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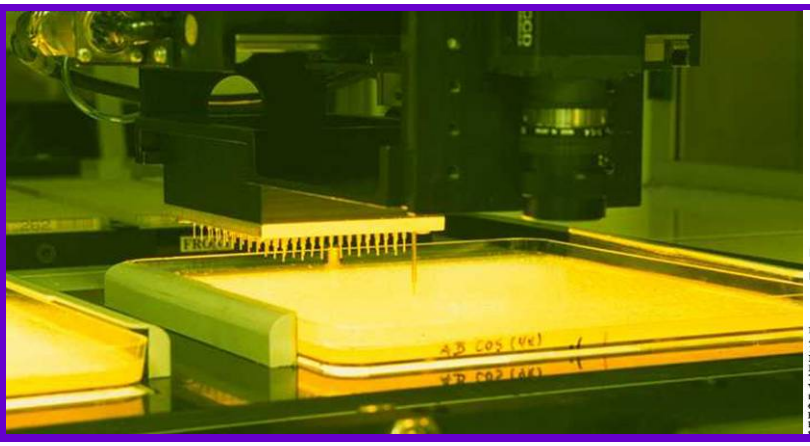
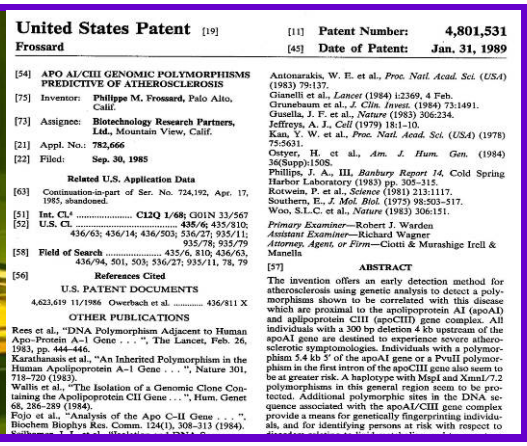
Patent Prosecution Strategies for Biotechnological Inventions

Wenrong Helen Huang, Jenny J. Yeh and Dennis Fernandez

Patent Prosecution in Pharmacogenomics

Wenrong Helen Huang, Nusrat Khaleeli and Dennis Fernandez





United States Patent [19]
Frossard

[11] **Patent Number: 4,801,531**
[45] **Date of Patent: Jan. 31, 1989**

[54] **APO AI/CIII GENOMIC POLYMORPHISMS PREDICTIVE OF ATHEROSCLEROSIS**

[75] Inventor: **Philippe M. Frossard**, Palo Alto, Calif.

[73] Assignee: **Biotechnology Research Partners, Ltd.**, Mountain View, Calif.

[21] Appl. No.: **782,666**

[22] Filed: **Sep. 30, 1985**

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[63] Continuation-in-part of Ser. No. 724,192, Apr. 17, 1985, abandoned.

[51] **Int. Cl.**[4] **C12Q 1/68**; G01N 33/567

[52] **U.S. Cl.** **435/6**; 435/810; 436/63; 436/14; 436/503; 536/27; 935/11; 935/78; 935/79

[58] **Field of Search** 435/6, 810; 436/63, 436/94, 501, 503; 536/27; 935/11, 78, 79

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[57] **ABSTRACT**

The invention offers an early detection method for atherosclerosis using genetic analysis to detect a polymorphisms shown to be correlated with this disease which are proximal to the apolipoprotein AI (apoAI) and apliporotein CIII (apoCIII) gene complex. All individuals with a 300 bp deletion 4 kb upstream of the apoAI gene are destined to experience severe atherosclerotic symptomologies. Individuals with a polymorphism 5.4 kb 5' of the apoAI gene or a PvuII polymorphism in the first intron of the apoCIII gene also seem to be at greater risk. A haplotype with MspI and XmnI/7.2 polymorphisms in this general region seem to be protected. Additional polymorphic sites in the DNA sequence associated with the apoAI/CIII gene complex provide a means for genetically fingerprinting individuals, and for identifying persons at risk with respect to

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Right image: First US patent issued with the word "genomic" in its title.

