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BIOTECHNOLOGY: HIGHLIGHTS OF THE SCIENCE AND LAW SHAPING THE INDUSTRY

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I. INTRODUCTION

The term "biotechnology" was coined in 1919 by Karl Ereky,[1] a Hungarian engineer. As generally understood, the term "biotechnology" refers to the use of living organisms or their products to modify human health and/or the human environment typically by using the techniques of gene splicing and recombinant DNA technology. As biotechnology has evolved from a basic research endeavor towards practical and commercial applications, protecting inventions by way of patents has become increasingly important. The primary recipients of biotechnology patents are universities, followed by public companies, non-profit institutions and small and large corporations, both U.S. and foreign-based.[2]

Patent law and the ability to patent new inventions has both affected the evolution of the biotechnology industry and has been a significant driving force behind the funding of biotechnology companies and resulting medical innovations. At present, every new biotechnology invention typically has one or more components that

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1. KÁROLY EREKY, BIOTECHNOLOGIE DER FLEISCH-, FETT- UND MILCHERZEUGUNG IM LANDWIRTSCHAFTLICHEN GROSBETRIEBE: FUR NATURWISSENSCHAFTLICH GEBILDETE LANDWIRTE VERFASST (1919); *see also* M.G. Fari, R. Bud & P.U. Kralovanszky, *Karoly Ereky Urged the Land Reform Based on Biotechnology – Some Realizations in the 20th Century*, *available at* http://www.redbio.org/portal/encuentros/enc_2001/conferencias/C-23%20Pendiente%20en%20conferencias/C-23.pdf (last visited Oct. 20, 2003).

2. CHEM. & ENG'G NEWS, Sept. 1, 1997 (citing *Technology Assessment and Forecast Report: Chemical Classes: 1996*, U.S. Patent & Trademark Office, *available at* http://www.uspto.gov/web/offices/ac/ido/oeip/taf/stchem.pdf [last visited Oct. 20, 2003]).

are the subject of patent claims to another entity. As a result, the biotechnology industry today is driven by the need to establish collaborations in order to develop a given product. This is increasingly significant as the number of biotechnology-derived approved drugs increases with substantial benefit in treatment of a variety of medical disorders.

Over the past 20 years, patent law relative to biotechnology-based inventions has struggled to strike a balance between reasonable patent protection versus the public interest in terms of access to technology, further complicated by moral and ethical issues. This paper endeavors to provide a historical perspective on the impact of patent law on the evolution of the biotechnology industry in the United States.

II. KEY EVENTS IN THE SCIENCE OF BIOTECHNOLOGY

Several key events in the evolution of biotechnology have centered around the discovery and characterization of DNA. First, DNA was identified as the carrier of genetic information in 1938,[3] followed by elucidation of the double helix structure of DNA in 1953.[4] Various discoveries followed which have enabled the manipulation of DNA and other nucleic acids in the laboratory. The discovery of restriction enzymes in 1970[5] led to the first "gene splicing" experiments described by Cohen (at Stanford University) and Boyer (at the University of California, San Francisco [UCSF]), in 1973.[6] This is often considered the birth of genetic engineering or recombinant DNA technology.

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3. William T. Astbury & Florence O. Bell, *X-ray Studies of Thymonucleic Acid*, 141 NATURE 747 (1938) (demonstrating the length between two bases in DNA to be 3.4 Ångström).

4. James D. Watson & Francis H. Crick, *Molecular Structure of Nucleic Acids; a Structure for Deoxyribose Nucleic Acid*, 171 NATURE 737-38 (Apr. 25, 1953) (suggesting a structure for DNA for which they later received the Nobel Prize in 1962, along with Maurice Wilkins).

5. Kathleen Danna & Daniel Nathans, *Specific Cleavage of Simian Virus 40 DNA by Restriction Endonuclease of Hemophilus Influenzae*, 68 PROCEEDINGS OF THE NAT'L ACAD. SCI. U.S.A. 2913 (1971); Stuart Linn & Werner Arber, *Host Specificity of DNA Produced by Escherichia coli, X. In Vitro Restriction of Phage fd Replicative Form*, 59 PROCEEDINGS OF THE NAT'L ACAD. SCI. U.S.A. 1300 (1968) (award of the Nobel Prize in 1978 went to Arber, Nathans, and Hamilton Smith for the discovery of restriction enzymes and their application to problems of molecular genetics).

