Although there is a central marketing authorization unit at the EU-level, namely the European Medicines Agency (EMA), the reimbursement policies of EU member states also differ, as in the case of tax incentives described above. Marketing approval does not automatically mean that the drug costs will be covered by national health systems. Member states have different criteria to decide whether the drugs will be reimbursed such as relative effectiveness analysis in France and Germany, cost-effectiveness analysis in England and other methods.[644] After evaluating these criteria,

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[642] Implementation Report on the Commission Communication on Rare Diseases: Europe's challenges and Council Recommendation of 8 June 2009 on an action in the field of rare diseases at p. 13 available at https://ec.europa.eu/health/sites/health/files/rare_diseases/docs/2014_rarediseases_implementationreport_en.pdf last visit 30.04.2020.

[643] SEOANE-VAZQUEZ E. et al. (2008). Incentives for orphan drug research and development in the United States. *Orphanet Journal of Rare Diseases*, Volume 3, Issue 33- doi: 10.1186/1750-1172-3-33. Last visit 30.04.2020 However, there is a broad tax bill in the US introduced on 2.11.2017 with several measures aiming to decrease the tax rate on corporations to 20% from 35%, but also to abolish the tax credit on orphan drugs. Full text of the bill can be read at. https://www.congress.gov/115/bills/hr1/BILLS-115hr1rh.pdf last visit 30.04.2020.

Biopharmaceutical industry replied to the bill by stating its approval to lower the corporate tax rate but also expressing its desire to encourage innovation by maintaining the Orphan Drug Tax Credit. The statement of Biotechnology Innovation Organization (BIO – a trade association representing biotech companies, academic institutions, state biotech centers and related organizations in the US and in some 30 other nations) can be read at https://www.bio.org/press-release/bio-statement-house-gop-tax-reform-bill.last visit 30.04.2020 The bill was passed by the House with repeal of the orphan drug tax credit abolishment on 16.11.2017.

[644] LEYENS, L. et al. (2015). Available Tools to Facilitate Early Patient Access to Medicines in the EU and the USA: Analysis of Conditional Approvals and the Implications for Personalized Medicine. *Public*

member states set the prices of the drugs and decide on the reimbursement schemes. Although there are faster evaluation processes leading to shorter assessment periods such as FDA priority review program or Early Access to Medicines Scheme in the UK, where patient access can be assured even before by the eventual EU approval of the drug[645], this evaluation may still take several years. This situation can constitute a problem for patient access. An example is the approval procedures of two identical products for the treatment of Fabry disease, which is a rare genetic disorder caused by the lack or decreased activity the enzyme α-galactosidase in human body. Two companies, Transkaryotic Therapies and Genzyme Corporation, applied for similar enzyme replacement products at the same time at the European agency, as then called European Agency for the Evaluation of Medicinal Products (EMEA), and in the US at the FDA. EMEA approved both products in 2001. Since the US orphan drug legislation allowed for only one drug to be authorized, FDA on the other hand approved after a close scrutiny on clinical efficacy, the product of Genzyme two years later in 2003.[646]Although the drug was approved 2 years earlier in the EU, patients in several member states have had several problems in terms of reimbursement due to cost-effectiveness analysis of member state healthcare systems, and patient access to the drug was severely impeded. For instance the Dutch Healthcare Insurance Board issued an advice in 2012 not to reimburse several orphan drugs one of which is the one that is used in treatment of Fabry disease with the reasoning that although the enzyme replacement therapy offered an added therapeutic value, it was not cost-effective at an incremental cost of EUR 3.3 million per quality adjusted life-year gained and the reimbursement of the drug would not allow resources to be made available to other more cost-effective health technologies.[647] It was argued by the experts that the effectiveness of the enzyme replacement therapy is different across patient sub-groups

Health Genomics, Volume 18, Issue 5, pp.249-259.

[645] Ibid. p. 253

[646] DESNICK, R.J. (2004). Enzyme replacement therapy for Fabry disease: lessons from two α-galactosidase A, orphan products and one FDA approval. *Expert Opinion on Biological Therapy*, Volume 4, Issue 7, pp.1167-1176.

[647] See SIMOENS S. et al. (2013). Cost-effectiveness Assessment of Orphan Drugs. *Applied Health Economics and Health Policy*, Volume 11, Issue 1, pp. 1-3.

and the proposal was to launch a compulsory EU-wide registry following the market authorization of an orphan drug.[648]A comparative study of Belgium, France, Italy, Sweden, the Netherlands and the UK, in which a survey was completed by national experts, revealed that these countries, although they were selected for comparable living standards and the fact that health expenditure is primarily financed by tax payers, have adopted different approaches towards the institutional context, marketing authorization procedures, pricing, reimbursement and redistribution channels.[649] Another finding indicates that availability of and access to orphan drugs vary considerable among EU member states and the ones that were formerly "western" have achieved better access for their patient groups. The objectives of budget impact analysis in formerly "eastern" member states stay unclear and untransparent. For instance, in Bulgaria average time period from market authorization to a positive decision by the health authorities on reimbursement takes 43 ± 29.1 months.[650]

In addition to the existing medical biotechnology companies, the orphan drug legislation also helped to the foundation of new companies. It is difficult for new companies to attract private funds at the early stage of development since private funds cannot have an accurate valuation of new technologies at this stage and may be unwilling to invest. Indeed, it is found that early-stage investment requires higher trust, and the investors are highly responsive to information about the founding team.[651] Private funds

[648] Ibid, p.2

[649] DENIS A., et al. (2010). A comparative study of European rare disease and orphan drug markets, *Health Policy*, Volume 97, Issues 2–3, pp 173-17. For instance there is an existing domestic market authorization only in France, there are incentives for R&D on rare disease / orphan drugs research only in France, Italy and the Netherlands, there are free pricing systems in Sweden and the UK, whereas the other countries have a fixed pricing system, Belgium and the UK do not allow community pharmacies to sell the drugs, these drugs can only be sold in hospital pharmacies, Belgium is the only country that allows for the partial reimbursement in addition to full reimbursement, the Netherlands and the UK allow general practitioners to prescribe the drugs, whereas it has to be a specialist physician in the other countries.

[650] ISKROV G., et al. (2012). Challenges to orphan drugs access in Eastern Europe: The case of Bulgaria. *Health Policy*, Volume 108, Issue 1, pp 10-18.

[651] BOTTAZZI, L., DA RIN, M. & HELLMANN, T., (2016). The Importance of Trust for Investment: Evidence from Venture Capital, *The Review of Financial Studies*, Volume 29, Issue 9, pp 2283-2318, also BERNSTEIN S., KORTEWEG A. & LAWS K. (2017). Attracting Early-Stage Investors: Evidence from a Randomized Field Experiment, *The Journal of Finance*, Volume 72, Issue 2, pp. 509-538 at p.511. The authors used an online platform that brings investors and start-ups together and concluded in their experiment that potential investors value the human capital of the start-ups a lot even after checking their

may tend to invest by informed decisions backed with solid evidence of scientific performance in later-stage projects with commercial feasibility. Indeed, a study confirms for venture-funded firms in Germany that these firms have a higher number of patent applications obtained even before the venture capitalists' investment and venture capitalists seem to focus on commercialization of existing innovations and growth of the firm.[652] As seen in Chapter 2.3.2 public funds can help in those cases to do more breakthrough medicinal research and bring related products onto the market. A study on the relationship between federal funds and local biotechnology firm creation in the U.S shows that federal funds towards academic institutions increase the local biotechnology firm birth rate by 5.9% and federal funds towards incumbent biotechnology firms increase the local biotechnology firm birth rate by 58.10 %.[653]

Orphan Drugs case is a good example where changing of the regulatory framework stimulated the development of such drugs, as well had positive effects on entrepreneurship in medical biotechnology even in its earlier years of enactment. The US Office of the Inspector General report of 2001 states that growth of orphan drug products mirrors the biotechnology industry growth after the Orphan Drug Act and affirms that market exclusivity has helped the biotechnology companies to attract venture capital.[654] For the profitability of the orphan drugs vis-à-vis non- orphan drugs it is difficult to make an estimate.[655] However the positive effect of supply-side tax incentives to stimulate the

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ideas.

[652] ENGEL D. & KEILBACH M. (2007). Firm-level implications of early stage venture capital investment-An empirical investigation. *Journal of Empirical Finance*, Volume 14, Issue 2, pp. 150-167.

[653] KOLYMPIRIS C., KALAITZANDONAKES N. & MILLER D., (2014). Public funds and local biotechnology firm creation. *Research Policy*, Volume 43, Issue 1, pp. 121-137.

[654] US Department of Health and Human Services, Office of Inspector General (2001) report the Orphan Drug Act Implementation and Impact available at https://oig.hhs.gov/oei/reports/oei-09-00-00380.pdf p.8 last visit 30.04.2020.

[655] In a related study for the US case, due to lack of detailed cost data (for instance on development of orphan and other drugs, general, administrative expenses, etc.) the researchers could not conclude a comparison of the net present value of profits for orphan v. non-orphan drugs. However, evidence was provided that clinical trials are shorter, and the regulatory success is higher for orphan drugs. And due to other benefits provided by the Orphan Drug Act such as fee waivers, R&D grants, tax incentives companies can lower their R&D costs. See MEEKINGS K.N., WILLIAMS C.S.M., ARROWSMITH J. E., (2012), Orphan drug development: an economically viable strategy for biopharma R&D, *Drug Discovery Today*, Volume 17, Issues 13–14, pp 660-664. at pp 662-663.

orphan drug development after the 1983 Orphan Drug Act show that pharmaceutical innovation was stimulated and the Act led to a 69% increase in the annual flow of new clinical trials for orphan drugs so that the Act not only generated greater levels of R&D, but also increased innovation in novel drugs technologies.[656] In order to increase better patient access to drugs, the process of reimbursement decisions should be clearer. Due to non-existence of drug price regulation in the US, per capita prescription drug spending in the US exceeds all other industrial countries where for instance per capita spending was US$ 858 compared to an average of US$ 400 for 19 other industrial nations in 2013.[657] Given the fact that majority of the orphan drugs are sponsored by biotechnology companies, and a considerable amount of blockbuster drugs i.e. brand name drugs with annual global sales greater than a billion USD, are orphan drugs and reach their blockbuster status within the 7 year of orphan drug market exclusivity period, it is considered that the Orphan Drug Act of the US may have led to some ethical and commercial abuses with excessive pricing, discontinuity of drugs due to financial concerns, and limitations in generic product development, hence a system of price regulation, subsidy paybacks and the establishment of an International Orphan Drug Office with regulatory powers is recommended.[658]

4.4 CRISPR implementations in the EU

As discussed in Chapter 4.2.1.3, CRISPR implementation in the US and the conflict between two research institutes (University of Berkeley and Broad Institute) mainly relied on which party would be eligible to what kind of patent protection, whether some patents should cover a broader scope than initially indicated, and how markets react to patent conflicts and how research collaboration is undermined with on-going disputes.

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[656] YIN W. (2008). Market incentives and pharmaceutical innovation, *Journal of Health Economics*, Volume 27, Issue 4, pp 1060-1077.

[657] KESSELHEIM A. S., AVORN, J. & SARPATWARI A., (2016), The High Cost of Prescription Drugs in the United States Origins and Prospects for Reform, *The Journal of the American Medical Association Volume* 316, Issue 8, pp 858-887.

[658] WELLMAN- LABADIE, O. & ZHOU, Y. (2010). The US Orphan Drug Act: Rare disease research stimulator or commercial opportunity. *Health Policy*, Volume 95, Issues 2-3, pp 216-228 at pp.221, 227.

Not only in health applications, but also in agricultural applications, the US has a dynamic approach in issuing of CRISPR patents , as with many other gene patents, and the EU on the other hand discusses the wider bioethical and public and environmental health considerations. Besides the EU applies the precautionary principle on environmental /human health and food safety issues.[659] Although the principle is not defined in TFEU, it is used in cases of scientific uncertainty, to prohibit certain activities that could potentially cause harm. Some scholars argue that the use of precautionary principle is arbitrary, costly and counterproductive hindering innovation.[660] Others believe that some plausible versions of the principle should be applied especially in the biotechnological field.[661]

Although the following CRISPR case is about gene- edited crops, rather than medical biotechnology applications, which is at the core of this dissertation, it is a very good example of how policy changes can quickly affect business decisions in the fast-paced biotechnology environment. The US has a different approach and does not regulate CRISPR-Cas gene-edited plants, as the technique is regarded to be risk-free (it does not involve insertion of genes from other species), allowing quick and precise results compared to conventional breeding techniques and saving a lot of precious time to bring new varieties that can protect the crops against diseases and other environmental hazards such as drought, but also helping create more nutritious, affordable and allergen-free

[659] Article 191 (2) TFEU.

[660] See for instance DURODIE, B. (2003). The true cost of precautionary chemicals regulation. *Risk Analysis*, Volume 23, Issue 2, pp 389-398, CASTRO D., MCLAUGHLIN M. (2019). Ten ways the precautionary principle undermines progress in artificial intelligence. Working paper, Information Technology and Innovation Foundation available at https://itif.org/publications/2019/02/04/ten-ways-precautionary-principle-undermines-progress-artificial-intelligence.

[661] STEINBRECHER, R.A and PAUL, H. (2017), New Genetic Engineering Techniques: Precaution, Risk, and the Need to Develop Prior Societal Technology Assessment, *Environment: Science and Policy for Sustainable Development*, Volume 59, Issue 5 pp 38-47. RIPPE, K.P. and WILLEMSEN, A. (2018), The Idea of Precaution: Ethical Requirements for the Regulation of New Biotechnologies in the Environmental Field, *Frontiers in Plant Science*, available at https://www.frontiersin.org/articles/10.3389/fpls.2018.01868/full, KOPLIN, J., GYNGELL, C. and SAVULESCU, J, (2020). Germline Gene Editing and the Precautionary Principle. *Bioethics*, Volume 34, Issue 1, pp. 49-59.

food.[662] Hence, this sub-chapter focuses on the discussions in the EU on the agricultural implications of CRISPR, and how it turned out to be a completely different narrative from the US example. GMOs is one of the areas where the precautionary principle is effectively applied in the EU. The following example is a good illustration of lack of full scientific certainty and the discussion around potential harms versus potential benefits.

In 2016 the French Supreme Court (Conseil D'Etat) asked the ECJ to interpret the EU Directive 2001/18/EC (GMO Directive) on the deliberate release into environment of GMOs, whether the new plant breeding techniques that have emerged since the adoption of the Directive should be included in the exempted methods. Over the years especially the CRISPR technologies had enabled many gene-edited crops to emerge and several EU member states were struggling whether to consider these crops as GMO – crops or not.[663] Many countries outside the EU did not have this kind of uncertainty because they were assessing these crops on a case-by-case basis such as in the US and regulating the organisms on the basis of the nature of the product, not according to the means it was obtained.[664]

The advocate general of the ECJ advised that the CRISPR gene-edited crops should not face the same strict rules[665] for GMO-crops as long as no foreign DNA is added to

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[662] See US Department of Agriculture press release of March 28,2018 on plant breeding innovation available at https://www.usda.gov/media/press-releases/2018/03/28/secretary-perdue-issues-usda-statement-plant-breeding-innovation.

[663] Gene editing in legal limbo in Europe (2017), *Nature*, Editorial, Volume 542, Issue 7582, p. 392, 23 February 2017.

[664] ABBOTT, A. (2015), Europe's genetically edited plants stuck in legal limbo, *Nature*, Volume 528, Issue 7642, pp. 319–320, 17 December 2015.

[665] In general GMO crops are authorized in the EU after a risk assessment process with upcoming labelling, monitoring and traceability requirements after the authorization has been granted. After the application for GMO –crop cultivation or GMO use for food and feed has been made to a member state, there is a lengthy authorization procedure where member states can also comment on the application referred to EFSA by another member state. The opinion of EFSA is submitted to the EU Commission, which drafts its decision and conveys this to the Member States Expert Committee, which decides by qualified majority. If the Committee cannot decide on whether to adopt or not (i.e. if there is no opinion), the Commission can convene and refer it to the Appeal Committee, which again decides by qualified majority. If there is still no opinion by the Appeal Committee, the Commission may adopt, but the member states can still introduce opt-out measures. See https://www.efsa.europa.eu/en/applications/gmo last visit 30.04.2020 for application details and Regulation (EC) No 1829/2003 on GM food & feed, Implementing Regulation (EU) No 503/2013 on applications for authorization of GM food and feed, Directive (EU) 2015/412 on restrictions

the crop.[666] The reasoning of the advocate general included that unlike transgenesis, mutagenesis techniques have evolved over time since the adoption of the EU GMO Directive allowing to develop seed varieties resistant to certain herbicides without insertion of a foreign DNA into the organisms.[667] In EU Directive 2001/18/EC, mutagenesis techniques are exempted from environmental risk assessment and other control measures. The reason for this exemption lies in the forerunner directive 90/220/EEC where it was stated that the "Directive should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record."[668] Hence mutagenesis was considered to have a safe use history in preparation of Directive 2001/18/EC, which replaced Directive 90/220/EEC.