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[1] Huang WH, JJ Yeh and D Fernandez. 2005. Patent Prosecution Strategies for Biotechnological Inventions. *IP Strategy Today* No 14-2005. pp. 1-10.

Executive Summary

This article describes patent prosecution strategies for new biotechnological inventions. The first part of the article discusses general strategies for patent prosecutors, including several prosecution considerations and methods for increasing patent prosecution speed. It is important for a company to build a patent portfolio based on its business objective through assessing and analyzing its own intellectual property inventory as well as acquiring and licensing patents. Conducting due diligence in patent prosecution and extensive search for potential infringement, employing a blocking strategy and licensing out non-utilized patents are several ways for a company to maximize the potential of its intellectual property portfolio.

The second part of the article presents patent prosecution challenges in genomics and bioinformatics-related patents and provides solutions to these challenges. Prosecuting patents for computer protocols or software related to bioinformatics technologies is specially challenging because of its interdisciplinary nature. Providing effective down-stream protection for potential therapeutic products resulting from the patented bioinformatics technologies is another challenge in the prosecution of such patents. Genomics patent applications face special problems in overcoming possible USPTO rejections based on the utility and written description requirements. The utility requirement for a gene sequence invention can be met by performing homology studies or functional assays. Rejection based on inadequate written description may be avoided by drafting narrower and more specific claims.

The last part of the article discusses how ethical and public policy issues play a role in the patentability of biotechnological inventions. Stem cell and cloning related patents raise special ethical and public policy concerns, which may be grounds for the USPTO to deny patenting. However, patent law should not be used as a means to regulate ethics and morality.

1. Introduction

In James Watson and Francis Crick's landmark publication in *Nature*, they revealed "the secret of life" by proposing a structure of deoxyribose nucleic acid (DNA). The structure has "novel features which are of considerable biological interest."[2] This discovery generated more than just considerable biological interest. Watson and Crick brought biological research to a new era and paved the road for modern biotechnology. Since the elucidation of the DNA double helix structure in 1953, the biotechnology industry has made significant scientific growth, resulting in many useful new products and methodologies in different fields. The latest significant contribution of the biotechnology industry is the decoding of human DNA sequences for the Human Genome Project. Patenting these inventions, therefore, plays a critical role in fostering the advancement of biotechnological research and commercial viability of the biotechnology industry.

The United States grants patents to "whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement," in addition to meeting the disclosure, novelty, and non-obviousness requirements.[3] Generally speaking, biotechnology patents are different from other patents because they require highly specific facts to meet these statutory requirements.[4] Thus, to successfully and efficiently patent emerging biotechnological inventions (see Table 1), the general strategies of:

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[2] James D Watson & Francis H. C. Crick, *Molecular Structure of Nucleic Acids*, Nature, Apr.2, 1953, at 737.

[2] 35 U.S.C. §§ 101-103 (2000).

[4] Dennis Fernandez and Mircea Achiriloaie, *Keeping-Up Intellectual Property Lifelines for Life Science Ventures*, 3 J. High Tech. L. 29, 30-31 (2004).

- carefully balancing patent prosecution considerations and
- speeding up the process of patent prosecution should be employed.

Further, specific patenting challenges unique to different areas of biotechnology such as genomics and bioinformatics patents, as well as ethical and public policy issues, should be taken into account.

Table 1: Some Protectable Applications in Biotechnology

Tools	
	Software
	Devices and methods
Health Care Products	
	Diagnostics
	Drugs
Composition	
	Nucleic acid sequence
	Protein and small molecules

2. General Patent Strategies

2.1 Patent Prosecution Considerations

2.1.1 Assessment and Analysis of a Company's Intellectual Property Inventory and Its Business Objective

For many biotechnology companies, prior to filing a patent application for an invention, the initial strategy is to carefully assess and evaluate the current state of the intellectual property owned or licensed by the company.[5] The company determines whether its goal is to expand new products or protect existing ones, based on the market demand. The next step requires an identification of a company's core and non-core technology. Depending on whether an invention provides short-term or long-term value, whether this invention is in the path of emerging technology, and the likelihood that competitors will wish to practice this same invention, patents can be separated into "utilize," "likely not to utilize," or "will not utilize." Based on these classifications, a sensible business plan for these technologies could then be developed.[6]

2.1.2 Building a Patent Portfolio Quickly by Acquiring or Licensing Patents or Applications from Universities or Defunct Companies

Many biotechnology companies build or strengthen their patent portfolios by negotiating with universities for exclusive or non-exclusive licenses of their inventions or by acquiring patents from defunct

[5] John P. Isacson, *Maximizing Profits Through Intelligent Planning and Implementation*, 18 Nature Biotechnology 565, 565 (2000).