6. Stanley N. Cohen et al., *Construction of Biologically Functional Bacterial Plasmids in Vitro* 70 PROCEEDINGS OF THE NAT'L ACAD. SCI. U.S.A. 3240 (1973). *See also* U.S. Patent No. 4,740,470 (issued April 26, 1988); U.S. Patent No. 4,468,464 (issued August 28, 1984); U.S. Patent No. 4,237,224 (issued December 2, 1980).

The Cohen/Boyer technology is based on the stable insertion of DNA into a bacterial plasmid followed by incorporation of the DNA into a cell such that the cell produces the protein product of the DNA in large quantity.[7] Recombinant DNA technology and the U.S. patents and publications describing it[8] have not only brought in millions of dollars in licensing fees to Stanford University and UCSF, but have also led to the development of numerous therapeutic products including tissue plasminogen activator, erythropoeitin, insulin, growth hormone and interferon.

Another scientific discovery important to the biotechnology industry was the identification of the enzyme reverse transcriptase.[9] This important enzyme allows a molecule of RNA to be converted into DNA,[10] thereby enabling cloning and further genetic manipulation in the laboratory. In 1975, David Baltimore, Renato Dulbecco and Howard Temin received the Nobel Prize in Physiology or Medicine for this break-through discovery.

Genentech, Inc., the first company founded on the basis of recombinant DNA technology, was incorporated in April, 1976. In 1977, Genentech reported the production of somatostatin, the first genetically engineered protein in bacteria. The gene encoding for human insulin was cloned into *E. coli* by Genentech scientists in 1978, and the technology was licensed to Eli Lilly. In 1982, human insulin became the first recombinant DNA drug approved by the FDA.[11] In 1985, Genentech's work also led to development and marketing of ProTropin® (growth hormone) for treatment of children with growth hormone deficiency. Growth hormone was previously isolated from the pituitary glands of human cadavers. Thus, the development of the recombinant protein provided advantages in the form of less expensive and more efficient production, while eliminating health risks associated with the cadaver-derived drug.

In addition to discoveries occurring at the molecular level, many important inventions occurred at the cellular level as well. One of the most important cellular inventions was hybridoma (cell fusion)

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7. *See, e.g., Id.*; John F. Morrow et al., *Replication and Transcription of Eukaryotic DNA in Escherichia Coli*, 71 PROCEEDINGS OF THE NAT'L ACAD. SCI. U.S.A. 1743 (1974).

8. *Id.*

9. D. Baltimore, *RNA-dependent DNA Polymerase in Virions of RNA Tumour Viruses*, 226 NATURE 1209 (1970); H.M. Temin & S. Mizutani, *RNA-dependent DNA Polymerase in Virions of Rous Sarcoma Virus*, 226 NATURE 1211 (1970).

10. Reverse transcriptase reverses the normal sequence of information flow.

11. Prior to the approval of the recombinant form of insulin, it was obtained from pigs, which had associated immunological and other health risks.

technology which allows the nuclei and cytoplasm from different cells to be combined, as first described in 1975 by Milstein and Koehler.[12] This technology enables the large-scale production of monoclonal antibodies, specialized proteins that recognize a specific target. Twenty years of further experimentation, development and human clinical trials led to the first commercially successful FDA-approved monoclonal antibody, Rituxan®, approved in November, 1997, for the treatment of patients with non-Hodgkin's lymphoma.[13] Soon thereafter, in September, 1998, Herceptin®, a humanized monoclonal antibody for treatment of patients with metastatic breast cancer was also approved.[14] Monoclonal antibody-based treatments for cancer have shown minimal side effects as compared to traditional cancer chemotherapy.

In addition to providing new, more effective treatments for serious diseases, the science of biotechnology has left its mark on other aspects of society, notably in the criminal courtroom. DNA-based evidence (DNA fingerprinting) was first used in a courtroom in 1985, and has resulted in exoneration of wrongly-convicted felons. Moreover, DNA evidence can prove critical to solving past crimes long thought unsolvable.[15] DNA fingerprinting relies on restriction fragment length polymorphisms to characterize subtle differences in DNA to prove that a particular biological sample was derived from a specific individual. Another method of analyzing DNA is based on the polymerase chain reaction which allows for accurate analysis of minute quantities of DNA.[16] DNA fingerprinting is currently

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12. Cesar Milstein, Georges Kohler and Niels Jeme developed monoclonal antibody technology and were awarded the 1984 Nobel Prize in Medicine for their contribution.