The Court was invited by the Advocate General to clarify whether the mutagenesis exemption shall apply to all techniques, or only some. Because some organizations that were party to the legal proceedings in France had argued that the techniques developed after the adoption of the Directive 2001/18/EC should not be covered. The reason they argued was that in 2001 only random and conventional mutagenesis techniques were used, however these techniques have evolved over time to include herbicide resistant seed varieties, which can pose a risk to environmental, human and animal health. Indeed, a

on the cultivation of GMO in member states.

[666] See the legal opinion at http://curia.europa.eu/juris/document/document.jsf?text=&docid=198532&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=779174 last visit 30.04.2020.

[667] Transgenesis techniques refer to the insertion of a gene into an organism that normally does not have this gene. In mutagenesis techniques on the other hand the DNA mutations are produced in the genes to have novel functions allowing commercial applicability. In the early attempts these mutant genes were produced in laboratory environment by generating random mutations through exposing the organisms to certain mutagens such as UV radiation and some chemicals. Today with the advancement of CRISPR technologies these mutations can be given easily to the genome in vivo (i.e., on the live cells). See MCWHIR, J. (2002). Biomedical and Agricultural Applications of Animal Transgenesis in Transgenesis Techniques, Principles and Protocols, Clarke, A.R, (Ed.), Second Edition, Humana Press Totowa, New Jersey pp.3-23. NARAYANAN, A. et al. (2016). In vivo mutagenesis of miRNA gene families using a scalable multiplexed CRISPR/Cas9 nuclease system, Scientific Reports 6, No: 32386 https://doi.org/10.1038/srep32386.

[668] Recital of the Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms.

technique called site-directed mutagenesis was already known since 1970s.[669] The exemptions in both Directive 90/220/EEC and Directive 2001/18/EC came with certain conditions that the mutagenesis technique shall not involve the use of GMOs as recipient or parental organisms[670] and shall not involve the use of recombinant nucleic acid molecules.[671] The Advocate General emphasized that the EU Directive did not intend to include solely the techniques that were developed prior to 2001 and concluded that the exemption in the Directive should include any type of mutagenesis provided that the specific conditions mentioned in the Directive for such exemption are met.

The opinion of the Advocate General is not binding on the Court. Hence, the ECJ did not grant this regulatory exemption to CRISPR-crops stating that organisms obtained by mutagenesis techniques are in the scope of the GMO-Directive and exceptions shall be given to organisms obtained by mutagenesis techniques, which have been proven to be safe for a long time. Hence the older mutagenesis techniques were meant by this conclusion and the techniques that have emerged since the adoption of the GMO-Directive shall not have an exemption. Because the Court considered that the new mutagenesis techniques might have similar effects as transgenesis techniques, the risks might be similar to the release of GMOs through transgenesis; i.e the new mutagenesis techniques might produce genetically modified organisms at an out-of-proportion rate compared to conventional techniques and including these new techniques in the exemption would fail to respect the precautionary principle, which aims to avoid the adverse effects of these techniques on the environment and human health.[672]

With this important decision of ECJ, the new CRISPR agricultural inventions will be subject to the authorization procedures in the EU, which is rather of considerable length. This would mean that the commercial application of CRISPR-crops would be

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[669] This technique is more complex than random mutagenesis and involves in vitro polymer chain reaction methods to create specific mutations in a known gene sequence. See KRESGE et al. (2006). The Development of Site-directed Mutagenesis by Michael Smith, *Journal of Biological Chemistry*, Volume 281, Issue 39, e31-e33.

[670] Directive 90/220/EEC Annex I B

[671] Directive 2001/18/EC Annex I B

[672] Decision on Case C-528/16 dated 25.07.2018 at 24 and 53.

costly, as a result of which many companies may not have the incentive to invest in such crops. In the middle, long-run the research on these crops may also move out of the EU, if the research is no longer properly funded. Indeed at the first anniversary of the ECJ decision, scientists from 120 European research institutions issued an open statement calling the European Council, the European Commission and the newly elected European Parliament to enable CRISPR techniques for sustainable agricultural and food production in the EU, in line with the UN sustainable development goals.[673] The scientists pointed out to the fact that the GMO legislation adopted in 2001 is no longer reflecting the "current scientific knowledge" and that the genome-edited crops, "which do not contain foreign genes are as safe as varieties derived from conventional breeding techniques". They also mentioned that this ruling of ECJ would cause the CRISPR techniques to be a privilege of large multinational companies for large cash crops and have a negative effect on the R&D investments in the EU. They claimed that the regulatory threshold is too complicated and expensive for research institutes and small breeding companies. Indeed, some European start-ups and non-EU companies operating for the European market have either lost their financing or had to put their projects on hold a few months after the ECJ ruling.[674]

The GMO-Directive also requires laboratories to detect unapproved GMOs. The scientists who signed the open statement also mentioned that the legislation requires a specific method to detect these crops, however some mutations introduced could even occur naturally without human intervention, so the legislation will hardly be applicable.[675]

Indeed, European laboratories are now struggling to detect gene-edited crops, since some of the gene alterations are so small that they are not distinguishable from naturally occurring organisms. Even if they detect a DNA variant, they need to prove that this is a result of gene-editing, rather than a natural mutation. In the past, researchers have been

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[673] See the statement dated 25.07.2019 at the Centre for Research in Agricultural Genomics (CRAG) website https://www.cragenomica.es/crag-news/european-scientists-call-review-european-union-legislation-genome-edited-crops last visit 30.04.2020.

[674] WIGHT, A. J. (2018). Strict EU ruling on gene-edited crops squeezes science. *Nature*, Volume 563, pp.15-16, 25 October 2018.

[675] See ibid statement of José Luis Riechmann, ICREA researcher and director of CRAG.

asking the regulatory agencies information about the approved GMO-crops. Since many non-EU countries have been choosing not to regulate gene-edited crops, this information is becoming hard to generate.[676]

Since countries such as Australia, Japan, Brazil, the US and China deem gene-edited foods as safe, the ban in the EU can hold back innovation and cause the European biotechnology industry to lose its competitive advantage in developing new breeding methods. Besides the EU Directive even allows single member states to restrict the sale and use of previously approved organisms.[677] As a result, there will also be difficulties for non-EU businesses to market their approved products in the EU member states. The European scientists citing the benefits of gene-edited plants in terms of food sustainability such as less use of chemicals and water in agriculture and their calling to the EU Institutions to reverse the ECJ ruling is the sign how different regulatory policies may affect business decisions and international trade flows and why globally harmonized rules may be backed by the scientific communities and businesses.

4.5 Human embryonic stem cell patents in the EU and the US

Human embryonic stem cells (hESC) are obtained from surplus embryos of fertility clinics that were donated for research purposes with the informed consent of the donors.[678] Once obtained these cells can be multiplied in the lab and can be used for different organ cells of the body. This makes embryonic stem cells very important tools for biomedical research with high potentials to treat several diseases.

The US Congress had forbidden as early as 1996 with the so-called Dickey–Wicker Amendment the federal funding of work related to the destruction or creation of human

[676] LEDFORD, H. (2019). CRISPR conundrum: Strict European court ruling leaves food-testing labs without a plan. *Nature*, Volume 572, p. 15, 23 July 2019.

[677] See Article 23 of the Directive 2001/18/EC.

[678] Basic stem cell information from National Institutes of Health website available at https://stemcells.nih.gov/info/basics/3.htm last visit 30.04.2020.

embryos for research purposes.[679] It was still possible to derive the cells using private funding. In 2001 President Bush softened the ban to prohibit the cell lines only derived after the publication of his order and there were still 71 cell lines that were created prior to that date and were eligible for public funding, however only 21 of them proved to be of any use.[680] Collaboration and the knowledge sharing among scientists were hindered due to the split of research environment based on federal vs. private funding.[681]

In 2009 a new executive order from was released by President Obama revoking previous order and making federally- funded researchers to experiment on cell lines restricted under the order of President Bush. Although the research community gladly welcomed this new order, it did not reverse the Dickey–Wicker Amendment and the researchers were still banned from creating their own cell lines by using federal funding.[682] Besides, the America Invents Act of 2011 also limited the patentability of human organisms.[683]

The most notable case law on the issue is Sherley v. Sebelius where the Obama order was challenged by adult stem cell scientists who claimed that the federal funding of human embryonic cell research was violating the Dickey–Wicker Amendment. In 2009 the plaintiffs sued NIH, which had published the implementing guidelines of Obama order. The Guidelines stated that research from already derived existing cell lines from donated embryos with informed consent will be eligible for funding and no new cell line derivation would be funded. The district court dismissed the case finding that the plaintiffs have no standing. The appeal court in 2010 partially reversed the case acknowledging that the plaintiff scientists have a standing because the new order puts their research in a competitive situation for NIH funds, hence, they are harmed by the

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[679] PL 104-99.

[680] MURUGAN V. (2009), Embryonic stem cell research: a decade of debate from Bush to Obama, *Yale Journal of Biology and Medicine*, Volume 82, Issue 3 pp.101-103.

[681] Ibid p. 101.

[682] Ibid p. 102.

[683] AIA – Section 33(a) reads as "Notwithstanding any other provision of law, no patent may issue on a claim directed to or encompassing a human organism."

order.[684]

Shortly after the Appeal Court decision, in August 2010 the District court judge issued a preliminary injunction to block NIH funds to embryonic stem cell research stating that the "language of the statute reflects the unambiguous intent of Congress to enact a broad prohibition of funding research in which a human embryo is destroyed".[685] When the NIH appealed to this decision, the District Court of Appeals vacated the injunction decision and granted an administrative stay only 19 days after the issuance of the injunction. The Court of Appeals gave its final decision in April 2011 vacating the preliminary junction, stressing that "private funding is not generally available for stem cell research" and the injunction issued by the district court would prevent "disbursements to researchers, who have already begun multi-year projects relying on the NIH grants".[686] Hence, the Court of Appeals referred the case back to the district since the NIH has "reasonably concluded that although the Dickey-Wicker amendment prohibits funding of the destructive act of deriving a stem cell from an embryo, it does not prohibit funding a research project in which embryonic stem cells will be used".[687] In July 2011, the district court ruled against the plaintiffs stating that it is bound by Circuit's interpretation and dismissed the case.[688] The plaintiffs have appealed to overturn the ruling. In August 2012 DC Circuit again confirmed with a different panel the decision of the district court and ruled that the wording of the law was ambiguous, but the interpretation of NIH is reasonable so that NIH can fund the research on the stem cell lines, though not their

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[684] 610 F.3d 69 (D.C. Cir. 2010) James L. SHERLEY, et al. v. Kathleen SEBELIUS, in her Official Capacity as Secretary of the Department of Health and Human Services, et al., United States Court of Appeals, District of Columbia Circuit.

[685] See the memorandum dated 23.08.2010 from the US District court for the District of Columbia available at https://ecf.dcd.uscourts.gov/cgi-bin/show_public_doc?2009cv1575-44 and the order at https://cases.justia.com/federal/district-courts/district-of-columbia/dcdce/1:2009cv01575/138107/45/0.pdf last visit 30.04.2020.

[686] Case 644 F.3d 388 (D.C. Cir. 2011) Sherley v. Sebelius, United States Court of Appeals, District of Columbia Circuit

[687] The NIH argued that the ""text is in no way an unambiguous ban on research using embryonic stem cells" because Dickey-Wicker is written in the present tense, addressing research "in which" embryos "are" destroyed, not research "for which" embryos "were destroyed.""

[688] Civ. No. 1:09–cv–1575 (RCL), Sherley v. Sebelius, Appeal from the United States District Court, District of Columbia July 27, 2011.

derivation.[689] As the last resort, the plaintiffs appealed to the Supreme Court. In January 2013 the Supreme Court refused to hear the case[690], therefore ended the legal battle in favor of the embryonic stem cell research.

This legal dispute shows us that although there is no statutory ban at the federal level in the US for hESC research, the restrictions on federal funding and the following court decisions have halted the research for some years. Private funding has always been possible but was difficult to generate as it was also stated in the April 2011 decision of District Court of Appeals. To make an accurate analysis, one needs to know how much of research has shifted to working with adult stem cells during the dispute years. The progress of science depends heavily on the political and legal environment. The uncertainties cause the research initiatives to be frozen and delay the commercialization of products that have a huge potential in personal and regenerative medicine.

In the EU, the landscape for hESC patents proved to be much different. The national patent offices have been granting patents on these cells.[691] A landmark decision of ECJ is Brüstle v. Greenpeace where the patenting of claims based on embryonic stem cells were banned, if they derive from the destruction of human embryos, regardless of the fact whether the cells stem from fertilized or unfertilized human egg cells (stimulated by parthenogenesis – development of the embryo from an unfertilized egg cell so that the

[689] 689 F.3d 776 (D.C. Cir. 2012) Sherley v. Sebelius, US Court of Appeals for the District of Columbia Circuit. The court states: "It is established that "research" as used in Dickey-Wicker is an ambiguous term, and that NIH's interpretation of the term "research" as a discrete project rather than an extended process is reasonable. Under that definition of "research," the destruction of embryos that occurs in the ESC derivation process is not a part of individual ESC research projects using already derived ESCs. Therefore, ESC research is no more "research in which . . . embryos are . . . subjected to risk" than it was "research in which . . . embryos are . . . destroyed." Appellants' theory shifts focus from the embryo destroyed in the past to embryos for which an ESC research project "incentivizes" future destruction. But none of those embryos are "destroyed" or "subjected to risk" in an ESC research project. The language of Dickey-Wicker does not ban funding for, e.g., "research which provides an incentive to harm, destroy, or place at risk human embryos." As we have held before, the NIH interpretation of the statute's actual language is reasonable".

[690] Docket No 12-454 of 07.01.2013 available at https://www.supremecourt.gov/docketfiles/12-454.htm last visit 30.04.2020.

[691] For instance, as early as in 1999 the German Patent Office had granted University of Bonn researcher Brüstle a patent for the method of deriving human nerve cells from embryonic stem cells. See the German patent of 29.04.1999 DE 19756864C1 - Neurale Vorläuferzellen, Verfahren zu ihrer Herstellung und ihre Verwendung zur Therapie von neuralen Defekten.

reproduction from an ovum without fertilization is possible).[692] The ECJ based its decision on EU Biotech Directive intending to exclude patentability of subject matters where respect for human dignity could be affected. However, in doing so, it defined the term "human embryo" in its broadest meaning.

The decision left many scientists, legal advisors and industry upset. The research community and the stem cell industry had many concerns about the future of research activities and biotech investments in Europe. One of the main goals of the Biotech Directive, as stated in Article 2 is to provide adequate legal protection to biotech investments so as to make them profitable. Without this protection the research community and the industry feared that the businesses would shift to Asia and the US and put the EU in a less competitive position.[693] In absence of legal protection, it is not easy to find the investors, who would fund the stem cell treatments.[694] But when basic research is funded by public institutions, one would expect the funding to be more smoothly

[692] Case C-34/10 of 18.10.2011. Brüstle was granted patents on "isolated and purified neural precursor cells, processes for their production from embryonic stem cells and the use of neural precursor cells for the treatment of neural defects". Greenpeace had applied for the annulment of the patents based on Paragraph 2.2(3) of the German Patent Law, (which is similar to Article 6(2) of the EU Directive) that stated, "patents shall not be awarded for uses of human embryos for industrial or commercial purposes". Greenpeace had argued that embryonic stem cells were derived from the fertilized egg cells, hence they should be excluded from patentability on the grounds on ordre public. Brüstle on the other hand stated that the patented technology did not involve the use of embryos, but used embryonic stem cells, already established in the laboratory environment. Many EU countries including Germany allowed the use of surplus embryos from fertility treatments for scientific research. The German Federal Patent Court agreed with Greenpeace and declared the patent invalid. Brüstle appealed to Federal Court of Justice, which referred the case to the ECJ asking what is meant by "human embryos within the meaning of Article 6(2)c of the Directive", firstly whether all the stages of development (unfertilized human ova, fertilization of the ova, blastocyst stage) should be included, secondly what is meant by "uses of human embryos for industrial or commercial purposes" and thirdly "whether an invention is unpatentable even though its purpose is not the use of human embryos, but the development of a product whose production necessitates the prior destruction of human embryos or a process, which requires a base material obtained by destruction of human embryos". The ECJ ruled that any human ovum fertilized / unfertilized "whose division and further development have been stimulated by parthenogenesis and into which the cell nucleus from a mature human cell has been transplanted", obtained by the destruction of that embryo constitute a human embryo and industrial or commercial purposes covers use for purposes of scientific research as well.

[693] NIELEN, M.G. et al. (2013). European stem cell research in legal shackles. *The EMBO Journal*, Volume 32, Issue 24 pp. 3107–3111.

[694] Research shows that venture capital (VC) funding of start-ups is very much related to their patenting activities. 97% of the biotechnology companies backed by VC and surveyed in 2008 held patents and/or patent applications. See. GRAHAM S.J.H et al. (2009). High Technology Entrepreneurs and the Patent System: Results of the 2008 Berkeley Patent Survey, *Berkeley Technology Law Journal*, Volume 24, Issue 4 pp. 255-327.

acquired, in comparison to VC funding where the timing of commercialization of the product, the and the market situation play integral roles.