[6] *Id.*

companies. Until the Bayh-Dole Act in 1980,[7] "the federal government sponsored basic research and encouraged its widespread publication in the public domain without regard for potential commercial applications."[8] After the Act, universities were able to transfer their patented technology to businesses in the industry. Both universities and companies gain from this arrangement. On one hand, universities benefit from the revenue generated from the licensed technology, as exemplified in Cohen-Boyer's recombinant DNA patent.[9] On the other hand, businesses can become more innovative and competitive than their competitors after the transfer of the technology to the industry.[10] Many small or start-up biotechnology firms often rely on exclusive licensing rights to ensure access to high-risk capital and to promote investment in downstream development.[11]

A license as such is an agreement for the university not to sue the company for patent infringement. Therefore, the licensing agreement terms play a critical role for both the licensees and the licensors in determining the activities that are allowed under the license.[12] While industry generally aims for profits and emphasizes protecting its patent rights, academia's primary focus is on innovative research and the free exchange of ideas, instead of extracting profits from their inventions. Thus, when negotiating the licensing agreement, licensees can avoid these potential conflicts by carefully assessing the financial and scientific issues and the culture gap between academia and industry.[13]

2.1.3 Due Diligence on Patent Applications and Extensive Search for Potential Infringement

Conducting due diligence on patent applications and extensively searching for potential infringement on issued patents are also important patent prosecution considerations. First, diligent organization of a patent portfolio and vigilant surveillance of competitors' activity or other third parties' potential patent infringement not only provides protection to an invention, but also minimizes the hazard of potential litigation.[14] Second, conducting an extensive search for potential infringement on issued patents and published patent applications could help patent applicants to decide whether to pursue patents for their inventions. A biotechnology patent is time-consuming and expensive. It requires an average of 3 years to complete and costs upwards of $15,000. Thus, prior to committing a vast amount of resources on developing a new product, potential infringement of all issued patents should be ruled out. [15]

Record-keeping of all invention records should also be strictly followed. It is generally recommended to maintain an inventor notebook with conception dates and concept diagrams that are signed by two witnesses. Further, all inventor notebooks, invention disclosure forms (IDF), patent proposals, and literature should disclose inventions as confidential. Information about all inventors should also be properly maintained.[16] A co-inventor not only has a right to enter into a licensing agreement independently, but can also impede other co-inventors' ability to sue infringers as "[a]n action of infringement must join all

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7 David C. Hoffman, "*A Modest Proposal: Toward Improved Access to Biotechnology Research tools by Implementing a Broad Experimental Use Exception*, 89 Cornell L. Rev. 993, 997-1000 (2004).

8 Rebecca S. Eisenberg, *Public Research and Private Development: Patents and Technology Transfer in Government-Sponsored Research*, 82 Va. L. Rev. 1663, 1689-95 (1996).

9 U.S. Patent No. 4237224

10 Behfar Bastani, Evelyn Mintarno and Dennis Fernandez, *Technology Transfer: From the Lab to the Shelf*, Stanford BioMedicine Quarterly, Fall 2003 at 23.

11 Michelle R. Henry et al., *DNA Patenting and Licensing*, Science, Aug. 23, 2002, at 1279.

12 *See* Bastani, *supra* note 9, at 23.

13 *Id.*

14 Leslie G. Restaino, Steven E. Halpern and Eric L. Tang, Patenting DNA-Related Inventions in the European Union, United States and Japan: A Trilateral Approach or a Study in Contrast, 2 UCLA J.L. & Tech. 1, 17 (2003).