13. Rituxan® is a monoclonal antibody for the treatment of patients with relapsed or low-grade B-cell non-Hodgkins lymphoma. Sales of Rituxan® were reported as $363 million for the first quarter of 2003. *See* http://www.gene.com/gene/ir/financials/quarterly-reports/2003/q1 (last visited Oct. 20, 2003).

14. Sales of Herceptin® were reported as $109 million for the first quarter of 2003. *See* http://www.gene.com/gene/ir/financials/quarterly-reports/2003/q1 (last visited Oct. 20, 2003).

15. Jim Herron Zamora and Charlie Goodyear, *DNA Links Man to 1978 Murder in Lafayette*, S.F. CHRON., Oct. 4, 2003, at A15 (describing how evidence derived from traditional sources, such as hair samples, failed to prove a link between the suspect and the victim in 1978, while analysis of DNA in 2003 showed a match between the suspect's genetic profile contained in a DNA database of convicted felons and blood found under the victim's fingernails).

16. This technique is also fundamental to the biotechnology industry. The method was conceived by Kary Mullis while at Cetus, and he subsequently received the Nobel Prize in Chemistry for the discovery. Cetus patented the process, and in the summer of 1991, sold the patent to Hoffman-La Roche, Inc. for $300 million. Cetus successfully defended the patents in a high profile conflict with DuPont in 1990. *See* E.I. Du Pont de Nemours & Co. v. Cetus Corp., 19 U.S.P.Q. 2d 1174 (N.D. Cal. 1990).

accepted by the majority of courts and, together with the polymerase chain reaction, is finding increasing use in the courtroom.[17]

Society is also likely to benefit in as yet unknown ways from the massive Human Genome Project initiated in 1990. The original plan was to map and sequence all of the then estimated 100,000 genes in the human genome by 2005, at an anticipated cost of $3 billion.[18] A "working draft" sequence of the entire human genome was completed simultaneously by both a publicly funded effort and Celera, a large genomics sequencing facility formed as a joint venture between Craig Venter and Perkin Elmer Corp., well ahead of schedule in June of 2000. This draft provided scientists with the location and sequence of an estimated 90% of the genes on every chromosome. Among the many genes identified by the genome project are those for cystic fibrosis, sickle cell disease, Tay-Sachs disease, fragile X syndrome and myotonic dystrophy. The advances in this and related technologies led to the development of DNA chip technology.[19] This technology has provided an increased ability to conduct genetic screening for inherited diseases with associated advantages in medical treatment options. However, this technology has increased concerns with respect to privacy and potential discrimination by insurance companies, employers and others.[20]

It is clear that biotechnology-based scientific discoveries will continue at an increasing rate. Recent Nobel Prize awards suggest the ensuing years will bring improved medicines to the sick and injured. For example, in 2001, the Nobel Prize in Physiology or Medicine was awarded to Leland H. Hartwell, R. Timothy Hunt and Paul M. Nurse

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17. Kamrin T. MacKnight, *The Polymerase Chain Reaction (PCR): The Second Generation of DNA Analysis Methods Takes the Stand*, 9 SANTA CLARA COMPUTER & HIGH TECH. L.J. 287, 305-325 (1993).

18. The U.S. Human Genome Project was started in 1990. It was initially proposed as a 15-year effort to be coordinated by the U.S. Department of Energy (DOE) and the National Institutes of Health with the goals of sequencing and characterizing the entire human genome. A suite of websites funded by DOE provides information on the project. *See* http://www.ornl.gov/TechResources/Human_Genome/home.html (last visited Oct. 20, 2003). *See also* SCIENCE (April 11, 2003) and NATURE (April 24, 2003) (presenting a series of articles on various aspects of the human genome project).

19. In 1996-1997, DNA chip technology was developed on small glass, or silica microchips, which contain large numbers of individual genes that can be analyzed simultaneously. *See, e.g.*, Bernadette Tansey, *Affymetrix Sells New Gene Chip*, S.F. CHRON., Oct. 3, 2003, at B1 (describing the first gene chip developed for the commercial market carrying fragments from all of the 35,000 known human genes. The efforts of rival companies Agilent, Inc. and Applied Biosystems, Inc. are also detailed. The presence of multiple companies in this field presumably indicates optimism about the commercial potential of this technology).