It was even argued that some biotechnology companies may move from the US to Europe to escape the patenting burden. Since the patents will not be enforceable in Europe, they could perform their hESC research activities more freely.[695]

On the other hand, some companies and research institutes changed their patenting strategies and started to patent the technologies that turn the stem cells into treatments rather than patenting the stem cells themselves.[696]

In a later decision the ECJ narrowed its ban on patents for human embryonic stem cells so that patents on stem cells from the unfertilized human eggs stimulated by parthenogenesis would be allowed.[697] It is difficult to know the exact reason why and how ECJ changed its view, and how many biotech companies and researchers had indeed moved out of Europe after the Brüstle v. Greenpeace decision. Nevertheless, the concerns of European biotech sector and the economic reasons might have played a role in the later decision of ECJ. Still the EPO, although not bound by ECJ decision, revised its examination guidelines in 2012 in line with this ruling to exclude from patentability of the human embryos concerning inventions which make use of hESC lines derived by methods involving the destruction of human embryos, irrelevant of the time of destruction.[698]

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[695] KOCH, N.J. et al. (2011). European Court Ruling on Embryonic Stem Cells: Ripple Effects. *Cell Stem Cell*, Volume 9, Issue 6, pp. 499-500

[696] For instance, Institute of Ophthalmology, London and Pfizer patents that were granted for the placement of their retinal cells in the eye, not the cells themselves to treat a degenerative retina disease that causes blindness based on a method involving hESC. See CALLAWAY, E. (2011), European ban on stem-cell patents has a silver lining, *Nature*, Volume 478, Issue 7370, p.441.

[697] Case C-364/13 of 18.12.2014 International Stem Cell Corporation (ISSC) v. Comptroller General of Patents, Designs and Trade Marks. UK Patent Office had refused to grant national patents to ISSC for inventions out of parthenogenesis, due to ECJ's Brüstle v. Greenpeace decision. ISSC appealed and asked the definition of human embryo to be narrowed to include the organisms that are fully capable of developing into a human being. Because an unfertilized human ovum is not "capable of developing into a human being." The ECJ also acknowledged that Article 6(2)(c) of Directive 98/44 must be interpreted so that an "unfertilised human ovum whose division and further development have been stimulated by parthenogenesis does not constitute a 'human embryo'."

[698] See the EPO Guidelines for examination Part G – chapter II – 5. 3 list of exceptions Rule (28): "A claim

4.6 Concluding Remarks

The disclosure requirement set by EPC has been interpreted in different measures by EPO appeal boards in biotechnological patent claims on medical use.[699] In the EU the required level of disclosure on medical claims has make it difficult for the inventor to do the filing, because a thoroughly disclosed claimed method may have an exemption to patent protection under EPC Art. 53 (c) due to being a method of treatment and a vague disclosure may not be seen as sufficient for patentability. For instance in in T 609/02[700] the Board concluded that if a patent description provides "a vague indication of a possible medical use for a chemical compound yet to be identified", detailed evidence given at a later stage cannot be used to resolve the lack of disclosure issue.

Indeed, under EPC 1973 the only accepted form of medical use claims is the so called Swiss-type claims established by the Enlarged Board of Appeal of the EPO in decision G 5/83[701] in which a therapeutic application is claimed "in the form of the use of a substance or composition for the manufacture of a medicament for a defined therapeutic application".

In the decision T 609/02 the Board also pointed out that where a therapeutic application is claimed in the form allowed by the Enlarged Board of Appeal in the above mentioned decision, (second medical indication), "attaining the claimed therapeutic effect is a functional technical feature of the claim".

The so-called Swiss-type claims have allowed the inventors to offer a commercial

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directed to a product which at the filing date of the application could be **exclusively** (emphasis by EPO) obtained by a method which necessarily involved the destruction of human embryos from which the said product is derived is excluded from patentability under Rule 28(1)(c), even if said method is not part of the claim … The point in time at which such destruction takes place is irrelevant."

[699] The revised EPC 2000 came into effect on December 13, 2007. The former EPC 1973 was the legal basis for applications that were pending before this date.

[700] T 0609/02 AP-1 complex/SALT INSTITUTE of 27.10.2004.

[701] G 5/83 Second medical indication of 5.12.1984 where it is stated that "a European patent with claims directed to the use may not be granted for the use of a substance or composition for the treatment of the human or animal body by therapy and that a European patent may be granted with claims directed to the use of a substance or composition for the manufacture of a medicament for a specified new and inventive therapeutic application."

use of a compound for the manufacturing of a medicament and to avoid having sole claims on therapeutic treatments. Under the revised EPC 2000 Swiss-type claims have become unnecessary because the new Art. 54(5) allowed for the "patentability of any substance or composition for any specific use in a method referred to in Art. 53(c)[702], provided that such use is not comprised in the state of the art". Hence the so-called Swiss type claims were abolished.

Following this revision, in its decision G 2/08[703] the Board pointed out that if the novelty of a claim is provided "only by a new therapeutic use of a medicament, such claim may no longer have the format of a so called Swiss-type claim as instituted by decision G 5/83."

Swiss-type claims have always been medical use claims, covering the first or the further medical use. Normally when a claim which has found to have a further medical use, could not be patented, since it would lack novelty under Article 54 of EPC 1973. Protection for second medical uses is prima facie provided in the revised EPC 2000, with the newly introduced Article 54(5), if the further uses are novel. And, in the application after the enactment of EPC 2000 on December 13, 2007 the claim wording has been replaced by exact medical use.[704] Claims on known substances with a new use in medicine are accepted. Likewise, claims on substances for use in the treatment of diseases are also accepted provided that the claim has an inventive step. However, claims on use of substances for the treatment of diseases are not accepted, since these are regarded as a method of treatment and are excluded from patentability. [705] In its 2010 decision G2/08

[702] EPC Art. 53 refers to patentability exceptions. Art. 53(c) states that treatments method for human/animal body by surgery/therapy/diagnostic methods are not patentable but substances and compositions for use in these methods are.

[703] G 2/08 Dosage regime/ABBOTT RESPIRATORY of 19.2.2010

[704] See Decision T 1599/06(Mycobacterium vaccinating agent/University of California) from 13.09.2007 stating that "Under the currently valid version of the EPC (EPC 1973) this claim is regarded as a product claim to a first medical use under Article 54(5) EPC, although the therapeutic use is indicated in a specific manner… Hence, under the legal situation as from 13 December 2007 claim will be regarded as a claim relating to a second medical use under Article 54(5) EPC 2000 since it defines the use in a specific manner."

[705] See EPO Examination Guidelines Chapter 7.1 Second or further medical use of known pharmaceutical products available at https://www.epo.org/law-practice/legal-texts/html/guidelines/e/g_vi_7_1.htm last visit 30.04.2020. See also See also Decision T 1823/11 from 20.5.2015 where the Board decided for Claim 1 "Phaseolamin for use an anticaries agent is a purpose-limited product claim in accordance with Article

the Enlarged Board of Appeal of EPO also concluded that the applicants can no longer claim Swiss type of second medical use, since EPC now allows use-related product claims. It is clearly stated that in the previous EPC 1973 the legislators' intention was not "to exclude second therapeutic use of a known medicament from patentability and Swiss-type claims constituted the adequate, but exceptional solution".[706]

The second medical use claims would be in the method of treatment format in the US. Swiss type of claims, use claims, claims to treat a specific disease, of pharmaceutical formulation of use claims would not be allowed in the US regime, as these claims are considered to be indefinite. [707]

It is seen in both in the EU and the US that sometimes the wording of the legislation is vague and allows broad interpretations by the courts. Long court cases result in delays in research initiatives and commercialization of technologies. On the issue of hESC, there has been no federal law in the US that bans the hESC research. The Dicker- Wicker amendment bans the federal funding of hESC research, in which embryos are destroyed or new embryos are created solely for research purposes. It was seen that there could be appeals to lower court decisions, which the Court of Appeal could again overturn. In the EU, the hESC are regarded as embryos, and the only way to change a ruling is by changing the EU Biotech Directive or the EPC. In both jurisdictions the patent offices are agile and adopt their patenting guidelines in accordance with the latest court decisions.

The reluctance in the EU on patenting of new technologies such as CRISPR and hESC especially based on ordre public and morality grounds, would make it more difficult for EU researchers to seek international collaborations, and they may opt for alternatives for EU patents such as trade secrets or patenting in the other countries outside of the EU. Because the research on hESC is not banned in the EU, and member states can decide individually whether to allow for research or not. But when hESC research itself

54(5) EPC. It relates to phaseolamin for use as anticaries agent."

[706] Case G2/08 at p. 42.

[707] ALTMAN, D. (2016), United States of America in *Patent Protection for Second Medical Uses*, Bühling J. (Ed.), Kluwer Law International BV, the Netherlands p. 245.

is regarded as contrary to ordre public and morality, with no prospects on getting European patents, it may also bring hesitations to continue with research in the EU. The hESC research has a different recognition in the EU than in the US. The US court decisions could differentiate between the creation of hESC lines as a separate procedure than their use in another research activity. In the EU, patents are not granted to inventions involving the destruction of a human embryo and it is irrelevant when embryo destruction has occurred, (it might have taken place even long before the invention) and the creation of hESC lines is indeed regarded as part of the research activity. In order to reach a conclusion what kind of consequences the ECJ ruling had on European stem cell research, one needs to investigate, whether it became difficult to acquire public /private funding for the research, whether the researchers in Europe have chosen other protection mechanisms such as trade secrets, whether some parts of the research activities have moved out of Europe.

Although legal certainty with clear legislation means predictability and precise implementation of the law by the patent offices and courts and results in well- informed decisions by innovators and businesses, which would also mean cost-effective investments and quick commercialization of patented technologies, some flexibility around the legal interpretation may also be beneficial in terms of social welfare depending on the incentive effects and the objectives of the legislators. Flexibility should not be understood as arbitrariness in decision making but rather as a discretion for the patent offices and judges to allow them to deviate around rules and regulations in certain cases as long as, some reasonable justification can be provided on the particularities of the case at stake and how they have reached their decision. If the rules are too rigid, they can be outdated in a short period of time for a fast-paced technology like the biotechnology. Even if these rules do not turn totally obsolete, they can obstruct biotech research efforts and hinder innovative activities.

The legislators should ideally create a legal environment that benefits the society at large: Concerning patenting of biotechnological materials, on one hand innovation and dissemination of information should be encouraged, on the other hand social cost of monopolies and patient access issues in treatment and diagnostic methods need to be

addressed. These decisions do not only rely on innovation policy, but also public health policy objectives of the legislators. Under unexpected circumstances such as a global pandemic, financial, economic, climate or social crisis, etc. these legislative objectives and priorities can shift very quickly, and rigid rules may render it hard to allocate resources and the regulatory preference to create the aimed incentive effects. But even under the usual circumstances, in order to find a balance between competing interests, a flexible legal interpretation in a broader sense would give the patent offices and the courts the discretion to adapt to the necessities of the biotech sector and respond quickly to disputed issues. The choice over legal certainty versus flexibility should be done according to legitimate and transparent policy objectives and by taking into account law and economics approach towards incentive effects.

5. THE ECONOMIC ASSESSMENT OF THE LEGAL DIFFERENCES BETWEEN THE EU AND THE US

5.1 Evolution of the legal systems

Patent laws must evolve to accommodate the fast changes in biotechnology. We see for instance a considerable shift from public to private R&D, but also more patenting of the government -funded R&D due to amendments to the patent law. An examination of cases concerning US and EU patents in biotechnology has been carried out in order to assess whether patent laws in different systems have been evolving efficiently.

The economic discussion on gene patents in medical biotechnology is often constituted around having innovation versus having access to information. Proponents of medical biotech patents claim that patents create incentives for innovation in diagnostics and especially personalized treatment possibilities. Opponents argue that patent thickets and other barriers constitute a threat for further innovation.

In gene patenting, the breadth of patent protection, ease of patent enforcement and responses of health -care services play a major role for the assessment of the economic debate. For instance, in the Myriad case, the Company could not replicate its US success in enforcing its patents in the US elsewhere in the world. It has tried to identify a single licensee in each country outside the US to market its tests. The local licensees would perform the less-expensive single mutation tests and send the samples to laboratories of Myriad in the US for full sequence testing (also called proband testing where the sequences of the first family member with a gene mutation become the reference sequence for the comparison of other family members' sequences). The British licensee of Myriad first permitted the use in the UK by the National Health Service (NHS), but then when the company went bankrupt the NHS and Myriad did not negotiate a replacement agreement. In France it became illegal to send blood samples abroad, so Myriad announced that it would allow local licensee to perform proband testing, as well. Nevertheless, no laboratory was licensed in France. Outside the EU certain healthcare authorities also believed that the case constitutes an abuse of monopoly power where the

costs are too high, hence the access to technology was very limited.[708] In an earlier cost-effectiveness study at French public laboratories alternative pre-screening techniques to Myriad patents have been tested and found to be reducing the average cost per mutation with acceptable effectiveness rates.[709] But with the June 2013 Decision of the US Supreme Court, some distinctive analysis could be made for the patent eligibility of the genes. The distinction made with regards to complementary DNA (cDNA) received by reverse transcription of RNA, which is patentable and genomic DNA (gDNA), which is a product of nature and not patentable. The discussions around the Myriad case caught a lot of attention in public in terms of innovation vs. access to medical care. The earlier discussions, also in Europe about the European patents of Myriad were not only about the patenting of genes, but also about licensing practices. The economics behind patent enforcement raised further questions on freedom of scientists in conducting research, commercial development of patented technologies, availability of genetic testing in medicinal practice to allow a broader participation of patients to therapeutics and diagnostics. OECD issued as early as 2006 guidelines for the licensing of genetic inventions, which promoted broad licensing practices to achieve a balanced patent system in encouraging the dissemination of information, economic returns, and ensure the widest public access to healthcare needs.[710]

It is very difficult for public authorities to assess the economic consequences of access issues and the effects thereof on research and innovation. For instance, if the clinical testing laboratories are also research laboratories, and if they fail to obtain a license from a patent-holder, the restriction on performing of tests may also mean that

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[708] See Gold and Carbone at supra note 177 for the full discussion on the patent story of Myriad patents outside of the US. For instance, in Canada patents have been obtained and being ignored by provincial health systems. All provinces except one ignored the injunctions of Myriad and continued to offer the genetic testing. In Japan authorities required clinical trials to demonstrate the effectiveness of BRCA testing for the Japanese population, The Japanese licensee of Myriad faced as a result significant costs in entering the market.

[709] SEVILLA, C. et al. (2003). Impact of Gene Patents on the Cost-Effective Delivery of Care: the Case of BRCA1 Genetic Testing. *International Journal of Technology Assessment in Health Care*, Volume 19, Issue 2, pp 287-300.

[710] OECD Guidelines for the Licensing of Genetic Inventions (2006), available at http://www.oecd.org/sti/emerging-tech/36198812.pdf last visit 30.04.2020.

research can be impeded. In an empirical study for the UK, it is found that gene patents have had in practice little or no impact on testing in the public sector. This conclusion is not a result of optimal patent protection, but due to the fact that patents have essentially been ignored, where the test centers have reported to have had very few contacts to the patent holders. In the US there is a different version of the story where cease and desist letters have been sent to genetic testing laboratories, and many laboratories have reported ceasing to offer those tests with patent protection due to having received such a letter.[711]

The gene patents, like other patents in the US law follow a utilitarian approach to promote progress in science and useful arts and should be designed the right to exclude others from making, using, offering for sale or selling or using the invention for a limited time.[712] In the US patent enforcement is easier, probably due to the costs associated with non-compliance.[713]

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[711] HAWKINS, N., (2011). The Impact of Human Gene Patents on Genetic Testing in the UK. *Genetics in Medicine: Official Journal of the American College of Medical Genetics*, Volume 13 Issue, pp 320-324. In the interviews test centers in the UK reported that they have not reduced services or failed to conduct testing due to patent protection. With very few exceptions, they did not license patents, either. They did not report any negative consequences of this failure to take account of existing IP rights, such as patent infringement lawsuits. They had not been approached informally or formally by patent holders.

[712] U.S. Constitution Article I, § 8, cl. 8.reads as "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries" see also 35 U.S. Code § 154 on contents and term of patent. See also OLSON, D. S., (2009), Taking the Utilitarian Basis for Patent Law Seriously: The Case for Restricting Patentable Subject Matter, *Temple Law Review*, Volume 82, pp 181-240 for a discussion of how the patents have been historically addressing the market failure problem and how today the immense expansion of the patentable subject-matter is no longer serving this purpose. Giving the example of business method patents, the author argues that the law should be re-designed for the patents to be granted only in those areas, where they are necessary to incentivize innovation. On the other hand, in later years the Supreme Court developed certain tests to assess the patent-eligibility of subject matters. In its Bilski decision in 2010 business method patents were not necessarily categorically exempted from patentability and it was concluded that "machine or transformation test" applied by USPTO patent examiners should not be the sole criteria testing patent-eligibility. Moreover, in the Alice decision in 2014 the Supreme Court invalidated the disputed business method patents.