15 *Id.*

16 *Id.*

co-owners as plaintiff."[17] For example, in the case of *Ethicon v. US Surgical*,[18] the plaintiff Ethicon failed to obtain consent from an omitted inventor to join its patent infringement lawsuit. This consequently resulted in the dismissal of the entire case. ,

2.1.4 Blocking Strategy

In addition to the defensive strategy of protecting a company's pre-existing core technology, offensive strategies of patenting claims covering future competitors from novel ideas of products, methods or improvements should be used. An intelligent offensive patent strategy can block future competition, secure emerging standards, increase company's valuation, collect licensing royalties, and also forecast future trends of a certain product. For example, although its business models have since diverged, the genomics company Incyte acquired a substantial patent portfolio from patents on mostly novel full-length genes and a few partial sequences obtained through its computer system. This strategy discourages its competitors from taking similar inventions to market and allows the company to collect potential licensing fees in the future.[19]

2.1.5 Deriving and Maximizing Value from Non-utilized and Utilized Patents

For many biotechnology companies, the general objectives of patenting a new invention are to discourage competitors, to seek technological advantage, to tie up customers, to make the transition from data collectors to product developers, to look appealing to investors, and to derive financial profits.[20] Thus, a patentee may elect not to license patented core-technological inventions to preserve its exclusive position in the market.[21] Further, to maximize the values of all of the patents in the portfolio, the patentee may consider: (1) licensing out patents that are unlikely to be utilized or will not be utilized because the patents do not meet the company's business objective; (2) infringement litigation against competitors to obtain monetary damages and exclusive positions in the marketplace; or (3) cross-licensing with competitors for necessary technology to gain market access.[22]

2.2 Speeding Up the Process of Patent Prosecution

2.2.1 Submitting a Provisional Application

If there is a lack of time or monetary resources for a complete non-provisional filing, one strategic option to increase the speed of patenting prosecution is to submit a provisional application under 35 U.S.C. § 111(b). This strategy establishes an effective early filing date under 35 U.S.C. § 111(a). It allows filing without a formal patent claim, oath or declaration, or any information disclosure (prior art) statement. The term "Patent Pending" can then be applied to company brochures and products. The patent applicant has a one-year limit to convert the provisional application into a nonprovisional application which can claim the benefit of the earlier filing date of the provisional application.[23]

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[17] *Ethicon, Inc. v. US Surgical Corp, Inc.*, 135 F.3d 1456, 1467-68 (Fed. Cir. 1998).

[18] *Id*.

[19] Reid G. Adler, *Corporate Patent Strategies in the Genomics Industry, Presentation to Yale Law & Technology Society*, 3 Yale Symp. L. & Tech. 1, 9 (2000).

[20] *Id*. at 9.

[21] Jerry R. Selinger, Patent Litigation Strategies Handbook, 4 (Barry L. Grossman & Gary M. Hoffman ed., BNA Books 2000) (2000).

[22] *See* Isacson, *supra* note 4, at 566.

[23] 35 U.S.C. § 111 (2000).

The major concern over filing an early provisional patent application is the enablement risk under 35 U.S.C. § 112. The enablement and sufficiency of disclosure and any drawing(s) in the provisional application must adequately support the subject matter claimed in the later filed nonprovisional application in order to benefit from the provisional application's filing date. Thus, a detailed description of a given biotechnological invention should be disclosed to avoid potential § 112 rejections in the future.

2.2.2 Submitting a Petition to Make Special

Another strategy to increase patent protection speed is to claim high priority within the U.S. Patent and Trademark Office (USPTO).[24] An application may be made to advance out of turn for examination or for further action if it is made special on the grounds of prospective manufacture, actual infringement, applicant's health and age, environmental quality, recombinant DNA-related invention, certain new applications, HIV/AIDS and cancer-related inventions, counter terrorism-related inventions, and applications relating to biotechnology filed by applicants who are small entities. Earlier examination of a patent application could result in earlier granting of a patent. This in turn could achieve the objectives of patenting a new biotechnology invention by reducing competitors, gaining technological advantage, tying up customers, and deriving values from the inventions sooner.