20. Naomi Obinata,, *Genetic Screening and Insurance: Too Valuable an Underwriting Tool to be Banned from the System*, 8 SANTA CLARA COMPUTER & HIGH TECH. L.J. 145 (1992).

for their discoveries of key regulators of the cell cycle. These discoveries may be especially relevant to the development of more effective cancer therapeutics. In 2002, the Prize was awarded to Sydney Brenner, H. Robert Horvitz and John E. Sulston for their discoveries concerning genetic regulation of organ development and programmed cell death. These advances may impact the development of future anti-cancer therapeutics as well as provide alternative treatments for other diseases (such as those of the liver) where transplantation is currently the only therapeutic option. In addition, the number of biotechnology-derived drugs gaining market approval has shown a steady increase in the past few years.[21]

As is evident from the discussion above, basic science provided the foundation for the biotechnology industry and continues to contribute to its growth and success. The industry has produced numerous important and effective human therapeutics. Biotechnology is a viable industry due to incentives and protection afforded by the patent system and related law. This aspect is explored in the next section.

III. BIOTECHNOLOGY AND PATENT LAW

The United States Patent statute provides that utility patents may be granted for the invention of "any new and useful process, machine, manufacture or composition of matter or any new and useful improvement thereof."[22] In *Diamond v. Chakrabarty*,[23] a case relating to bacteria genetically modified to digest oil, thus enabling their use to clean up oil spills, the United States Supreme Court interpreted the scope of patentable subject matter to "include anything under the sun that is made by man."[24]

The practical effect of this broad definition of patentable subject matter is that if the invention claimed in a patent application is new,[25]

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21. *See, e.g.*, Biotechnology Industry Organization's web site *at* http://www.bio.org/er/approveddrugs.asp (last visited Oct. 20, 2003); Food & Drug Administration's web site *at* http://www.fda.gov (last visited Oct. 20, 2003).

22. 35 U.S.C. § 101 (2000) (delineating patentable subject matter stating, "[w]hoever 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 therefor, subject to the conditions and requirements of this title").

23. 447 U.S. 303 (1980).

24. *Id.* at 309.

25. 35 USC § 102 (2000) (describing conditions for patentability, including novelty and loss of right to a patent).

useful[26] and not obvious,[27] and the specification of the patent application meets the written description, best mode and enablement requirements of the patent statutes, the inventor(s) may obtain a patent.[28] A patent gives one the right to exclude others from making, using, offering for sale, or selling an invention in the United States or importing an invention into the United States.[29] A patent does not give one the right to make, use, sell, or import a given invention as the right is one of exclusion.

In the area of biotechnology, patents may be obtained with claims directed to compositions of matter such as DNA sequences in purified or isolated form, vectors, vaccines, new or improved organisms, new chemical compositions, kits, methods of treatment, new methods of making or using a new or known compound and research tools. A recent publication from the Biotechnology Industry Organization stated that "[t]he biotechnology industry is the most research and development intensive and capital-focused industry in the world."[30] The protection afforded by the patent statutes and federal case law interpreting those statutes, together with legislation which provides favorable incentives to patenting biotechnology-based inventions, have contributed to the leading position of the United States in the biotechnology industry worldwide.

An important event in the evolution of the biotechnology industry was enactment of the Bayh-Dole Act[31] which makes licensing of patents based on government-funded research considerably more attractive to private industry. Prior to Bayh-Dole, discoveries made by way of federally-funded research, if not simply dedicated to the public, were owned by the government with only a non-exclusive license available to private industry. As a result, companies lacked the incentive to undertake the financial risk to

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26. 35 U.S.C. § 101 (2000).

27. 35 USC § 103 (2000) (describing what is considered non-obvious subject matter).

28. 35 U.S.C. § 112 (2000) (stating "[t]he specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention").

29. 35 U.S.C. § 154 (2000).

30. *Bayh-Dole and Technology Transfer Before the President's Council on Science and Technology Office of Science and Technology Policy*, BIOTECHNOLOGY INDUS. ORG., Apr. 11, 2002, at 1, *available at* http://www.bio.org/ip/pdf/bd20020509.pdf (last visited Oct. 20, 2003).