[713] In the United States cases on validity of claims can be decided by the courts or by the USPTO. All other cases related to the validity, enforcement and infringement can be brought to the court. Pre-trial discovery requirement in the US legal system, which is opposed by many civil law systems, obliges the opposing party to reveal any confidential information before the trial. See RUBINO-SAMMARTANO, M., (2015), No Sanctions Is Not a Deterrent against Production of Useless Documents, *Journal of International Arbitration*, Volume 32 Issue 1, pp. 107-109. Especially for non-US companies this procedure can be seen as costly and time-consuming. Similarly, enforcement of US patents outside of the US is also subject to difficulties due to different patent laws in the countries where the infringement takes place. Studies show an increase in patent litigation by the so-called patent trolls; sometimes also referred as non-practicing

The moral discussion and public controversy in the EU about the patenting of genes must have contributed to the lack of patent enforcement in the EU in the early years of patenting activities. The Commission proposal for the EU Biotech Directive came out in 1988, and it took a decade of discussions among the EU Institutions, the industry, and the civil society for the directive to be adopted in 1998, yet it was challenged by the Netherlands for annulment. Though the ECJ did not grant any of the pleas set forth by the Netherlands, it took almost another decade for the member states to implement the Directive. The ordre public clause has shaped the European patent law in such to consider the wider social, environmental, and economic implications of gene patenting. Hence the commercialization of biotechnological research has not been at the same level as in the US. The US biotech companies receive almost five times more private funding than Europeans, and US biotech IPOs (Initial Public Offering) are three times larger on Nasdaq than on European exchanges. Since 2012 almost one out of three European biotech companies filed for an IPO directly on US exchanges.[714]

Researchers have begun patenting genes without fully understanding their function, yet the total impact of gene patents and licensing practices on academic research cannot be fully estimated.[715]

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entities, which do not invent or manufacture, but buy the patents to extract revenues from alleged infringers. See TRIMBLE, M. (2014). Foreigners in U.S. Patent Litigation: An Empirical Study of Patent Cases Filed in Nine U.S. Federal District Courts in 2004, 2009, and 2012, *Vanderbilt. Journal of Entertainment and Technology Law*, Volume 17, Issue 1, pp 175-210. The author points to the magnitude and difficulties of cross-border enforcement of patent rights and suggests a large-scale international instrument on cross-border IP litigation. When this is not possible, the US could consider concluding bilateral or multilateral treaties to enhance cross-border IP enforcement through civil litigation.

[714] LE DEU, F. & DA SILVA, J.S. (2019). Biotech in Europe: A strong foundation for growth and innovation, sector report by McKinsey & Co available at https://www.mckinsey.com/industries/pharmaceuticals-and-medical-products/our-insights/biotech-in-europe-a-strong-foundation-for-growth-and-innovation# last visit 30.04.2020.

[715] See COOK-DEEGAN R. et al. (2010). Impact of Gene Patents and Licensing Practices on Access to Genetic Testing for Inherited Susceptibility to Cancer: Comparing Breast and Ovarian Cancers with Colon Cancers, *Genetics in Medicine*, Volume 12, Issue 4 pp 15-38 for a discussion of genetic testing for breast and ovarian and colon cancers. The major difference is that Myriad Genetics is the sole provider of breast and ovarian testing in the US due to its BRCA1/2 gene patents and has not enforced the patents against basic research and has a Memorandum of Understanding with the National Cancer Institute for institutional BRCA testing in clinical research. Colon cancer-associated genes are also patented, but they have been nonexclusively licensed and there are multiple laboratories available for this testing.

Both systems require the disclosure of a function or industrial application of the gene related patents. While the USPTO Guidelines require specific, credible, and substantial utility, EPO also follows this approach in its decisions. However, the Guidelines do not clearly express what constitutes such utility, or in an application with various claims whether all the claims should show such utility, or one claim or function would be enough.

Novelty requirement affects the level of disclosure and ex-ante incentives of research. If the aim of the regulator is to disseminate technical information by means of disclosure, then a weak novelty requirement should be chosen. If the aim is to increase ex-ante incentives to do research and protect the profit of the innovator, then a strong novelty requirement should be chosen. However, by a weak novelty requirement, the innovators may want to avoid imitation by other firms, thus they might choose not to patent and disclose the information. Especially in case of a patent race for a biotechnological invention where close substitutes of technical information are easy to produce, the competing firms may choose to patent minor improvements, if these patents will give them a competitive advantage at a later stage of the race.

First to file and first to invent rules have different incentive effects and need to be compared from social efficiency point of view. First to file rule stimulates more incentives to disclose then first to invent rule. However, in case of a patent race, first to file rule may cause the firms to stay in the race, even if this is not socially efficient.

If there is a weak novelty requirement and first to file rule, minor improvements can be patented quickly as well as the final product. Hence society can be better off since the consumption of the first products will start immediately, and the final product will be developed more quickly.

These differences may have allowed more small sized companies to emerge in the EU. According to OECD data for 2016, out of 18 of the EU member states, 75.8% of the biotech companies were small sized – having less than 50 employees, whereas this ratio

is 68.6% in the US.[716]

Uncertainties around the scope, validity and enforcement of the patents in different EU member states have also been an issue for inventors. The costs for a patent application in a number of EU member states have been higher than a single application done at the USPTO; mainly due to translation, representation and publication costs, and other related fees. Once unitary patents will be granted in the EU, it will no longer be necessary for inventors to apply for national patent protection in member states. This will especially benefit SMEs due to simplified procedures, less translation, validation, renewal fees. In cases of disputes, legal fees related to the cost of litigation and revocation will also be lower.

In the US, some legal uncertainties can be addressed more quickly and efficiently. For example, patent eligibility of subject matters has become a big issue in the US after two landmark decision of the Supreme Court in Alice and Mayo cases, which are explained briefly in the following section. The inconsistencies around the application of the two-step test developed through these decisions made not only the US Congress members in IP Subcommittee to introduce some bill proposals to address the issue, but also USPTO to revise its patent-eligibility subject matter guidance twice in 2019 in order to shed some light on the enforcement.

Finally, the implications of the TRIPS on the two jurisdictions have also been different. Naturally, it must be noted that TRIPS do not explicitly refer to biotechnological inventions. However, in Article 27(2) members are provided with the opportunity to exclude inventions contrary to ordre public from patentability, and likewise in Article 27(3) diagnostic, therapeutic and surgical methods for the treatment of humans or animals, and plants and animals and essentially biological processes. The application of these provisions has been different in the EU and the US. The ordre public considerations of gene patenting dominated the EU for almost 20 years before the EU Biotech Directive

[716] OECD Key Biotechnology Indicators, October 2019 available at https://www.oecd.org/innovation/inno/keybiotechnologyindicators.htm last visit 30.04.2020

could be enforced, and is embedded into the law, both in the EU Biotech Directive and in the EPC and also defined in the case law of EPO.[717] In the US there are no statutory provisions on ordre public and morality. But Bagley (2003) notes that the USPTO and the courts have refused in certain cases to grant patent protection for morally controversial subject matters under the fiction that such inventions were not "useful". This has resulted in a "patent first, question the patentability later" approach in the US, rather than "ask questions first, patent later" in other countries.[718] The recent effects of the ordre public / morality considerations have also been seen in human embryonic stem cell patents where such patents and claims are banned in the EU, but the existing patents are not denied in the US. Still even in the US we see that the scope of the claims has been narrowed and some companies and researchers have abandoned the research in the area and switched to working with adult stem cells. The adult cell research is not hindered by the ethical concerns that surrounded the embryonic cell research. However, the embryonic stem cells have certain advantages over adult cells, since the latter are fewer in number, difficult to grow in culture and give rise to a limited number of cell types. Besides, they have been exposed to environmental toxins and as a result accrued genetic mutations. All of these make it difficult to isolate stem cells from adult tissues.[719] Still stem cell therapies are growing around the globe, and there are a lot of offerings to patients, even if the research is in its early stages. The US Food and Drug Administration (FDA) sends warning letters to US companies that commercially market stem cell products, which are not approved by the Agency and which put the public health at risk.[720] Naturally, the FDA warnings

[717] See for instance EPO decision T 0866/01 (Euthanasia Compositions/Michigan State Univ.) of 11.5.2005 "…Article 53(a) EPC ruled out … a restrictive interpretation of the exception to patentability, with the consequence that the mere possibility of a misuse contrary to "ordre public" or morality should in itself be regarded as sufficient "indicative evidence" of the immorality of an invention…. The legal approach based on morality for the EPC can be found in the concepts of the European cultural and legal systems. Morality constitutes actual ethically based norms of behaviour that have become socially binding through being generally accepted. The exploitation of an invention only infringes morality if it is regarded as reprehensible by society in general or at least by the trade concerned."

[718] BAGLEY, M. A. (2003). Patents first, ask questions later: Morality and biotechnology in patent law. *William Mary Law Review*, Volume 45, pp 469– 547.

[719] FISCHBACH, G. D. & FISCHBACH R. L. (2004). Stem cells: science, policy, and ethics, *Journal of Clinical Investigation*, Volume 114, Issue 10, pp. 1364-1370 https://doi.org/10.1172/JCI23549.last visit 30.04.2020.

[720] See for instance FDA press release of 06.12.2019 available at https://www.fda.gov/news-events/press-

concern only the companies and the patients in this country. At the international level, there is a stem cell tourism, which attracts worldwide many patients affected by untreatable diseases and who are open to new, experimental trials. Some of these stem cell facilities have offered very controversial but highly priced treatments with poor clinical pre-trials and have been closed by national authorities.[721] But even if one clinic is shut down, another one opens somewhere else in the world. Experts in the area call for tighter global regulations and an effective WHO coordination with national authorities.[722]

Similarly, the Myriad decision of the Supreme Court in the US left the isolated DNAs not patentable where cDNAs can still be patentable. One can argue there has been some convergence in gene patenting between the EU and US jurisdictions in recent years. Yet, the patentability bar is still lower in the US than in the EU and this would make the commercialization of research and patents difficult in the EU.

It took almost two decades of discussions and court proceedings between 1988 and 2007 to enact, ratify and enforce the EU Biotech Directive. Although EPO is not legally a party to the Directive and not bound by its provisions, some provisions of EPC were amended to comply with the Directive. In 2017 for instance Rules 27 and 28 of the Implementing Regulations to the EPC were amended to exclude plants and animals obtained by essentially biological processes[723] from patentability under Article 53(b) of

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announcements/fda-sends-warning-companies-offering-unapproved-umbilical-cord-blood-products-may-put-patients-risk last visit 30.04.2020.

. It is mentioned in the press release that the Agency has recently sent 20 such letters to manufacturers and health care professionals and urge them to engage with the Agency.

[721] For instance, in Düsseldorf, Germany the state health authorities closed the Clinic XCell, after 5 years of operation in 2011, where mainly international patients were treated at prices of EUR 7000 - 26.000. These patients were primarily attracted by the reputation of Germany's high healthcare standards. See the news https://www.wiwo.de/technologie/xcell-nrw-schliesst-umstrittene-stammzellklinik-in-duesseldorf/4638034.html https://www.spiegel.de/wissenschaft/medizin/xcell-klinik-chronologie-eines-vermeidbaren-todesfalls-a-852230.html last visit 30.04.2020.

[722] SIPP, D. et al. (2017), Marketing of unproven stem cell–based interventions: A call to action, *Science Translational Medicine*, Volume 9, Issue 397.

[723] According to Rule 26(5) of the Implementing Regulation of the EPC, "a process for the production of plants and animals is considered to be essentially biological, if it consists entirely of natural phenomena such as crossing or selection". This rule is also incorporated into Article 2(2) of the EU Biotech Directive.

the EPC.[724] The amendment came after the consolidated decisions of G 2/12 (Tomatoes II) and G 2/13 (Broccoli II) where the Enlarged Board of Appeals had ruled that products achieved by a product-by-process claim would be patentable and would not fall under Article 53(b) of the EPC, which deems essentially biological processes unpatentable. In giving this decision, the Enlarged board of Appeals referred to previous decisions, which concluded a narrow interpretation of Article 53(b) where a process can be deemed unpatentable, but the product claims developed with such processes cannot. [725] So even if the EPC excluded essential biological processes from patentability, this exclusion should not apply to animals and plants derived from such processes.

The European Parliament found this ruling in conflict with the plant breeders' rights and asked the Commission to look into the matter taking into account the aims of the EU Biotech Directive.[726] Although the European Commission acknowledged that the Directive does not state whether plants and animals obtained through essentially biological processes can be patented, it was stressed that "the EU legislator's intention when adopting the Biotech Directive was to exclude from patentability products that are obtained by means of essentially biological processes". [727] Hence, the Commission concluded that animals and plants derived from essentially biological processes should also be excluded from patentability, in line with the aims of the EU Biotech Directive. As a result, the Rules of EPC were changed to clarify that the exclusion from patentability

[724] See the Administrative Council decision of 29.7.2017 available at https://www.epo.org/law-practice/legal-texts/official-journal/2017/07/a56.html last visit 30.04.2020.

[725] See Decisions G 1/08 (Tomatoes) and G 2/07 (Broccoli). One of the referred questions (in Broccoli case) was whether "a non-microbiological process for the production of plants which contains the steps of crossing and selecting plants escape the exclusion of Article 53(b) EPC merely because it contains, as a further step or as part of any of the steps of crossing and selection, an additional feature of a technical nature?" And the decision of the EPO Enlarged Board of Appeal was negative: …A non-microbiological process for the production of plants which is based on the sexual crossing of whole genomes and on the subsequent selection of plants, even if there is a human intervention which solely helps with performance of process steps is in principle excluded from patentability under EPC Art. 53 (b) for being "essentially biological". However, if these processes contain steps that substantially change the plant breeding such as introduction of a trait into the genome, they can be patentable.

[726] See European Parliament resolution of 17 December 2015 on patents and plant breeders' rights (2015/2981(RSP)) available at http://www.europarl.europa.eu/doceo/document/TA-8-2015-0473_EN.html?redirect last visit 30.04.2020.

[727] See Notice 2016/C 411/03 of the European Commission dated 8.11.2016.

applies not only to processes, but also to products derived from these processes.

Another change within EPO system was made when the ECJ gave its hESC decision in 2011 and defined human embryo within the meaning of Article 6(2)(c) of the EU Biotech Directive. The EPO examination guidelines were amended in line with this decision.

5.2 Incentive effects – increased judicial review in the US

The current patent laws in the EU and the US for biotechnological inventions are not always creating efficient incentives according to the economic theory of patents. Although they have created incentives to invent and disclose, it is not clear to say whether this naturally leads to increased innovation at the socially optimal level, or whether there is an increased propensity to patent by the innovators, because of the financial returns of the patent system. Patent races, anticommons problems, difficulties for patients to access health care are also seen and these problems could partially be addressed by the courts. It can be argued that granting gene patents failed to promote innovation at the socially optimal level. The case law answers some of these inefficiencies, but it has also its limits. Indeed, the Federal Circuit of the US has been criticized for being too pro-patent increasing uncertainty by flawed arguments and its goal of setting up a regime that, within the limits of statutory language, promotes innovation is less clear, as a result of which patent trolls emerged.[728] In fact, there is an increasing review of the Federal Circuit for the appeals sourcing from the USPTO. In the recent years; the number of terminations has risen considerably, as it can be seen at the following table. Indeed, the number started increasing especially after the enactment of America Invents Act of September 2011, which assigned USPTO's appeal board post grant reviews to the Federal Circuit.

[728] RAI A. K. (2014), Competing with the "Patent Court": A Newly Robust Ecosystem, *Chicago - Kent Journal of Intellectual Property*, Volume 13, Issue 2, pp 386- 393.