2.2.3 Not Making Broad Claims

The USPTO requires a limited claim scope for biotechnological patents and usually restricts support for claims to working examples in the specification. As a result, broad patent claims are likely to be rejected if insufficient working examples are provided.[25] The Federal Circuit Court in *Amgen v. Chugai* held that § 112 requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art.[26] Thus, claiming all possible genetic sequences that have a particular protein-like activity by merely making a protein's generic DNA sequence is insufficient and invalid. The court in *University of California v. Eli Lilly* further ruled that a description of rat insulin cDNA is not a description of the broad classes of vertebrate or mammalian insulin cDNA. A written description of an invention involving a chemical genus, like a description of a chemical species, requires a precise definition of the claimed subject matter sufficient to distinguish it from other materials.[27] Accordingly, narrow and specific claims are more likely to increase the speed of patent issuance. Broader claims may then be sought in a continuing application(s).

2.2.4 Responding to the USPTO Office Actions Quickly and Maintaining Efficient Communication with the Examiner

Responding to all of the USPTO actions in a timely fashion and maintaining an efficient communication between the examiner and the patent prosecutors should also increase the speed of patent prosecution**.** Scheduling an interview to talk about the claim rejections with the examiner may aid in a better understanding of the reasons and concerns for rejection of an invention. In this way, the patent prosecutors may target the issues in a surgically precise manner.

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[24] Manual of Patent Examining Procedure 708.02 (8th ed. 2001).

[25] Marianne Fuierer, *Patenting Pharmaceutical Compositions, Their Manufacture and Therapeutic Use: Strategic Issues,* IPTL, Spring 2002, at 1.

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

[27] *University of California v. Eli Lilly*, 119 F.3d 1559, 1568 (Fed. Cir. 1997).

3. Specific Patent Prosecution Challenges in Unique Areas of Biotechnology

3.1 Bioinformatics-related Software Patent Prosecution

Bioinformatics is the use of computational tools and databases in relation to genomic, proteomic medical and health data.[28] Its rapid growth and potential payoffs, such as a market of over $40 billion by 2005,[29] motivated many bioinformatics companies to seek patent protection to capitalize on their inventions. To respond to this fast-growing demand for patent applications, the USPTO created a special examination unit, Art Unit 1631, in December 1999, to review bioinformatics-related patent applications. By November 2001, 1776 patents had already been issued by the USPTO for bioinformatics-related inventions.[30]

The majority of bioinformatics inventions involve applications of computer-implemented protocols or software in collecting, storing, processing, or analyzing biological data. The patentability and protectability of software inventions have been an intensely debated topic for decades. According to the U.S. Court of Appeals for the Federal Circuit (CAFC) in *In re Warmerdam*[31] and *In re Lowry*,[32] claims to data structures *per se* do not constitute patentable subject matter pursuant to 35 U.S.C. § 101. However, a machine (such as computer) or a computer-readable medium (such as a CD-ROM or floppy disk) encoded with a data structure is patentable.[33] These rulings are consistent with the USPTO's guideline for patentable subject matter in computer-related inventions: "when functional descriptive material is recorded on some computer-readable medium it becomes structurally and functionally interrelated to the medium and will be statutory in most cases since use of technology permits the function of the descriptive material to be realized."[34] Thus, a machine or manufacture, such as software, having a practical application in the technological arts is patentable.[35] Technical application could be identification of a drug target or prediction of a protein structure. For example, Affymetrix developed a software with special technical application that enables researchers to perform gene expression, single nucleotide polymorphism (SNP) mapping and resequencing analysis with integrated data management, and scalable client-server configuration.[36]

Patent prosecution in bioinformatics presents a certain degree of difficulty. First, the most valuable aspect of the bioinformatics industry is based on the value of the therapeutic products, instead of the tools (software) used to identify these products. Many bioinformatics companies employed the tactic of "reaching through" claims by establishing mechanisms to claim profitable bioinformatics-derived therapeutic products rather than bioinformatics tool used for their identification. However, because these patents are mostly related to screening methods that are usually upstream from the therapeutic prod-

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[28] Alex Wilson, *Patents in the Bioinformatics Field: Releasing the Gene Genie*, Bio-Science Law Review, October 2002, *available at* http://pharmalicensing.com/features/disp/1034368662_3da73696212e0?1034858001 (last visited on Jun. 24, 2004).

[29] Steven J. Hultquist, Robert Harrison, and Yongzhi Yang, *Patenting Bioinformatic Inventions: Emerging Trends in the United States*, 20 Nature Biotechnology 743, 743 (2002).