31. Bayh-Dole Act of 1980, 35 U.S.C. §§ 200 et. seq., *amended by* Pub. L. No. 98-620 (1984) (with language added to remove term limitations placed on exclusive licenses). *See also* 37 C.F.R. § 401.

develop a product based on such research. The enactment of Bayh-Dole allows any organization that conducts government-funded research the right to patent inventions. The Bayh-Dole Act and amendments thereto[32] have provided the basis for current university technology transfer practices, which often involve co-development and commercialization by academic institutions and private industry.

As discussed in the prior section, the founding scientific developments of biotechnology centered on the cloning and manipulation of nucleic acids in the laboratory. Thus, the ability to patent DNA sequences including gene fragments such as expressed sequence tags, single nucleotide polymorphisms, complementary DNA (cDNA), full gene sequences and products thereof, as well as proteins and methods of use, has transformed the biotechnology industry. Initially, the United States Patent and Trademark Office (USPTO) granted broad patents on biotechnology-based inventions. Reversing that trend, however, the USPTO, together with the courts, have whittled away at the scope of allowable claims in biotechnology patents. In response to public concern regarding patenting of gene sequences, the USPTO issued new utility guidelines in January 2001,[33] adopting two alternative tests for showing utility of a patentable invention: (1) the "specific, substantial, and credible" utility test; and (2) the "well-established utility" test. Claims to DNA sequences must recite a utility which is considered "specific" by being particular to the subject matter claimed.[34] The utility must be "substantial" by defining a real world use, [35] and any asserted utility must be "credible" based on the view of a person with ordinary skill in the art. Alternatively, the claims must satisfy the "well-established utility" test which expanded to include the "specific, substantial, and credible" standard.[36]

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32. *Id.*

33. *Guidelines for Examination of Applications for Compliance with the Utility Requirement*, 66 FED. REGISTER 1092-1099 (Jan. 5, 2001). *See* www.uspto.gov/web/offices/com/sol /notices/utilexmguide.pdf (last visited Oct. 20, 2003). The new Utility Guidelines were clearly put in place in response to the controversy surrounding patenting of gene-related inventions, although they technically apply to all U.S. patent applications.

34. *Id.* (indicating that claims to gene fragments for use as a gene probe or chromosome marker must identify the gene or chromosome target; furthermore, for the utility of a gene to be sufficiently specific as a "diagnostic," the condition that is diagnosed must be recited).

35. Brenner v. Manson, 383 U.S. 519, 536 (1966) (stating "[a] patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion"). Thus, an invention is not patentable if its only use is that it might be an "object of scientific research."

36. *See supra* note 34.

Coincident with the publication of the new Utility Guidelines, the USPTO also issued new Written Description Guidelines.[37] According to these guidelines, patent examiners determine whether the written description requirement of 35 U.S.C. §112 is met by a review of the entire application. Examiners look for support for the claimed invention by studying each element to determine whether there is sufficient written description to inform one of skill in the art that the applicant was in possession of the invention as claimed at the time the application was filed.[38]

Numerous recent decisions of the United States Court of Appeals for the Federal Circuit involve the written description requirement of 35 U.S.C. § 112 as it relates to biotechnology patents. However, the standard for satisfying the written description requirement remains elusive. In *Amgen, Inc. v. Chugai Pharmaceutical Inc.*,[39] the Court applied the rules of chemical patent practice to gene patents and held that, based on the state of the art in 1981, inventive conception of a gene cannot occur until the sequence is known. Soon thereafter, in *Fiers v. Revel*,[40] the Court held that a gene could not be adequately described for patent purposes by reference to a potential method of isolating it, the DNA itself must be described. In *Fiddes v. Baird*,[41] the United States Board for Patent Appeals and Interferences stated that "[o]ne cannot describe what one has not conceived."[42]

In *Regents of the University of California v. Eli Lilly & Co.*,[43] a case that involved DNA sequences, the Federal Circuit opined that if conception of a DNA sequence requires a specific definition (such as by structure, formula, chemical name, or physical properties) then a description also requires that degree of specificity. The Federal Circuit upheld the district court's invalidation of patent claims broadly directed to vertebrate insulin-encoding cDNA when the patent applicant had only disclosed the genetic sequence of rat cDNA. The Court concluded that disclosure of a single species of genetic

37. *Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1, "Written Description" Requirement*, 66 FED. REGISTER 1099 (Jan. 5, 2001).