Table 2: Federal Circuit terminations of USPTO appeals

Year	Number of terminations
1997	92
1998	60
1999	80
2000	64
2001	98
2002	74
2003	76
2004	64
2005	81
2006	60
2007	69
2008	60
2009	101
2010	79
2011	78
2012	152
2013	114
2014	194
2015	233
2016	404
2017	538
2018	580
2019	658
Total	**4009**

Source: U.S. Court of Appeals for the Federal Circuit—Statistics on Appeals Filed, Terminated, and Pending during the 12-month period ending September 30 of the fiscal year - available at http://www.cafc.uscourts.gov/the-court/statistics last visit 30.04.2020

Another point to take into consideration according to my findings is the increased intervention of the US Supreme Court in patent law cases in recent years, since the foundation of the Federal Circuit in 1982. The number of Federal Circuit decisions reviewed by the Supreme Court has risen over the years as it can be seen from the below table:

Table 3: Cases sourcing from the Federal Circuit reviewed by the Supreme Court

Case	**Year**	**Supreme Court Decision**
Christianson v. Colt Industries Operating Corp 486 U.S. 800	1988	Vacated and remanded
Bonito Boats, Inc. v. Thunder Craft Boats, Inc. 489 U.S. 141	1989	Affirming Florida Supreme Court judgement, and finding on a similar case Federal Circuit's Interpart Corp. V. Italia (777 F.2d 678 (Fed. Cir. 1985)) opinion "defective".
Eli Lilly & Co. v. Medtronic, Inc. 496 U.S. 661	1990	Affirmed
Cardinal Chemical Company v. Morton International, Inc. 508 U.S. 83	1993	Vacated and remanded
Asgrow Seed Co. v. Winterboer 513 U.S. 179	1995	Reversed
Markman v. Westview Instruments, Inc. 517 U.S. 370	1996	Affirmed
Warner-Jenkinson Company, Inc. v. Hilton Davis Chemical Co. 520 U.S. 17	1997	Reversed and remanded
Pfaff v. Wells Electronics, Inc. 525 U.S. 55	1998	Affirmed
Florida Prepaid Postsecondary Education Expense Board v. College Savings Bank 527 U.S. 627	1999	Reversed and remanded
Dickinson v. Zurko 527 U.S. 150	1999	Reversed and remanded
Nelson v. Adams USA Inc. 529 U.S. 460	2000	Reversed and remanded

Case	Year	Supreme Court Decision
J. E. M. Ag Supply, Inc. v. Pioneer Hi-Bred International, Inc 534 U.S. 124	2001	Affirmed
Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co. 535 U.S. 722	2002	Vacated and remanded
Holmes Group Inc v. Vornado Air Circulation Systems Inc. 535 U.S. 826	2002	Vacated and remanded
Merck KGaA v. Integra Lifesciences I, Ltd. 545 U.S. 193	2005	Vacated and remanded
Unitherm Food Systems, Inc. v. Swift-Eckrich, Inc. 546 U.S. 394	2006	Reversed
EBay Inc. v. MercExchange, L.L.C. 547 U.S. 388	2006	Vacated and remanded
Illinois Tool Works Inc. v. Independent Ink, Inc. 547 U.S. 28	2006	Vacated and remanded
MedImmune, Inc. v. Genentech, Inc. 549 U.S. 118	2007	Reversed and remanded
KSR Int'l Co. v. Teleflex Inc 550 U.S. 398	2007	Reversed and remanded
Microsoft Corp. v. AT&T Corp. 550 U.S. 437	2007	Reversed
Quanta Computer, Inc. v. LG Electronics, Inc 553 U.S. 617	2008	Reversed
Carlsbad Technology, Inc. v. HIF Bio, Inc 556 U.S. 635	2009	Reversed and remanded
Microsoft Corp. v. i4i Ltd. Partnership 564 U.S. 91	2010	Affirmed
Bilski v. Kappos 561 U.S. 593	2010	Affirmed
Global-Tech Appliances, Inc. v. SEB S.A 563 U.S. 754	2011	Affirmed
Board of Trustees of Stanford University v. Roche Molecular Systems, Inc. 563 U.S. 776	2011	Affirmed
Mayo Collaborative Services v. Prometheus Laboratories, Inc. 566 U.S. 1289	2012	Reversed

Case	Year	Supreme Court Decision
Caraco Pharmacautical Laboratories v. Novo Nordisk A/S 566 U.S. 399	2012	Reversed and remanded
Kappos v. Hyatt 566 U.S. 431	2012	Affirmed
Bowman v. Monsanto Co. 569 U.S. 278	2013	Affirmed
Association for Molecular Pathology v. Myriad Genetics 569 U.S. 576	2013	Affirmed and reversed in part
Alice Corp. v. CLS Bank International 573 U.S. 208	2014	Affirmed
Octane Fitness LLC v. Icon Health & Fitness Inc. 572 U.S. 545	2014	Reversed and remanded
Highmark Inc v. Allcare Health Management System 572 U.S. 599	2014	Vacated and remanded
Limelight Networks Inc. v. Akamai Technologies Inc. 572 U.S. 915	2014	Reversed and remanded
Nautilus, Inc. v. Biosig Instruments, Inc. 572 U.S. 898	2014	Vacated and remanded
Teva Pharmaceuticals USA, Inc. v. Sandoz, Inc. 574 U.S. 318	2015	Vacated and remanded
Commil USA, LLC. v. Cisco Systems Inc. 575 U.S. __	2015	Vacated and remanded
Halo Electronics Inc. v. Pulse Electronics Inc. 579 U.S. __	2016	Vacated and remanded
Samsung Electronics Co. v. Apple Inc. 580 U.S. ___	2016	Reversed and remanded
TC Heartland LLC v. Kraft Foods Group Brands LLC 581 U.S. ___	2017	Reversed and remanded
Impression Prods., Inc. v. Lexmark Int. Inc. 581 U.S. ___	2017	Reversed and remanded
Life Technologies Corp v. Promega Corp 580 U.S. ___	2017	Reversed and remanded
SCA Hygiene Products Aktiebolag v. First Quality Baby Products 580 U.S. ___	2017	Vacated in part and remanded
Oil States Energy Services, LLC v. Greene's Energy Group, LLC 584 U.S. ___	2018	Affirmed

Source: Supreme Court Opinions available at https://www.supremecourt.gov/opinions/opinions.aspx last visit 30.04.2020.[729]

According to my findings, out of 46 decisions given by the Supreme Court so far, only 12 of them affirmed and 1 partially affirmed the Federal Circuit judgements. A total of 46 decisions may seem less compared to the total number of 4.009 cases reviewed by the Federal Circuit during 1997-2019 period, however it must be noted that Supreme Court grants on average plenary review, with oral arguments by attorneys, in about 80 cases each term.[730] This number includes cases referred from all 12 circuit courts in addition to the Federal Circuit.

In contrast in the EU, the ECJ is rarely involved in patent cases. That's because patent enforcement is still a national issue of the EU member states. In the US the parties can appeal to the Federal Circuit and the Supreme Court. In the EU mostly national courts refer to the ECJ, though direct appeal by individuals to the General Court is possible if they are affected by EU decisions / institutions. Hence EPO cannot refer the patent appeals to the ECJ.

As explained in Chapter 6.2, the generosity of USPTO in granting more and broader patents compared to EPO may also indicate the rise of challenged patents. The wider the patents, the more likely they are to be challenged afterwards. The USPTO patent examiners receive more patent applications, have less time to review them, which may also explain the strict approach by EPO in granting narrower patents in addition to the moral and ethical concerns. More time to review applications means less patents in a narrow scope, which are less challenged after the grant.

[729] Although a similar table for the years 1987-2008 appears in HOFER, R.E. (2010). Supreme Court Reversal Rates: Evaluating the Federal Courts of Appeals available at https://www.americanbar.org/content/dam/aba/migrated/intelprop/magazine/LandslideJan2010_Hofer.authcheckdam.pdf, Table 3 was prepared independently.

[730] https://www.supremecourt.gov/about/justicecaseload.aspx last visit 30.04.2020.

5.3 Differences in legal interpretation and law-making

As mentioned in the previous sub-section, the US system is faster to address legal uncertainties and make changes to the law. The reason for the relatively slow – moving EU law-making procedures can be attributed to the complicated mechanisms of the EU-law involving the Commission, European Parliament and the Council and the difficulty to agree on European interests which sometimes clash with the national interests. [731]

It is seen that a narrow or broad interpretation of law can totally change the case decisions, as a matter of which the law itself can be re-written and/or implanting rules and guidelines can be amended. The EPO does not have the political oversight by the

[731] The ordinary legislative procedure, which is the main mechanism of law-making in the EU is initiated with a proposal from the Commission, which is the supranational body of the EU. The European Parliament (EP), of which the members are directly elected by the citizens of EU member states, receives the proposal for the first reading. Depending on the subject, the EP committees prepare a report on the proposal and during this procedure some amendments can be proposed to the draft legislation. Meanwhile the Council also examines the proposal in its first reading. The Council – depending on the sector of the drafted legislation – consists of the relevant ministers from member states and the COREPER (Committee of Permanent Representatives, i.e., head and deputy heads of permanent missions of the member states to the EU. If the EP and the Council cannot reach an agreement after the first reading, the second reading is conveyed, where the Council is required to vote unanimously if there is a negative opinion by the Commission for the EP amendments. If there is still no jointly agreed text, a conciliation committee with EP and Council representatives is launched. If they still cannot agree on a joint text, the legislative procedure ends. If they can, the joint text is forwarded to the third reading, where it can be approved or rejected. A final rejection at this stage means the proposal will not be adopted and the procedure can only re-start with a new proposal from the Commission. The text agreed by the EP and the Council can substantially deviate from the Commission proposal. It must be noted that the three EU Institutions can enter tripartite negotiations (triologues) at any stage of the legislative proposal. However, the agreed text must again be voted at the Institutions. Although the Commission is supranational and is required to represent the overarching European interests, the Council by its very nature represents the national interests of the member states. Especially during those times when a member states holds the Presidency of the Council, the push for national agenda can be stronger, despite the fact that Presidency is presumed a neutral chairing role. The US on the other hand can act on a single voice, as it pursues the "American" interests. Though the US Congress also has two chambers (the Senate and the House of Representatives), the federal laws can be initiated by the members of both. After the introduction of the proposal (the bill), it is discussed in the assigned committee and voted in the chamber it was introduced at first place. If it passes, the bill goes to the other chamber for discussion and voting. If the two legislative bodies of the US Congress can agree on the same text, the bill is sent to the US President. When the President approves the bill, it is signed into law. If the bill is not approved by the President, the Congress can still overrule the veto of the President in most cases and the bill becomes law. Hence, the US system offers a less complicated law-making procedure than the US, obviously so, as the US is a single country, and the EU is a melting pot of diverse national backgrounds.

European Parliament (EP) similar to the oversight of USPTO by the US Congress.[732] Still, we see that the EP can act as the moral guardian of gene patenting, as a result of which the European Commission and the EPO examiners can change their attitude towards gene patents and the EPO can refuse the grant of a patent due to ordre public reasons. Recent examples of this are the EPO decision on Edinburgh patent.[733] We also see the CJEU's Greenpeace v. Brüstle decision was adopted by the EPO. Hence, the EU law with the Biotech Directive and the EPC have co-evolved over the years.

In the US on the contrast USPTO has direct congressional oversight. United States Senate Judiciary Subcommittee on Intellectual Property oversees the work of USPTO at regular oversight hearings. The subcommittee had been inactivated in 2007 but was reestablished in February 2019.[734] Although the Federal Circuit had been monitoring USPTO decisions for a long time, recently more of Federal Circuit decisions have been revoked by the Supreme Court. This has reduced the strength of the Federal Circuit in reviewing the USPTO decisions. The review by the Senate Subcommittee is on the other hand not related to patent office decisions, but to the activities of the patent office, its budget, policy strategies, implementation along with the others. Still issues such as clear patent examination guidelines, subject matter eligibility and written description, quality of patents granted are discussed in these hearings.[735] The US Supreme Court decision of

[732] The Administrative Council of the European Patent Organization is the legislative and supervisory body of the organization and consists of members of contracting states; mainly the heads of the national patent offices as representatives. EPO is the executive body of the organization and the Administrative Council ratifies the budget of EPO, approves its President and generally oversees the work of EPO. It has also competence to change the implementing rules of EPC, but the amendments to the EPC can be done by the contracting states only. Hence there is no political scrutiny on the work of EPO by law to be exercised by the European Parliament.

[733] Patent EP 0 695 351 granted in 1999 to University of Edinburgh for a method of isolation, selection and propagation of animal transgenic stem cells. Since the term "animal cell" embraces also human cells, the patent was opposed by Greenpeace, as well as German, Italian and Dutch governments on ordre public and morality grounds (Art. 53(a) EPC) and failing to disclose the invention in a manner sufficiently clear (Art. 83 EPC). In 2002 EPO narrowed down the scope so that human or animal embryonic stem cells were not covered.

[734] See the press release of the Subcommittee Chairperson US senator Thom Tillis from 7.2.2019 available at https://www.tillis.senate.gov/2019/2/tillis-coons-to-lead-senate-judiciary-subcommittee-on-intellectual-property last visit 30.04.2020.

[735] See for instance the statement of USPTO President at the oversight hearing of 13.03.2019 available at https://www.judiciary.senate.gov/imo/media/doc/Iancu%20Testimony.pdf last visit 30.04.2020.

Mayo v. Prometheus[736] has changed the gene patenting landscape in diagnostics. The patent-eligibility of the claims in the application has become a major concern. The Supreme Court analyzed the patent-eligibility in two steps a) by using the exceptions in Section 101, namely abstract ideas, laws of nature and natural phenomena b) by considering that an invention even if based on an exception, could still be patentable, if the third-party use of the exception is not restricted by the patents. Patent claims in diagnostic methods involve both these exceptions in the law, i.e., laws of nature / natural phenomena, and also inventive processes and methods. This two-step approach also overruled a previous decision, which analyzed the claims as a whole and ruled that a claim is not patent-ineligible simply due to containing one of the unpatentable concepts. [737] The two-step criteria were later also embedded into the USPTO Manuel of Patent Examining Procedure. [738]

In a following decision in 2015, the Federal Circuit followed this two-step approach and invalidated a patent for being patent-ineligible in the case Ariosa v. Sequenom.[739] The Supreme Court refused to hear the case[740], thereby the patent – eligibility criteria of Mayo decision were preserved.

On the other hand, in its 2018 Vanda v. West-Ward[741] decision, the Federal Circuit held that since the claims were not related to patent-ineligible subject matter, there was

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[736] Case 566 US 66 (2012) Mayo Collaborative Services v. Prometheus Laboratories Inc.

[737] Supreme Court decision 450 U.S. 175 (1981) Diamond v. Diehr.

[738] See https://www.uspto.gov/web/offices/pac/mpep/s2106.html last visit 30.04.2020.

[739] Case 788 F.3d 1371 (Fed. Cir. 2015) Ariosa Diagnostics, Inc. v. Sequenom, Inc. The US Patent No 6,258,540 claimed methods of using cell-free fetal DNA (cffDNA) to identify fetal abnormalities. Prior to the patent, prenatal diagnoses involved invasive methods that could be harmful for the mother or the fetus. The Court concluded that the claims are patent-ineligible, since the method starts with cffDNA, which is a natural phenomenon, and also concludes with cffDNA, failing to develop this natural phenomenon into an application.

[740] Docket no. 15-1182, The petition for a writ of certiorari by Sequenom was denied on 27.06.2016 see https://www.supremecourt.gov/docketfiles/15-1182.htm last visit 30.04.2020. Indeed, Sequenom had received strong support from the biotechnology community, which submitted 22 amici curiae to the Supreme Court.

[741] Vanda Pharmaceuticals Inc v. West-Ward Pharmaceuticals International Limited, 887 F3d 1117 (Fed Cir. 2018).

no need to perform the two-step Mayo test. In order to pass the patent-eligibility criteria, the claims were formulated in such a way that they were "directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome. They are different from Mayo." In Mayo the claim was directed to a method of optimizing therapeutic efficacy for treatment of a disorder by administering a drug without naming a specific dosage. In Vanda it was a claim for treating a schizophrenic patient with iloperidone at an amount 12-24 mg/day. We see that the term "method of optimizing a treatment" in Mayo is very general Federal Circuit found that they are not "directed to a novel method of treating a disease" When a specific treatment is claimed, the subject matter becomes patent-eligible. Still, a petition for a writ of certiorari was filed to the Supreme Court after the Federal Circuit decision, and the Supreme Court requested in March 2019 the Solicitor General to file a brief expressing the views of the United States (administration).[742] He recommended that the petition should be denied, because the Court correctly concluded that the claims are patent-eligible. In January 2020, the Supreme Court denied certiorari.[743]

In January 2019, the USPTO revised its Patent Subject Matter Eligibility Guidance to provide more certainty and predictability for its examiners and administrative patent judges on how Section 101 shall be applied.[744] The new guidance firstly defines what constitutes an "abstract idea"; namely mathematical concepts, mental processes, and certain methods of organizing human activity[745]. Previously (after the Supreme Court's Alice decision) the courts had to compare disputed claims with those ones that were deemed ineligible in earlier court cases.[746] Secondly, some clarification is given on when to apply the (Alice)/Mayo test if the claims are directed to a judicial exception, i.e., they

[742] See https://www.supremecourt.gov/search.aspx?filename=/docket/docketfiles/html/public/18-817.html last visit 30.04.2020.

[743] Ibid docket no: 18-817 The petition for a writ of certiorari denied on 13.01.2020.

[744] Notice, 01.07.2019, 2019 Revised Patent Subject Matter Eligibility Guidance, *Federal Register Volume 84 No. 4* available at https://www.govinfo.gov/content/pkg/FR-2019-01-07/pdf/2018-28282.pdf, last visit 30.04.2020.

[745] Ibid p. 16.

[746] Ibid p. 51.

are patent – ineligible. Accordingly, the USPTO shall consider the claim patent-eligible, if the claim recites to an exception, but can integrate a practical application such as effecting a particular treatment. If the claim recites a judicial exception but cannot integrate this exception into a practical application of the exception, then further analysis in accordance with second step of (Alice)/Mayo test shall be applied. Then the examiners can inquire whether the claim recite additional elements that amount to significantly more than the judicial exception. If it does, then the claim can still be qualified as patent-eligible.[747] This is the biggest change to prior guidance. Yet there were still some problems and inconsistencies in the application of the (Alice/)Mayo test. In October 2019, the USPTO revised its guidance once again. The October guidance clarifies further the 1st and 2nd steps of (Alice/)Mayo test, particularly addresses how "significantly more" and "integration" determinations shall be made.[748]

Members of the Senate Judiciary Committee's Subcommittee on Intellectual Property, as well as some other Congress members felt that the Supreme Court had confused and narrowed Section 101 of the Patent Act on patentable subject matter and that this legal uncertainty made the investors reluctant to pursue innovation.[749] In order to "incentivize development R&D into the exciting prospects of individualized diagnostics and precision medicine", they drafted a proposal to address the issue.[750] The draft bill provides that the provisions of section 101 shall be construed in favor of eligibility and that eligibility shall be "determined only while considering the claimed invention as a whole, without regard to any claim limitation (from sections 102,103 and 112 of the Patent Act)". The bill also proposes the elimination of the exceptions to patentability such as "abstract ideas," "laws of nature," or "natural phenomena". To be

[747] Ibid pp 9-16.