[30] *Id.*

[31] *In re Warmerdam*, 33 F. 3d 1354, 1360-61 (Fed. Cir. 1994).

[32] *In re Lowry*, 32 F.3d 1579, 1583-84 (Fed. Cir. 1994).

[33] *See* Hultquist, *supra* note 21, at 743.

[34] *See* Manual of Patent Examining Procedure 2106 (8th ed. 2001).

[35] *Id*. (citing *In re Alappat*, 33 F.3d. 1526, 1544 (Fed. Cir. 1994); *State Street Bank & Trust Co.* v. *Signature Financial Group, Inc.,* 149 F.3d 1368, 1373 (Fed. Cir. 1998)).

[36] *See* Software, at http://www.affymetrix.com/products/software/index.affx (last visited July 4, 2004).

uct,[37] drafting the claims purely based on the tools sometimes may be insufficient. One solution is to limit the scope of the claim. Alternatively, if it can be shown that the claims are enabling to one of ordinary skill in the art, rejection for insufficiency of this type of claim can also be overcome.

Another problem is the variety of business models being used in the industry. Some bioinformatics market participants may license access to databases, while others may sell software, systems, or testing equipment or perform tests for clients. Since effective patent claims cover what is sold, patent prosecutors should anticipate such diverse business models and aim to block future competitors when drafting claims.[38]

The interdisciplinary nature of bioinformatics-related patents also present challenges both to the USPTO and patent prosecutors. The scarcity of judicial precedents and the difficulty of finding a patent drafter or examiner who is well versed in information technology, biology, and patent law increases the difficulty and effort of obtaining a bioinformatics patent. Furthermore, since the bioinformatics field develops quickly, the success of drafting patent applications should be based on a vision of the future progress of bioinformatics, in addition to knowledge of patent law and business.

3.2 Genomics Patent Prosecution

Certain challenges exist for prosecuting genomics-related inventions to meet the utility requirement. According to the USPTO's new utility guidelines,[39] inventions must have well-established utility, such that a person of ordinary skill in the art would immediately appreciate why the invention is useful based on the characteristics of the invention, and the utility is credible, substantial, and specific. For genomics-related patents, the utility of a specific DNA sequence is often unclear until further characterization of a particular DNA sequence's function and activity. Merely claiming a sequence of DNA fragment without any indication of a function or specific asserted utility is not patentable.[40] For example, Incyte and similar genomics companies filed thousands of provisional patent applications with the USPTO for Expressed Sequence Tags (ESTs), which have unknown functions at the present. Opponents of this tactic argue that patent rights should be reserved for uncovering the true biological function of a gene, not merely sequences of the gene fragments.[41]

To strategically overcome the utility requirement, one tactic is to perform homology studies on the gene sequence to be patented. Homology refers to the establishment of a relationship or common thread between the novel gene sequence to be patented and another gene that has been discovered, but not patented. The USPTO may allow the claims if an expert in the field would agree that the common thread is strong. However, since our knowledge of genes is constantly improving, previously granted patents based on this homology reference may become invalidated in the future.[42]

Another tactic to meet the utility requirement is to conduct several functional assays. The inventor can submit a declaration on sequence behavior asserting that the sequence is more likely than not to have some function. The invention is still protected even if a new usage is discovered for the original DNA claims. For example, the active compound of Viagra was originally patented as a heart remedy.[43]

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[37] *See* Wilson, *supra* note 24.

[38] *See* Fernandez, *supra* note 3, 33-34.

[39] *See* Manual of Patent Examining Procedure 2107 (8th ed. 2001).

[40] *See* Restaino, *supra* note 13, at 11.

[41] Mary Chow and Dennis Fernandez, *Intellectual Property Strategy in Bioinformatics*, Partnering Focus, Jun. 2004, at 9.