38. *In re* Wright, 866 F.2d 422, 425 (Fed. Cir. 1989) (holding the specification must be considered as a whole when determining whether the written description requirement is met); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64 (Fed. Cir. 1991) (holding the purpose of the written description requirement is to ensure that the specification conveys to those skilled in the art that the applicants possessed the claimed subject matter as of the filing date sought).

39. 927 F.2d 1200 (Fed. Cir. 1991).

40. 984 F.2d 1164 (Fed. Cir. 1993).

41. 30 U.S.P.Q.2d 1481 (B.P.A.I. 1993).

42. *Id.* at 1482-83.

43. 119 F.3d 1559 (Fed. Cir. 1997).

material does not provide an adequate written description to support patent claims to a genus of genetic material. Description of a genus of cDNAs may only be achieved by recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or by a recitation of structural features common to the members of the genus. Thus, a definition by function alone does not suffice to define the genus.[44]

More recently, on April 2, 2002, the Federal Circuit decided *Enzo Biochem, Inc. v. Gen-Probe Inc.* (Enzo I).[45] The Court affirmed a decision by the District Court granting a motion for summary judgment by Gen-Probe that claims of Enzo's patent were invalid for failure to satisfy the written description requirement of 35 U.S.C. § 112, ¶ 1.[46] In its decision, the Federal Circuit continued the trend towards increasing the stringency of the written description requirement for biotechnology inventions.

Then, in a surprising reversal, the Federal Circuit on July 15, 2002 granted Enzo's request for rehearing and remanded the case to the district court for resolution (Enzo II).[47] The Federal Circuit in Enzo II held that deposit of biological materials in a public depository, which makes its contents accessible to the public when not otherwise available in written form, constitutes an adequate description sufficient to meet the written description requirement of 35 U.S.C. § 112, ¶ 1.[48] Also significant in the Enzo II decision is text stating approval of the USPTO guidelines regarding the written description[49] and further text (consistent with *Lilly*)[50] stating that a description of the structure itself is still a necessary condition of § 112, ¶ 1.[51] In *Amgen Inc. v. Hoechst Marion Roussel Inc.*,[52] the Federal Circuit concluded that disclosure of how to practice the invention in two species out of many did enable one to practice the

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44. *Id.* at 1568-69.

45. 285 F.3d 1013 (Fed. Cir. 2002).

46. *Id.* at 1019.

47. Enzo Biochem, Inc. v. Gen-Probe Inc., 296 F.3d 1316 (Fed. Cir. 2002).

48. *Id.* at 1325.

49. *Id.* at 1324 (stating that "[i]n its Guidelines, the PTO has determined that the written description requirement can be met by 'show[ing] that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics . . . *i.e.*, complete or partial structure, other physical and/or chemical properties, *functional characteristics when coupled with a known or disclosed correlation between function and structure*, or some combination of such characteristics'" (emphasis in original).

50. 119 F.3d at 1559.

51. 296 F.3d at 1327-28.

52. 314 F.3d 1313 (Fed. Cir. 2003).

invention. References to *Lilly* indicate that the application of the structural test for written description set forth in *Lilly* remains in question.

In addition to changes in U.S. patent law, several international treaties have mandated modifications to U.S. patent practice as well. These treaties include the North American Free Trade Agreement (NAFTA),[53] the General Agreement on Tariffs and Trade (GATT), and, in particular, the Trade Related Aspects of Intellectual Property Rights (TRIPS) agreement.[54] Based on NAFTA, the patent statutes were amended to permit reliance on research activities in a NAFTA country (limited to Canada and Mexico) to prove a date of invention for the purpose of obtaining a patent.[55] The GATT-TRIPS Agreement (GATT) expanded the ability to establish a date of invention in a large number of countries other than the U.S., Canada and Mexico for the purpose of obtaining a patent. GATT also created the provisional application,[56] and modified the rules with respect to patent term.[57]

For applications filed prior to GATT, the term of protection for a U.S. patent is 17 years from the date of issue. Post-GATT, patents have a term of protection that begins on the date of the grant and ends on a date 20 years after the earliest filing date of the application.[58] Another post-GATT change is that the 20-year patent term may be extended for delays in the issuance of a patent caused by a patent

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53. NAFTA was implemented on Dec. 8, 1993. North American Free Trade, Pub. L. No. 103-182, 107 Stat. 2061 (approved and entered into force at 19 U.S.C. § 3311 [1993]).