[748] See the USPTO revised subject matter eligibility guidance from October 2019 available at https://www.uspto.gov/patent/laws-and-regulations/examination-policy/subject-matter-eligibility, last visit 30.04.2020.

[749] See the statement of the IP Subcommittee Chairperson Tillis and Ranking Member Coons from 24.06.2019 available at https://www.tillis.senate.gov/2019/6/tillis-and-coons-what-we-learned-at-patent-reform-hearings, last visit 30.04.2020.

[750] See the draft bill proposal from 22.05 2019 https://www.tillis.senate.gov/services/files/E8ED2188-DC15-4876-8F51-A03CF4A63E26 last visit 30.04.2020.

patent – eligible, the subject matter should still fulfil the Section 101 criteria, which remain unchanged in the bill, but should also be "useful", by providing "specific and practical utility in any field of technology through human intervention". However, the meaning of specific and practical utility is not defined.

It was announced after the draft bill proposal that the legislators shall continue receiving stakeholder feedback and consider a provision to "exempt research and experimentation from infringement liability" to allow basic research to continue unimpeded by patents.[751] In order to prevent granting of too broad patents, the draft bill amends Section 112 requirements on best mode, enablement and written description by the amended provision of 112(f), which states that when an element is claimed only by a specified function and the structure / material or the acts supporting this function are not recited in the claim, , then this element will be constrained by the corresponding structure, material, or acts described in the specification and their equivalents so that the applicants cannot claim "all possible solutions to a problem", as again announced by the legislators. In the current provision 112(f), patent claims are permitted as means to perform a specific function. If the bill passes, only those claims that constitute the structure and/or act of the performed action will be permitted. The bill, if passed will not only challenge the Mayo test, but also have significant amendments on the patent-eligibility criteria.

Concerning the licensing agreements, the question we need to answer is that how can the licensing agreements be narrowed down in scope to cover for instance only certain genes and not the whole genome, or if it is not going to be the university licensing offices at all, what would be the framework for the governments and taxpayers to decide how the innovation stemming from public funding can accrue back to public domain? An example is the experimental use exception. This exception has been integrated into national patent laws of the most EU member states and provide sufficient scope for research activities for testing and experimenting patented products in order to uncover new knowledge, and to perform preclinical tests and clinical trials with the purpose of registering and

[751] See the statement in supra note 749.

marketing medicinal products.[752] But the exemptions covered under this rule and their scope vary significantly across member states in medicines (also protected by SPC), active pharmaceutical ingredients and medicinal products for human use.[753] In the US, although there has not been a statutory experimental use exemption, the law has developed allowing for exemptions from infringement liability for the medical activity of a medical practitioner,[754] but not allowing for commercial activities. The Federal Circuit interpretation of this exemption has been narrow. In Roche v. Bolar[755] the Court ruled that the exemption did not apply to commercial use and declined the experimental use defense of Bolar to produce a generic pharmaceutical, of which the active ingredient was patented by Roche. Bolar also argued that public policy required "to create a new exception to the use of prohibition" so that the patent monopoly ends after the patent expiry.[756] The Federal Circuit concluded that "it is the role of Congress to maximize public welfare through legislation" and reversed and remanded the case. The Congress enacted quickly in the same year with the so-called Hatch-Waxman Act[757] providing a safe-harbor for manufacture, use or sale of drugs that would otherwise be considered to be infringing the existing patents.[758] In the following years, the Supreme Court interpreted

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[752] JAENICHEN, H. R. & PITZ, J. (2015). Research exemption/experimental use in the European Union: patents do not block the progress of science. *Cold Spring Harbor perspectives in medicine*, Volume 5, Issue 2 available at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4315916/ last visit 30.04.2020.

[753] CRA Charles River Associates, (2017), *Assessing the economic impacts of changing exemption provisions during patent and SPC protection in Europe*, European Commission, DG GROW report retrieved from the Commission website http://publications.europa.eu/resource/cellar/6e4ce9f8-aa41-11e7-837e-01aa75ed71a1.0001.01/DOC_1, at. p. 5 last visit 30.04.2020.

[754] 35 USC § 287(c) reads as: "With respect to a medical practitioner's performance of a medical activity that constitutes an infringement under section 271(a) or (b), the provisions of sections 281, 283, 284, and 285 shall not apply against the medical practitioner or against a related health care entity with respect to such medical activity."

[755] Case 733 F.2d 858 (1984) Roche Products, Inc. v. Bolar Pharmaceutical Co.

[756] Since the commercial success of a generic drug depends on its fast marketing after the patent expiry, and the FDA approval of a drug can take more than 2 years, Bolar had immediately started its efforts to obtain an approval, not waiting for the patent to expire.

[757] Drug Price Competition and Patent Term Restoration Act Pub. L. No. 98-417, § 202, 98 Stat. 1585, 1603 (1984) amending 35 USC § 271(e)(1) and the Federal Food, Drug and Cosmetic Act Public L. 75-717.

[758] The amended 35 USC § 271(e)(1) reads as "It shall not be an act of infringement to make, use, or sell a patented invention (other than a new animal drug or veterinary biological product (as those terms are used in the Federal Food, Drug, and Cosmetic Act and the Act of March 4, 1913) which is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes

this exemption even more broadly to cover not only drugs, but also medical devices,[759] and preclinical tests and the information developed in preclinical activities.[760] Regarding the information generated after the marketing approval has been obtained, and the information routinely reported to the FDA, the Federal Circuit had a different view, and held that the exemption does not apply.[761] The Federal Circuit had already narrowed further the scope of safe harbor provision in an earlier case, refusing to use the provision on research tools.[762] The provision in the US patent law amended by the Hatch-Waxman Act (35 U.S.C § 271(e)(1)) is not clear enough so as to qualify research tools as well for exemption. The Federal Circuit noted that the amendment 35 U.S.C § 271(e)(1) "sought to eliminate de facto patent term extension and the basic idea behind this provision was to allow competitors to begin the regulatory approval process while the patent was still in force, followed by market entry immediately upon patent expiration".[763]

Still the Hatch-Waxman Act had a significant effect on the development of generic drug industry in the US. The ratio of the generic drugs prescribed increased from 13% in 1984 to 50% in mid - 2000s and to 84% in 2012.[764]

The wider implications of statutory amendments in patent law and case law interpretations can be seen by the economic assessment of these amendments and court rulings. Even a patent office decision is shown to bring significant impact on research and commercialization decisions, on share prices of companies and investment and trade patterns.

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involving site specific genetic manipulation techniques) solely for uses reasonably related to the development and submission of information under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."

[759] Case 496 U.S. 661 (1990) Eli Lilly & Co. v. Medtronic, Inc.

[760] Case 545 U.S. 193 (2005) Merck KGaA v. Integra Lifesciences I, Ltd.

[761] Case 659 F.3d 1057 (Fed. Cir. 2011) Classen Immunotherapies, Inc. v. Biogen Idec,

[762] Case 536 F.3d 1256 (Fed. Cir. 2008) Proveris Scientific Corp. v. Innova Systems, Inc.

[763] Ibid.

[764] BOEHM G. et al. (2013). Development of the generic drug industry in the US after the Hatch-Waxman Act of 1984. *Acta Pharmaceutica Sinica B*, Volume 3, Issue 5, pp. 297-311.

6. CONCLUSION

6.1 Main findings in brief

The optimal patent system is characterized by an efficient trade-off between static efficiency losses in monopoly situations and dynamic efficiency gains resulting from innovation, dissemination of information, better products and processes, increased investment. Patent protection aims mainly at fostering innovation, and efficient allocation of resources may be neglected. Designing the patent law for medical biotechnology in such a way to address both static and dynamic efficiency issues would be a way of maximizing social welfare. The research question discussed in this dissertation is whether the gene patents granted in medical biotechnology have been providing efficient incentives in encouraging innovation and creating an optimal allocation of resources to increase the social welfare, especially by means of patient access to diagnostic and treatment opportunities at reasonable costs, but also by facilitating the R&D activities for researchers and bringing legal certainty for them and the businesses for the commercialization of products. Impact on consumer welfare has also been discussed in terms of access to health care. Alternative mechanisms to patent protection can be reward / prize system, public funding with open access and compulsory licenses.

Reward / prize system as an alternative to patent protection would be difficult to implement in medical biotechnology, since firstly according to survey results innovators in this field heavily rely on patents and secondly due to ownership and liability issues for pharmaceuticals and other medicinal products on the market. As a result, prize system can be used as complementary means of providing incentives to innovators to address some problems such as provision of generic drugs and production of low-cost pharmaceuticals for large-scale diseases as in the case of a pandemic or a disease outbreak in poorer parts of the world like for instance HIV/AIDS in Africa. Public funding with open access could be another alternative to patents but this requires ex-ante funding by taxpayers and is also problematic in medical biotechnology since adequate up-front funding is required to make break-through innovations. This necessitates a good oversight of funding mechanisms in order to avoid waste of public resources, which is in itself also costly. Finally, compulsory licensing is also a means of offsetting the monopoly pricing.

It enables wider access to patented medicines when the license is issued by the governments to generic drug producers so that the drugs can be offered at lower prices. Although TRIPS allows for this practice, these licenses are subject to various conditions and it was mentioned in the dissertation that innovating pharmaceutical companies rather choose to make price reductions or provide royalty free licenses to generic companies in order to avoid compulsory licenses.

To sum up some differences and similarities between the EU and US patent systems in medical biotechnology: Biotech sector is a sum of overlapping patterns, it is difficult to assess even the absolute bars to patentability. Besides due to merged research and diagnostic / clinical facilities it is also difficult to make upstream v. downstream differentiation. Very broad patents granted initially restricted in scope in both jurisdictions, but this is more evident in the US as the scope was narrowed down by later Supreme Court decisions. We see that public funding in initial phase for the innovative activities was exceeded by private funding & R&D in later stages. Patents are also used for licensing and other commercial negotiations, i.e. strategic patenting is apparent. USPTO receives more applications & grants more patents (patent first, question later approach). Actually, EPO administrative board is made of representatives from national patent offices, hence they should also have an interest in increased number of patents (due to increased fee accruals), but at EPO a more thorough analysis is carried out. USPTO has more administrative workload with almost double figure applications per examiner. High number of applications and means less time to make a detailed analysis. Studies hint that more time given to examiners means less grants and less litigation. Problem of patent trolls is more acute in the US. EU system is more costly due to national differences in application, grant and enforcement. Morality and public order have mainly been EU concerns, but latest US Supreme Court decisions Myriad & Mayo hint to some changes. US executive response is also much quicker to adapt to requirements of the biotech sector, as the utilitarian approach in patenting prevails in the US also for biotech patents and there is not a special Biotech Act as in the EU. Biotech subject matters are required to meet the same patentability criteria as with other technologies. Only in recent years in the US after some Supreme Court decisions some discussion is made on patentability v. patent-eligibility of biotech inventions. On the other hand, the Biotech Directive of the

EU acts as a safeguard on morality / ordre public issues and has special provisions on purpose limited patentability of gene sequences, as well as absolute bars to patentability for plant and animal varieties, human body, essentially biological processes, and commercial/industrial use of human embryos. The general nature of the complex law-making procedures at the EU level makes it a hard task to challenge the EU Biotech Directive. Besides in the EU the biotech patent applications are also governed by the EPC. Although some harmonization between the Biotech Directive and EPC Rules has been reached in recent years, after CJEU decisions, EPC provisions are not per se EU law and EPO does not have judicial oversight in the EU legal system. There are several non-EU countries which are part of the EPO and CJEU decisions are not binding on EPO. EPC rules can only be amended by the Administrative Council of the European Patent Organization, which also includes non-EU member countries. This uncertainty is difficult for innovators and can be the reason why many European biotech start-ups apply to IPOs directly in the US. The unitary patent and the Unified patent Court will bring more harmonization, but still EPO will not be able to refer to CJEU, only UPC will be able to do that. Hence legal uncertainty in this regard will continue.

6.2 Main findings in detail

The analysis from law and economics perspective questioned whether the current legal treatments in the EU and in the US are optimal and reflecting the economic theory, or whether there is a scope for change, and on what basis this change should take place. Although the statutory patentability criteria are similar in both jurisdictions, the interpretation of law and the scope of protection have been different. Since the duration of the patent protection is fixed in both jurisdictions, patent breadth and non- patentability and patent-eligibility are the most important instruments shaping the patent policies.

Besides, this law and economics analysis of gene patents in medical biotechnology aimed to explain why particular legal rules exist such as patentability criteria for gene patents, assess and predict what effect particular legal rules will have, such as effects of change after the introduction of certain legislations and court decisions, as well as what regal rules should exist to address the problems of patents in licensing and thicket issues.

Some very early patent office decisions and years-long disputes at different court levels are also referred throughout the dissertation in order to show the evolution of the case law.

On answering the research question whether the increased number of patents granted in the EU and US is really encouraging innovation we see that in the general discussion in favor of or against patents, similar arguments are put forward since the 19th century stressing the effects on the patents on the innovation process. The opponents of patenting have been arguing that there is no real evidence of patents increasing innovation. In the medical biotechnology, the opponents of gene patents have in addition brought especially in the EU the arguments around ordre public and morality issues. As a result, the EU has been more careful in granting gene patents; several claims that were patentable in the US were not granted protection in the EU, and when they were, their scopes were much narrower.

The number of patents granted in biotechnology are increasing both in the EU and the US. But this does not always imply increased innovation. In some cases, we see a strategic patenting in order to close the market for competitors. In others, it was shown that granting of very broad gene patents with limited licensing hinders research, innovation and access to life-saving diagnosis and treatment possibilities. Unlike in some other industries, one cannot think of gene patents in medical biotechnology as isolated innovation. It is a complex sector with overlapping patents. They accumulate and build up on each-other to develop the diagnostics / treatment.

Evidence suggests that companies in the manufacturing sector patent their products not only to prevent copying, but also to strengthen their position in licensing and other commercial negotiations. A survey needs to be done in biotechnology industry among US and EU firms, to see if they have different incentives in patenting, i.e. if for instance US companies patent more in order to be able to have quid pro quo in lawsuits, in licensing / settlement negotiations.

Universities give exclusive licenses to their spinoff companies to market the patents. These companies engage in further exclusive licensing agreements with third

parties, which can be very broad in their scope covering the entire genome and potentially having a wide range of applications in biomedical therapeutics, drug discovery, further R&D, but also in agricultural and animal health sectors.

The theory that we need patents to solve the problem of R&D incentives, and dissemination of knowledge holds also in the case of medical biotechnology. But the short and medium-term deadweight loss and the static inefficiency created by biomedical monopolies result in many challenges for the sector, as well as for the patients. The innovation in the sector is mainly a collaborative process, depending on the results of the previous and on-going R&D activities. There are many stakeholders including law-makers, the civil society, basic research institutes, the businesses and the courts that can shape the scope of the patent protection, especially by the breadth of the claims. Empirical studies show that patents are also used as means of strategic bargaining tools, which may explain the increase in the propensity to patent in biotechnology, but which does not necessarily indicate increased innovation per se and depends on whether efficient incentives are provided. Increased litigations also come at the cost of the society, which is reflected in the possible commercialization and in the price of the product.

According to the invisible hand process of law, the law evolves into economically efficient outcomes.[765] It was shown for several court cases that efficient rulings were reached where the judges either amended / narrowed down the scope of the claims or entirely invalidated granted patents and clarified the patent eligibility criteria.

Obviously, the granting of patents and the commercial exploitation of patents are two different issues. However, they are not apart from each-other. The patenting per se

[765] Rubin (1977) argues that common law evolves into efficiency through court cases not only because the judges are smart, but because the parties develop incentives to utility maximization and reducing the incentive for future litigation. If the legal rules are inefficient, parties will have incentives to use litigation, if rules are efficient, litigation will not be necessary and the inefficient rule will be overturned by time through litigation, whereas the efficient ones will be maintained. Intelligent judges may accelerate the process of attaining efficiency; they do not drive the process so that efficient rules can still be attained even if the judges do not have efficiency considerations. See RUBIN, P. H. (1977). Why is the Common Law Efficient?, *Journal of Legal Studies*, Volume 6, Issue 1 pp 52-55. For a general discussion of invisible hand in legal theory see VERMEULE, A. (2009). The Invisible Hand in Legal Theory, *Harvard Public Law Working Paper* No. 09-43. Available at SSRN: https://ssrn.com/abstract=1483846, last visit 30.04.2020.

may not be regarded as immoral. But once the patent is granted, the likelihood of having a commercial exploitation is large.

On the research question whether the biotech patents are increasing social welfare, the social welfare can be measured by means of patient access to health care at reasonable costs, decreased illnesses, better diagnostic and treatment opportunities, as well as the ease of performing R&D activities for the researchers and of the commercialization of the products. Personalized medicines will be the future of drug evolution and pharmaceutical R&D using biotechnological materials, hence incentives given as in the case of orphan drugs are likely to stimulate innovation. However, it is also not to forget that a substantial part of pharmaceutical R&D relies on basic life sciences, which are paid by public funds. Besides bioprospecting namely, the discovery and commercialization of new pharmaceutical material based on traditional knowledge from local communities is becoming more and more widespread and are found to have transformed the success rate in drug discovery by 78%.[766]

In order to find a balance between the incentives to innovate, and the externalities in decreased access to research activities, as well as diagnostics and treatment opportunities, other incentives can be considered such as compulsory cross-licensing, tax incentives, direct government grants on R&D activities of private companies, especially for SMEs, shorter patent terms.

Uncertainties around the patent battle between the universities in CRISPR case also create difficulties for third party research institutions and companies in finding negotiation partners. This battle is likely to last for years. A patent pool between the two institutions is very unlikely to emerge under the circumstances of ownership disputes, although the Broad Institute has announced to propose 22 of its patents (both EP and US) to a pool.[767] The efficiency of patents pools depends on number of participants to the pool

[766] OGUAMANAM, C. (2004). Localizing Intellectual Property in the Globalization Epoch: the Integration of Indigenous Knowledge. *Indiana Journal of Global Legal Studies*, Volume 11, Issue 2 pp 135-170.

[767] See the submission letter of Broad Institute to the MPEG-LA pool from 28.06.2017 available at https://www.broadinstitute.org/files/news/pdfs/MPEG-LA-Broad-joint-submission.pdf last visit 30.04.2020.

and the ease of negotiations on licensing conditions, royalty fees, and getting around the hurdle of acquiring several licenses from multiple parties etc. If the transaction costs of getting a license from the patent owner are less than in case of a pool, the third parties would not engage in the pool. In cases especially where a few patent licenses are required in order to develop medicines or therapeutics, the companies would not need a patent package and would directly deal with the patent owner.

If the law is written in an ambiguous way, different interpretations can be made by the Courts. In encouraging commercialization of products, cautious policy-making is required in order to balance the public and private interests. Markets do not always provide the necessary incentives for the innovators to engage in R&D activities and appropriate the benefits. That's why the governments intervene and try to set up the adequate regulatory framework to provide an efficient environment for the inventors and the public. The Courts not only focus on legal protection of patents but can also help to create an efficient patent system where the level of incentives given to the inventor does not exceed the expected social value of the invention. However, amendments to the law or changes in the interpretation of the law may take longer than market solutions to inefficiency issues. There are high transaction costs related to biotechnological patents such as privatization of knowledge, setting up a regulatory framework to ease access to genetic resources, as well as the products stemming from patented biotechnological materials, but also protecting the interest of the inventors, adapting policy instruments to encourage investment in the field. Unfortunately, market solutions such as patent pools or policy instruments such as compulsory licensing and a reward system are not always possible to implement.

The US Federal Circuit has been able to adapt patent law to the needs of medical biotechnology in several cases. However, its decisions are also subject to scrutiny of the Supreme Court and some of its decisions were reversed. The final decisions of the Supreme Court bring legal certainty on what shall be regarded as patentable and patent-eligible.

Hence the question whether the different patent systems in the EU and the US have a positive or negative impact on social welfare by means of increased innovation and dissemination of information can also be answered looking at the evolvement of the law by court rulings and the changes brought to the scope of the patents. Increased innovation and dissemination of information do indicate an aspect of increased social welfare, but as noted often throughout the dissertation, the measuring of the social welfare depends also on other factors such as better and cost-efficient diagnostics, treatment of (hereditary) diseases, and allowing these novel methods to be available to patients around the world under fair and reasonable terms and conditions.

On the cost of funding of R&D, it is seen that the public (government) contribution to biotechnology R&D was essential in the beginning, but then the private investments accelerated and exceeded the public ones. The patent protection in its earlier forms started in Europe already as early as the 15th century, mainly as forms of certain monopoly rights. In the US in the beginning, it was a practice of registration system. The criteria on patenting, especially inquiries into the utility of the invention came much later. Today it is also important to have possession of the claimed invention. After important court rulings the patent offices revised their guidelines so that plans per se are not accepted in the filing, even if they enable someone skilled in the art to make the inventions. Some additional criteria such as “best mode”, which is a part of the US system, but not EU, brings additional requirements to the inventors not to hide any better means of making the invention without undue experimentation.

In both jurisdictions there are explicit exclusions to patentability, but in cases where the statutory law is ambiguous, some court cases enlighten the patentability criteria. Even in cases that fall under the exclusions, it is difficult to assess for the patent examiners and the courts what is a mere discovery, what is man-made, what is naturally occurring. The statutory patent eligibility has also its limits and the courts interpret the law in such a way so as to eliminate the ambiguities. As a result, the legislators may feel the need to bring amendments to statutory law at later stages. Some examples are the amendments in the EU for EPC 2000, which did no longer necessitate the Swiss-type of claims, patent-eligibility reform discussions in the US after Supreme Court decisions.

Changes in law favoring certain sectors such as orphan and generic drugs have also helped to increase in the establishment of new firms and the amounts of the pharmaceuticals available on the market. In some other cases we see the civil society groups and scientists calling for greater actions for changes in regulatory environment, which no longer reflects the necessities of current realities.

In the US there is not a special law on patenting of biotechnological inventions, but in the EU, there is the Biotech Directive, which was implemented by all member states despite prior discussions that took almost two decades. Thus, the EU Biotech Directive gives guidelines to apply the specific concepts in gene patenting that are normally not existent in general patent law. This gives a clear indicator to the researchers and investors on what is patentable in the EU and brings a legal certainty to their everyday activities and decisions. It must also be noted that in the US Congress it is relatively easier to make amendments to the Patent Act than making changes at the EU level to the EU Biotech Directive due to the complex law-making procedures in the EU, or making changes to the EPC where each signatory member state has to agree.

In shaping of the patent law for biotechnological inventions, the competitiveness of the regions compared to other parts of the world played an important role. Both the EU and the US aimed to increase the competitiveness of their biotechnology sector vis-a-vis each-other, but also against Japan, China, Australia, and so on. These considerations contributed especially in the US to a system of easier patent grants in comparison to the EU. Some attribute the EU patens to be of higher quality than the US ones. The problem of patent trolls and litigation is much acute in the US than in the EU. The US has had the habit of patenting first and then discussing the patentability or patent-eligibility of the claims that were already granted patent protection. In the EU moral and ethical considerations were nevertheless an integral part of gene patent discussions, hence the propensity to patent was lower. Or even in some cases such as the Onco-mouse, the European patent was revoked after lengthy discussions and in contrast the patenting of Onco-mouse was very straight-forward and broad in the US also with follow-up patent grants. In other cases, we see the European patents being much limited in scope than their US counterparts. But patenting of biotechnological innovations is seen more as a

technical and straight-forward issue in the US like many other patents. In the EU, the EU institutions, and the member states, both political and civil society actors approach the issue as having greater moral, societal, economic and environmental impacts. This is rather in contrast with the idea of EU Biotech Directive which aims to provide adequate legal protection to biotech investments so as to make them profitable, but we see the evolvement of law to compromise all parts of the society.

One other factor that contributed to a higher number of patents in the US is the cost issue. The cost of patent application and enforcement is much higher in the EU than in the US due to national applications, verifications, and enforcement at each member state after a European patent is granted. There are several costs associated with translation, administrative and legal fees. These costs are likely to decrease once the unitary patents will be granted in the EU. One has to see than if the propensity to patent biotechnological (and also other) inventions increases then. Although the reduced costs, single enforcement mechanism and harmonization will be the main advantages of the unitary patent system in the EU, there are still some uncertainties on how revocation procedures will be dealt with, as both EPO shall continue to have opposition procedures and the UPC will have the legal basis to revoke a patent. Besides, it is also not clear how to deal with the national patent enforcement once a unitary patent is revoked. Because once a patent is deemed unitary, its national rights are abolished, and some inventors may wish to re-establish national patent protection depending on their market structure. Another difference between the European and unitary patent oppositions is that at EPO any legal person is entitled to bring opposition, but at UPC this person has to be concerned by the patent. So, the persons shall need to show how and to what extend they are affected by the patent as a whole and/or by some of the claims within. This is likely to decrease the number of opposition proceedings. But it may be very costly for innovators and investors in the EU to deal with fragmented structures at EPO, UPC and national patent offices and legal systems.

Currently there is no central data registration on market demand for patents or on patent licenses or sales. In a review of transactions at USPTO for the patent applications published 1930-2014, it was found that patent licenses /acquisitions do not necessarily

hint to an actual innovation or a technology transfer.[768] In case of patent trolls, the innovators, who are considered to be infringing a patent may opt for a license agreement or other forms of settlement in order to avoid litigation costs. In a survey of in-house attorneys of product companies, who know at best whether their company actually implemented the new licensed technology, it was found out that most patent license demands by patent trolls or non-practicing entities and even by product-producing companies and universities simply involved payment for the freedom of keep doing what the licensee was already doing.[769] Hence when patents become a tool to charge fees instead of improving innovation, they constitute a hindrance to drug and treatment development in medical biotechnology, and the desired social welfare from the patent system declines. However, it is also obvious that the firms holding patents are attractive for venture capitalists since they can as such identify innovative companies with investment potential and commercialization opportunities. It was shown in the dissertation that stock prices of biotech companies are very much responsive to USPTO and court decisions in the US.

Besides, in the US, there is no clear differentiation of discovery and invention in the statutory law.[770] The case law has evolved making exemptions from patentability for abstract ideas, laws of nature and natural phenomena. But some of these judicial exemptions have also been found to be patent-eligible in view of the recent decisions by the Supreme Court and the Federal Circuit. For the courts it has become important to make a distinction between patentability and patent-eligibility. Specific case law examples show that the law can produce economic outcomes to deal with the problems of anti-commons and other inefficiencies. As indeed introduced in the introductory chapter of the dissertation, it is observed especially in case law that although the

[768] GRAHAM, S.J.H. et al. (2018). Patent Transactions in the Marketplace: Lessons from the USPTO Patent Assignment Dataset. *Journal of Economics and Management Strategy*, Volume 27, Issue 3, pp.343-371.

[769] FELDMAN, R. & LEMLEY, M. A. (2015). Do Patent Licensing Demands Mean Innovation? *Iowa Law Review*, Volume 101, pp. 137 – 189.

[770] Section 101(a) of the US patent act reads as "Whoever invents or discovers any useful process, machine, manufacture, or composition of matter, or any useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title".

regulatory law and the patentability requirements create some inefficiencies, these inefficiencies are resolved by court cases. And especially in the US, the legislators can act more quickly, when the USPTO examiners' or courts' understanding of law become inconsistent in granting patents. In the EU there is a special directive on the legal protection of biotechnological inventions. In the EU Biotech Directive, it is recited that a mere discovery shall not be patentable.[771] The EPC Art. 52(2)(a) also excludes discoveries from patentability. In the EPO examination guidelines, it is further stated that "a mere discovery is not patentable, because it has no technical effect and is therefore not an invention." However, a gene, which exists in nature can be granted patent protection "if a technical effect is revealed such as its use in making a certain polypeptide or in gene therapy".[772]

The statutory patentability criteria in both jurisdictions are similar, be it called industrial application vs. usefulness, inventive-step v. nonobviousness, etc. Yet the EU concept of industrial application is much narrower than the US concept of usefulness. Similarly, the could-would approach and the problem-solution approach by EPO to assess inventive step are much clearer and stricter than the obviousness tests of USPTO, which mainly rely on the case law.[773]

That is why some very broad genetic claims could be granted patent protection in the US, which would not be the case in the EU. And afterwards these patents are challenged in courts, in different levels to be reviewed finally by the Federal Circuit and the Supreme Court. As discussed in the dissertation, USPTO first grants the patent and then it is discussed in courts whether the claims have been patentable and patent-eligible.

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[771] See recital 16 of the Directive, as well as Art. 5(1) on the unpatentability of a simple discovery of one of the human body elements.

[772] See in the EPO Guidelines for Examination Part G, Ch. II – 3. Exclusions, 3.1 Discoveries – November 2019 version.

[773] In Manual of Patent Examining Procedure (MPEP) of USPTO some exemplary rationales that may support a conclusion of obviousness are cited, which do not indicate an all-inclusive list. For further details and some case law examples, see MPEP Section 2143 -Examples of Basic Requirements of a Prima Facie Case of Obviousness available at https://www.uspto.gov/web/offices/pac/mpep/s2143.html last visit 30.04.2020.

EPO on the other hand applies a much stricter criteria before granting patent protection. This is seen by some scholars and practitioners as the EU granting a higher quality of patents. Without commenting on the quality of the patent, we can conclude that the EU system gives more legal clarity to innovators on what is patentable and saves a lot of litigation costs and also prevents patent trolls. Similarly, as the publication date could be postponed in the US before the enactment of the TRIPS agreement in 1995, submarine patents were kept secret for several years and these had significant costs on the R&D and the society in general. In the EU even before the TRIPS, the EPC did not allow for this practice.[774] In general the European practice can be regarded to be more socially beneficial, if it substantially reduces enforcement, litigation, and related costs. Since the enforcement, infringement, revocation of patents in the EU is a national issue, there is less case law referred in the dissertation from EU member states in comparison to the US. This will certainly change with the foundation of the Unified Patent Court in the EU.

TRIPS Article 31 on use without the authorization of the right holder (upon governmental authorization) allows in both jurisdictions (also in other WTO member states) for compulsory licensing practices and other administrative processes with reasonable terms and adequate renumeration, including an exclusion of injunctive relief for government use, or making price reductions and providing royalty-free or low-royalty licenses in developing countries for better patient access. The law should take into account economic interests of all parties involved and try to maximize aggregate welfare in terms of creating incentives for R&D and facilitating patients' access to medical care. The patent holders may opt for voluntary settlements in order to avoid compulsory licensing. Indeed, according to WTO data, when two pharmaceutical companies GSK and Boehringer Ingelheim refused the issue of voluntary licenses for their HIV / AIDS treatment antiretroviral drugs at a fair royalty rate of 4-5% in South Africa in early 2000s, the Competition Commission of South Africa announced in 2003 that it would refer the

[774] Art. 93(1) of EPC 1973 reads as "A European patent application shall be published as soon as possible after the expiry of a period of eighteen months from the date of filing or, if priority has been claimed, as from the date of priority. Nevertheless, at the request of the applicant the application may be published before the expiry of the period referred to above. It shall be published simultaneously with the publication of the specification of the European patent when the grant of the patent has become effective before the expiry of the period referred to above."

case to Competition Tribunal with the request of compulsory licenses and a penalty of 10% annual turnover. Before the case was heard at the Competition Tribunal, the two companies reached a settlement with a local generic drug producer to offer licenses at a maximum royalty rate of 5% and also with the permit to export to other Sub- Saharan African countries. This settlement had a direct effect on prices with up to 70% reductions.[775] In the US there has never been a law to generally authorize compulsory licensing of patents in public interest, but in some cases compulsory licenses were issued mainly in medical devices sector, rather than pharmaceuticals by the Federal Courts in patent infringement cases by rejecting requests for permanent injunctions.[776] Or the compulsory licenses were issued not only in the US but also in Europe, as part of the consent for the merger of different pharmaceutical companies.[777] In the EU, Germany's Federal Patent Court issued a compulsory license allowing Merck against the Japanese patent holder to continue to market a HIV / AIDS treatment drug, considering the health risks and public interests.[778] In Italy several compulsory licenses were issued by the Competition Authority for pharmaceuticals in competition law-related cases to allow for widespread use of generic products and improve market conditions where the pharmaceutical companies were found to be abusing their dominant position.[779]

TRIPS Section 5 also clarifies the steps for patentability requirements and exceptions. Member states are then free to name the requirements on being useful vs. capable of industrial application or non-obviousness vs inventive step. Still the case law suggests that the term usefulness is applied in a much broader sense in the US than the industrial application requirement in the EU.

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[775] Briefing note: Country experiences in using TRIPS safeguards: Part II, (2017), *World Health Organization*, pp 3-4. available at https://apps.who.int/iris/handle/10665/272978 last visit 30.04.2020.

[776] Briefing note: Country experiences in using TRIPS safeguards: Part I, (2017), *World Health Organization*, p.4 available at https://apps.who.int/iris/handle/10665/272977 last visit 30.04.2020.

[777] Supra note 775 p. 5

[778] Supra note 776 p.4

[779] In some cases, the generic companies were not given the authorization by patent holders to export to even third countries without patent protection. See supra note 775 pp 5-6.

Besides TRIPS, the European Patent Convention (EPC) and the EU Biotech Directive are the two fundamentals of the legal system in the EU.

European patents granted by EPO are based on EPC, which is a multilateral treaty. However European patents are not unitary and need to be validated and enforced at the national level in each member state. The unitary patent, which is expected to come into effect soon will solve this problem of individual validation and enforcement in member states and will allow for a uniform protection within the EU. This centralized system will create especially a lot of benefits for SME applicants in terms of reduced application and enforcement fees. The new system was mainly designed to address the inefficiencies of the fragmented system in promoting growth, innovation, and competitiveness. The aim was to create the single market for patents and make the EU more attractive for businesses with efficient, simplified procedures and increase EU's competitiveness vis-à-vis US, Japan and China.[780] The Unified Patent Court is also expected to deliver quicker and more efficient results in dispute and litigation cases. There are significant variations between the national court systems in terms of procedures, collecting of factual evidence, cost structures, examinations, hearings of experts, etc.[781] The case law and statutory law evolve together. The evolvement of the biotechnology patent law has been different in the EU and the US. Morality and ordre public were important aspects taken into consideration when making of the EU Biotech Directive and granting of patents at EPO. The patentable subject matters are treated from a moral point of view and some safeguards were granted by Article 53 of EPC and Article 6 of the EU Biotech Directive. There is no similar statutory ethical safeguard in the US patent system. For instance, the granting of the Onco-Mouse patents was a rather straightforward process with a very broad scope in the US with even two following patents granted in the following years. In the EU it caused 20 years of disputes, oppositions, narrowing down of claims, still it was finally revoked.