54. GATT/TRIPS (also known as the "WTO Agreement") was implemented on Dec. 8, 1994. Uruguay Round Trade Agreements, Pub. L. No. 103-465, 108 Stat. 4814 (approved and entered into force at 19 U.S.C. § 3511 [1994]).

55. Prior to NAFTA, a patent applicant could not establish a date of invention by reference to activity in a foreign country except as provided in 35 U.S.C. §§ 119, 365 (2000). Thus, to establish a date of invention before their U.S. filing date, applicants who made their invention outside the United States were only able to rely on the filing date of a foreign priority application or the filing date of an international application filed under the Patent Cooperation Treaty (PCT). The date of invention is important for interference proceedings under 35 U.S.C. § 135, and to overcome a prior art rejection (citing a patent or publication) by filing an affidavit or declaration under 37 C.F.R. § 1.131 (2002).

56. A provisional application is a simple, inexpensive patent application that does not require claims and is not examined except for minimal formal requirements.

57. Most provisions of the GATT implementing legislation went into effect on January 1, 1996. 19 U.S.C. § 3511 (2000). However, provisions relating to patent term and provisional applications took effect on June 8, 1995. 35 U.S.C. §§ 119, 365 (2000).

58. 35 U.S.C. § 154(a)(2). For an original application filed under 35 U.S.C. § 111(a), the term of protection ends 20 years from the filing date of the original application. For a continuing application filed under § 111(a), the term of protection ends 20 years from the filing of the first application to which reference is made under §§ 120, 121, 365(c).

interference, a secrecy order, and/or a successful appeal of the patent examiner's refusal to grant the patent.[59]

Another significant legal decision, concerning the "experimental use" doctrine, was made in 2002. The Federal Circuit, in *Madey v. Duke University*,[60] essentially eliminated any exemption to patent infringement based on "experimental use." The case arose when Madey, employed as a laboratory director at Duke, sued Duke for infringement of patents he had obtained prior to employment by Duke. Duke defended on the grounds that, as a non-profit academic institution, its activities were exempt from patent infringement as long as they were solely for research purposes. The Federal Circuit disagreed and stated that neither commercial gain nor the profit or non-profit status of the defendant was dispositive. The Court also stated that so long as the act was in furtherance of the alleged infringer's legitimate business and not "solely for amusement, to satisfy idle curiosity, or for strictly philosophical inquiry,"[61] the act does not qualify for the experimental use defense.[62] The Court in *Madey* made reference to the decision in *Roche Products Inc. v. Bolar Pharmaceutical Co.*[63] which held the experimental use doctrine did not apply to FDA-required pre-marketing testing by a generic drug manufacturer and that such activities constituted patent infringement.

Following the 1984 *Roche v. Bolar* decision, Congress responded quickly to overrule the case by enacting the Drug Price Competition and Patent Term Restoration Act of 1984, also known as the Hatch-Waxman Act (enacted as 35 U.S.C. § 271(e)(1)). This statute states that certain activities which would otherwise constitute patent infringement are exempted from infringement liability so long as the conditions specified in the statute are met. Generally, use of a patented product or process is an act of infringement under 35 U.S.C. § 271(a).[64] However, 35 U.S.C. § 271(e)(1), also known as the "safe harbor" clause, provides that "[i]t shall not be an act of infringement to make, use, offer to sell, or sell within the United States or import into the United States a patented invention . . . solely for uses reasonably related to the development and submission of information

59. 35 U.S.C. § 154(b) (2000).

60. 307 F.3d 1351 (Fed. Cir. 2002).

61. *Id.* at 1362.

62. *Id.* at 1362-63.

63. 221 U.S.P.Q. 937 (Fed. Cir. 1984).

64. 35 U.S.C. § 271(a) (2000) (stating that "[w]hoever without authority makes, uses, offers to sell, or sells any patented invention, within the United States or imports into the United States any patented invention during the term of the patent therefor, infringes the patent").

under a Federal law which regulates the manufacture, use, or sale of drugs or veterinary biological products."[65] The legislative history of 35 U.S.C. § 271(e)(1) shows that Congress intended the exemption to allow generic drug manufacturers to develop data in preparation for commercialization of a generic drug after expiration of patents to an approved brand name drug.[66]