[780] See European Commission, (2007), Communication from the Commission to the European Parliament and the Council - Enhancing the patent system in Europe - /* COM/2007/0165 final */ available at https://eur-lex.europa.eu/legal-content/EN/TXT/HTML/?uri=CELEX:52007DC0165&from=EN last visit 30.04.2020.

[781] For instance, in some countries the Courts have competence to hear both infringement and revocation cases, where in others there is a separation of courts. See the Commission Communication at supra note 780.

Embryo patents have also been always very controversial in the EU. As early as 2002, in a case of much debated Edinburgh patent, the EPO narrowed down the scope so as not to cover human or animal embryonic stem cells and maintained the patent in this amended form. The patenting of hESC was later prohibited by the Brüstle decision of the CJEU.

On the other hand, the US Congress is capable of adopting faster amendments and regulations with regards to patenting of biotech inventions. In the EU, although there is the Biotech Patent Directive and the EPC, patents still remain a national issue, there will be no centralized enforcement mechanism till the unitary patents will be in force.

Patent offices and courts are seen to be inter-acting with each-other. As a result, we see administrative rule changes and revised patent examination guidelines in both jurisdictions. The EU Biotech Patent Directive and the CJEU decisions have affected the EPO proceedings, although CJEU decisions are not binding on EPO.

In the US, it is possible to file for a provisional patent application for one year, which is not counted as part of the 20-year patent term. The application does not grant patent protection, but it is beneficial especially for SME applicants, since the application fee at the USPTO is relatively lower[782] and the applicants have flexibility in their submission format without the need to put forward claims, so that they can save on patent attorney fees and USPTO review fees, as well. The main rationale in making a provisional application is to obtain a pending-patent status with a filing date at the early stages of R&D activities and to be able to disclose the available information, have some time to do own prior-art search, consider possible functions to meet the utility requirement and possible means to market their product. Within one year, if the prospects are good, the applicant may make a non-provisional application in full format and ask for a twenty-year patent protection. Obviously granting a provisional patent protection with a shorter term in biotechnological inventions would allow for an increased competition in

[782] See the USPTO fee schedule available at https://www.uspto.gov/learning-and-resources/fees-and-payment/uspto-fee-schedule last visit 30.04.2020Provisional application fees are USD 70-280 plus some surcharge of USD 100-400 for each additional 50 sheets, if the application exceeds 100 sheets. The non-provisional applications can cost several thousands of USD depending on the number of claims drafted by the patent attorneys / agents and to be examined by the USPTO.

biomedical research and better medicinal access conditions for patients due to reduced monopoly power. But as explained throughout the previous chapters, the patent terms are fixed 20 year. A policy change to give patent protection in line with the commercialization (time necessitated for putting the product on the market plus the commercial lifetime) of the product may be effective in creating better social welfare.

The EU has a more thorough examination of the patent claims at the granting stage due to involvement from different actors such as the Commission, the European Parliament, civil society groups and the EU member states. In the US the granting is seen as a more technical and straightforward process by the USPTO, although there certainly are legal requirements for the patentability criteria, and the questions are raised after the patents have been issued such as the ones on the patent-eligibility. This indicates a higher quality of patents in the EU and a higher legal certainty for patent applicants.

It was also found to be difficult in the US setting to identify the patent owners due to incompleteness and inaccuracy of patent records. In some cases, especially for small companies, what the author of the study refers as "recordation failure" is due to related costs, in others, companies withhold this information deliberately to gain strategic advantage.[783] In regulated industries such as the pharmaceuticals, delayed market entry for years is an incentive for the (bio)pharmaceutical companies to look for stronger patent protection and they rely on the exclusivity coming with the patent rights. As a result, they identify prior art thoroughly. Mass patent litigations seem to be more of a problem in the US than in the EU, due to the higher quality of patents in the EU, that reduces the propensity to litigate, but also due to different institutional and administrative frameworks in the two jurisdictions. For instance, at EPO there is a Review Panel of 3 examiners for each application.[784] This leads to more scrutiny and a lower rate and narrower scope of

[783] CHIEN, C.V. (2012). The Who Owns What Problem in Patent Law. *Santa Clara Univ. Legal Studies Research Paper No. 03-12*. available at http://ssrn.com/abstract=1995664 last visit 30.04.2020. The author found that in about a third of the cases out of 915 filings of patent litigations by patent trolls, the plaintiff was not the patent owner of record as of the day the litigation was initiated.

[784] See the "Guidelines for Search and Examination at the EPO as PCT Authority" available at https://www.epo.org/law-practice/legal-texts/html/guidelinespct/e/b_vii_7_2.htm last visit 30.04.2020.

patents granted. Very broad patents are more likely to be sued for infringement. In the US there is one examiner, who has found to be allocating on average 13-27 hours (depending on the technology category) for each application[785] and also depending on his /her experience at the USPTO, where more experienced examiners' examination time is roughly the half of the less experienced ones, but the grant rate of patents rises from the lowest grade rate of examiners to highest by roughly 13 to 28%. If the examiners were all to be given the same amount of examination time, the overall granting rate would fall by 20%. [786]

Giving more time to examiners and having higher quality patents were estimated to save between approximately USD 103,000 and USD 950,000 litigation costs per patent and patent-case pair depending on the amount at stake and stage of litigation,[787] despite an estimated increase of USD 520 to USD 1,123 (depending on the technology category) in terms of examination costs at the USPTO.[788] Making a cost-benefit analysis we can conclude that the society will be better off with higher quality patents.

The staff and application figures are also very different at EPO and USPTO. In 2018 at USPTO some 8,185 patent examiners received around 596,000 patent applications and issued around 307,000 patents.[789] In the same year at EPO some 174,000 applications were received and 128,000 issued[790] by some 4,300 examiners.[791] Although the number

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[785] FRAKES, M. & WASSERMAN, M. F. (2014). The Failed Promise of User Fees: Empirical Evidence from the United States Patent and Trademark Office. *Journal of Empirical Legal Studies*, Volume 11, pp 602-636.

[786] FRAKES, M. & WASSERMAN, M. F. (2017). Is the Time Allocated to Review Patent Applications Inducing Examiners to Grant Invalid Patents?: Evidence from Micro-Level Application Data. *Review of Economics and Statistics*, Volume 99, Issue 3, pp 550-563.

[787] FRAKES, M. & WASSERMAN, M. F. (2019). Irrational Ignorance at the Patent Office. *Vanderbilt Law Review*, Volume 72, Issue 3, pp.1-25.

[788] See Frakes and Wasserman at supra note 785 Table A1.

[789] See USPTO FY 2018 Performance and Accountability Report available at https://www.uspto.gov/sites/default/files/documents/USPTOFY18PAR.pdf last visit 30.04.2020.

[790] See EPO 2018 Annual report available at https://www.epo.org/about-us/annual-reports-statistics/annual-report/2018.html last visit 30.04.2020.

[791] See EPO staff figures available at https://www.epo.org/about-us/at-a-glance.html last visit 09.12.2019 last visit 30.04.2020.

of patent examiners is roughly twice as much at USPTO than at EPO, the workload is almost triple.

Patent trolls are also found to be rather a US problem. Of the cases filed in the UK during 2000-2010, only 11% involved NPE (non-practicing entities) patents, which overwhelmingly tended to be ICT (information and communications technology)-related.[792] But in general there are significant differences in litigation rates and outcomes across the EU countries. In a study comparing the UK, Germany, France and the Netherlands, the Netherlands was found the have the shortest judgement in 10 months and France the longest with 24 months for infringement cases. Again, a revocation judgement is given on average in 11 months in the UK and in 27 months in France. The number of cases heard in Germany exceeds the total of the other three countries. This is mainly explained by the size of the economy in Germany, but also the bifurcation system in the patent law where the infringement and validity of the patents are heard by different courts and the general patentee-friendliness of the German courts.[793]

Due to ordre public and morality concerns in the EU, the patenting and the commercialization of the patented products have been much faster in the US, which puts the US in a competitive advantage to set-up companies, find financing and bring the products onto the market. It is true that the patents help especially small companies to find funding, but these companies can also be more easily blocked from doing follow-on research, due to patents held by larger companies. Small companies do not have the financial means to make appropriate research on patent owners, to negotiate with them and license the products. Increased patent protection does not yield the same results for small medical biotechnology companies as for the big ones. For the small ones, subsidies on R&D, commercialization and market-entry with different tax benefits can be considered. To be able to make accurate calculations on the costs and benefits, the real valuation of gene patents and their contribution to diagnostics and treatment should be

[792] HELMERS et al. (2014). Is There a Patent Troll Problem in the U.K.? *Fordham Property, Media and Entertainment Law Journal*, Volume 24, Number 2, pp. 510 -553.

[793] CREMERS et al. (2017). Patent litigation in Europe, *European Journal of Law and Economics*, Volume 44, Issue 1, pp 1–44.

done both for the EU and the US.

The AIA will bring considerable changes to the US, just like the unitary patents to the EU patent system. Some case law examples were referred in the dissertation on how priority was awarded by the courts in dispute cases under the former US first-to-invent system. In medical biotechnology where social welfare is dependent on applied and cumulative research, future social and economic impacts of these changes in both jurisdictions are yet to be seen. In the EU, some research needs to be done in the aftermath of CJEU decisions in order to evaluate how the future of hESC and CRISPR R&D and businesses will be affected.

To sum up making an efficient trade-off between the dynamic efficiency gains and static efficiency losses according to economic theory of patents leads to the optimal patent system in medical biotechnology. As a result, we see that patent breadth especially in this field is a very important element of achieving this goal. Efficient incentives to innovate and disseminate information, as well as fair patient access to novel treatment and diagnostic methods have been reached in the EU and the US in which several court rulings have narrowed down the scope of the patent or invalidated various claims or invalidated the patent fully. The discussions around patentability and patent-eligibility of biotechnological subject matter have contributed a lot to the improvement of the biotechnological patent systems in the two jurisdictions. The Biotech Directive in the EU brings even further legal clarity for the innovators, however in certain circumstances where a flexible legal system becomes desirable, it becomes difficult to challenge the Directive. Likewise, the relative easiness of granting patents in the US has increased the competitiveness of the US Biotech sector, and made it even appealing for European innovators to commercialize their products / processes in the US. What we also see is spin-off companies with very high market value for the commercialization of products of which the initial R&D is based on funding from public universities / research institutes. Although one can conclude the EU patents can be of better quality and higher legal certainty due to the relatively easier granting stage in the US (be it because of having more applications, and less application per examiner time at the USPTO or other factors such as “patent first and question it later” approach) the US system offers more judicial

scrutiny at the highest level such as the Federal Court and Supreme Court appeals for USPTO decisions and the national enforcement of European patents in EU member states makes it also costly for the innovators. At least until unitary patents and UPC come into force in the EU, some empirical research into social welfare effects of the two systems would yield better qualitative and quantitative answers on the level of innovation, dissemination of information and patients' own sense of well-being around access to novel diagnostic and treatment methods.

6.3 Limitations

The complexity of the EU patent system with its national and supra-national approach has limited the analysis to EU law only and national enforcement mechanisms could not be examined in detail. Due to language barriers national laws and court cases could not be addressed; some examples could be given from the UK and Germany. No significant case study could be identified from Ireland or Malta regarding their national laws or patent office / court cases, though there was no language issue concerning these two countries.

Majority of the publications on patents come from the US, hence the empirical studies mentioned throughout the dissertation rely primarily on US data. The few "European" studies are mainly focusing on the "bigger" member states such as Germany, France, Italy, etc. In a way this is comprehensible since these countries produce the majority of the patents in the EU. Still there are countries like Belgium and the Netherlands, which are smaller in population size, but make a good number of patent applications each year.[794] The studies sometimes give evidence from a cluster of countries such as Benelux, Scandinavia etc. and the whole "European" picture is missing.

[794] In 2019 the Netherlands holds the 8th. place in European patent applications and grants at EPO, and Belgium the 12th. in applications and 15th. in the granted patents. In terms of applications per million of inhabitants the Netherlands holds the 4th. place ahead of Germany and Belgium the 8th. ahead of countries like France, the UK, the US and Italy. See EPO 2019 patent statistics available at https://www.epo.org/about-us/annual-reports-statistics/statistics.html last visit 18.04.2020.

Access to litigation data is very limited even in the US case; hence some analytics could not be developed in comparing disputed parties, and claims, court responses, parties' appeal ratios, invalidations and so forth.

The efficiency of different policy changes could not be measured, since this necessitates further research such as interviews with field professionals, court case analytics, cost benefit analysis of strengthened and weakened patentability requirements in gene patents. Some estimations on possible outcomes of the legal changes are mentioned throughout the dissertation and that the social welfare will increase with more innovation, unambiguous rules, and better access to health care.

6.4 Suggestions for future research

Non-legislative programs such as tax and other financial initiatives can still be deployed to promote innovation in the sector and bring an optimal allocation of resources. Nevertheless, patents are fundamental policy tools both in the EU and the US to create incentives for R&D and scientific progress, as well as for the commercialization of products that deliver new diagnostic and therapeutic methods. In the EU, where member states can be characterized as social welfare states, the ethical considerations around gene patents did not only flourish from the philosophical perspectives on patentability of living beings, but also on growing concerns about blocked innovation and reduced patient access to available products. The US on the other hand has not acknowledged the morality and ordre public concerns as significantly as in the EU, instead has been fast-forward in granting gene patents, funding and setting-up of companies and commercialization of products. However, in recent US Supreme Court decisions such as Myriad and Mayo, we see that the ethical considerations have started to play a role and some harmonization between the two jurisdictions in its early stage may be forthcoming. Balancing of public and private interests is an ambitious task for the different stakeholders of the patent system in both jurisdictions and requires both sufficient compensation of private actors as well as meeting public demands. One challenging situation with medical biotech inventions is the reduced effective term of protection on the market, due to lengthy

approval and authorization procedures of the products by healthcare authorities. Discussions on the opportunities that these patents bring versus the dangers they pose are likely to remain on the agenda for many years to come. In order to arrive at evidence-based conclusions, we need more research and data on the following points:

What is the real cost of patent protection, especially in EU member states regarding enforcement and litigation? What effects have the issuance of European patents had on national patents and vice versa? Because as though the unitary patents are expected to offset filing and enforcement costs in the EU, the innovators and downstream product companies may still choose to file for national patent protection depending on their business strategies.

To what extent have medical biotech patents been effective in fostering R&D by increased disclosure of information and incentives as opposed to monopolizing specific lines of follow-up research?

To what extent do R&D incentives come from patent protection or from other instruments such as trade secrets, prize awards and other regulatory frameworks such as public funding and tax incentives, market access and public or private reimbursement rules so far?

The reason that biopharmaceuticals and other medical applications are heavily priced is their high R&D costs, but also other investment and authorization costs coupled with lengthy delays. What would be the real impact of decreasing the patent term for different sectors and differentiating between diagnostics and treatment applications depending on their effective patent terms? Diagnostics may be utilized as a one-off matter, but the treatment can be applied during the life-time of a patient. The patent term for biopharmaceuticals is quasi-increased in some cases nevertheless by supplementary product certificates. Would shorter patent terms backed with a prize system increase the overall efficiency?

How many gene patents have been invalidated so far after the ground-breaking decisions? In the US all district courts, Federal Circuit, and the Supreme Court data plus the data from USPTO Patent Trial and Appeal Board decisions and the ITC (US

International Trade Commission) data should be examined for the cases citing these important decisions. For the EU, in addition to CJEU and EPO decisions, national court decisions need to be examined in order to see the differences in the enforcement of law. Is the number of patent lawsuits declining as a result of policy changes? Is there a significant difference in litigation and invalidation figures of gene patents compared to other sectors?

Looking at litigation and patent court data we can also analyze whether certain type of rejections is increasing after legislative amendments / court cases.

Interviews can be conducted with field professionals who are involved in the commercialization of the products in order to find out how the changes in the law such as the AIA in the US or a court decision be it a district court / Supreme Court/ CJEU and /or a national court in the EU have affected their patent strategy, and especially their claim-drafting. For professionals who are merely involved with R&D similar interviews can be conducted in order to find our whether legal changes and court decisions result in a brain-drain or R&D policy / funding changes. It would also be interesting to interview patent examiners / offices to analyze the impact of court decisions in the amount of their administrative work, such as having the need to make more substantive analysis, having more or less appeals regarding opposition, revocation, limitation, whether their analysis of and the time they devote to prior art review has changed and so on. Such interviews could also indicate how policy changes, case law and litigation outcomes are changing the patenting circumstances, whether patents are still desired, or we see an increased propensity to patent because for instance competitors are also patenting.

Depending on the answers to above questions, far-reaching or less drastic amendments to the patent policy landscape can be suggested.

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