Until recently, courts had liberally interpreted 35 U.S.C. § 271(e)(1) to remove potential liability for a number of uses of a patented product or process. A series of decisions have interpreted § 271(e)(1). *Scripps Clinic & Research Foundation v. Genentech, Inc.*[67] states the exemption applies if the accused infringer can demonstrate that it made and used the patented invention solely for the purpose of meeting FDA reporting requirements.[68] *Intermedics, Inc. v. Venitrex Inc.*[69] held that some commercial activity does not eliminate the exemption.[70] Cases have also been decided that extend the protection afforded by the "safe harbor" to medical devices[71] and to situations where the patented invention was a process used to obtain a product not previously submitted for FDA approval.[72]

The courts' interpretation of 35 U.S.C. § 271(e)(1) took a new turn with the recent Federal Circuit decision in *Integra LifeSciences I, Ltd. v. Merck KgaA*.[73] Five patents issued to Integra with claims to a short tri-peptide having the sequence arginine-glycine-aspartic acid ("RGD").[74] Merck funded research at Scripps that led to identification of cyclic RGD peptides as drug candidates.[75] Integra offered Merck a license and Merck refused, arguing that the safe harbor afforded by 35 U.S.C. § 271(e)(1) applied.[76] The Federal

65. 35 U.S.C. § 271(e)(1) (2000).

66. Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

67. 666 F. Supp. 1379 (N.D. Cal. 1987), *aff'd in part, rev'd in part, vacated in part & remanded*, 927 F.2d 1565 (Fed. Cir. 1991).

68. 666 F. Supp. at 1396-97.

69. 775 F. Supp. 1269 (N.D. Cal. 1991).

70. *Id.* at 1273, 1278.

71. *See* Eli Lilly & Co. v. Medtronic, Inc., 496 U.S. 661 (1990); Telectronics Pacing Sys., Inc. v. Ventritex, Inc., 982 F.2d 1520 (Fed. Cir. 1992).

72. NeoRX Corp. v. Immunomedics, Inc., 877 F. Supp. 202 (D.N.J. 1994).

73. 331 F.3d 860 (Fed. Cir. 2003) (affirming the district court's finding that the infringing activity did not fall within the safe harbor provision, reversing the order granting the royalty award and remanding for recalculation of damages).

74. *Id.* at 862.

75. *Id.* at 863.

76. *Id.*

Circuit affirmed a district court's determination that Merck's infringing activities were not protected by the safe harbor because they were not "solely for uses reasonably related" to provision of information to the FDA under 35 U.S.C. § 271(e)(1).[77] In the wake of *Integra*, it is not clear what activities will be considered "solely for uses reasonably related" to FDA approval or what damages may be associated with a finding of infringement.

IV. CONCLUSION

Since 1982, when recombinant human insulin became the first biotechnology drug to gain market approval, many other biotechnology-derived drugs have become standard therapies. The fully capitalized cost to develop a new drug, including studies conducted after receiving regulatory approval, average $897 million.[78] Clearly, the biotechnology industry will continue to be a major driving force in the development of new and improved medical treatments. The ability to obtain patent protection on such inventions is essential to continued research and development efforts that will lead to the next generation of exciting and innovative therapies. While continued changes in patent law with respect to biotechnology may be fodder for allocations of injustice and long hours of discussion on the part of industry representatives and patent practitioners, the law must adjust to keep up with the rapid developments in biotechnology.

77. *Id.* at 860.

78. *Post-approval R&D Raises Total Drug Development Costs to $897 Million*, TUFTS CENTER FOR THE STUDY OF DRUG DEVELOPMENT (May/June 2003) *available at* http://csdd.tufts.edu/InfoServices/ImpactReportPDFs/ImpactReportSummaryMayJune2003.pdf (last visited Oct. 20, 2003).

Kamrin T. MacKnight, *The Polymerase Chain Reaction (PCR): The Second Generation of DNA Analysis Methods Takes the Stand*

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This Article describes to the non-scientist attorney the technologies used in DNA testing, potential uses for PCR, and proposed regulations. It also addresses some of the criticisms of DNA testing and the exculpatory potential DNA analysis provides.

Examplary citations to the original article include:

Hoffman-LaRoche v. Promega, 323 F.3d 1354 (Fed. Cir. 2003).

Hughes v. State, 735 So. 2d 238 (Miss. 1999).

State v. Tankersley, 956 P.2d 486 (Ariz. 1998).

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State v. Hill, 895 P.2d 1238 (Kan. 1995).

State v. Russell, 882 P.2d 747 (Wash. 1994).