[42] *Id.*

[43] *Id.*

Some genomics-related claims are too general to meet the written description requirement. Under the guidelines for the written description, a patent specification must describe the claimed invention in sufficient detail that one skilled in the art could reasonably conclude that the inventor had possession of the claimed invention.[44] The Federal Circuit in *University of California* v. *Eli Lilly* held that merely naming a type of known material, without any knowledge as to what that material consists of, is not a description of that material.[45] For example, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. A definition by function is not sufficient to define the genus because it is only an indication of what the gene does, rather than what it is.[46]

Such rejection can be overcome by drafting a narrower and more specific claim, such as specifically defining genes within its definition. Alternatively, if it can be shown that one of ordinary skill in the art would be expected to visualize or recognize that particularly disclosed members of the genus family by the claimed method, the rejection can also be defeated.

4. Ethical Issues and Public Policy

Recently, the patentability of new biotechnological inventions, including human embryonic stem cells, human cloning and human/non-human chimera, have raised not only technical challenges to patent prosecution, but also moral and ethical concerns. The USPTO determines patentable subject matter under 35 U.S.C. § 101 on a case-by-case basis following tests set forth in *Chakrabarty*.[47] For example, one such test says that “a nonnautrally occurring manufacture or composition of matter” is patentable.[48]

On one hand, the USPTO considers purified and isolated stem cells and human cloning-related inventions patentable subject matter and rarely rejects patentability based on public policy and morality grounds, as long as these inventions meet the criteria of novelty, utility and nonobviousness.[49] For example, the USPTO has issued several patents on cloning methods specifically related to non-human animals, such as patents granted to Geron-Biomed and the University of Massachusetts at Amherst.[50] On the other hand, the USPTO did not grant a patent on the claimed human/non-human chimera based on the argument that granting patents on people would violate the 13th Amendment to the Constitution abolishing slavery, claiming that neither the USPTO nor Congress has ever defined "human.” Further, in a media advisory issued in 1998, relying on the decision from *Tol-O-Matic, Inc. v. Proma Produckt-und Marketing Gesellschaft*, the USPTO stated that the utility requirement of § 101 excludes inventions deemed to be "injurious to the well being, good policy, or good morals of society."[51]

These seemingly conflicting decisions from the USPTO raise the question of whether the United States patent laws are used as a means of regulation.[52] First, the patent system lacks the expertise and re-

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[44] *See* Guidelines for Examination of Patent Applications under the 35 U.S.C. 112, para. 1, "Written Description" Requirement, 66 Fed. Reg. 1099 (Feb. 2003).

[45] *University of California v. Eli Lilly*, 119 F.3d at 568.

[46] *Id.*at 568 (citing *Fiers v. Revel*, 984 F.2d 1164, 1169-71 (Fed. Cir. 1993)).

[47] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980).

[48] *See* Manual of Patent Examining Procedure 2105 (8th ed. 2001).

[49] Audrey R. Chapman, Mark S. Frankel and Michele S. Garfinkel, *Stem Cell Research and Applications Monitoring the Froniters of Biomedical Research,* American Association for the Advancement of Science, Nov. 1999, at 26,

[50] Duane Nash, *Recommended Response for Human Cloning Patent Applications*, 42 IDEA, 279, 295 (2002).

[51] Jasemine Chambers, *Patent Eligibility of Biotechnological Inventions in the United States, Europe, and Japan: How Much Patent Policy is Public Policy*, 34 Geo Wash. Int'l L. Rev. 223, 230 (2002) (citing *Tol-O-Matic, Inc. v. Proma Produkt-und Marketing Gesellschaft*, 945 F.2d 1546 (Fed. Cir. 1991)).

[52] *See* Nash, *supra* note 45, 299-300.

sources to engage in regulating outside the USPTO's expertise, and the USPTO is not in the position to make regulatory changes or any societal concerns for all of its applications. Second, a refusal to grant a patent for such controversial biotechnological inventions does not prevent that application from being applied.[53]The patent right is a right to exclude others from making, using, and selling the invention, instead of performing any particular act.[54] Thus, by not granting a patent, the PTO may instead enable anyone to practice the disrupted technology. Third, patent law only enables the USPTO to either grant or not grant a patent. The USPTO does not have the qualifications to give a wide range of options to regulate inventions on moral grounds.[55] Therefore, even though the USPTO may grant or reject these controversial biotechnological inventions, it does not and should not attempt to regulate the ethical and moral concerns regarding these inventions through patents. That role should be left to the legislature.

5. Conclusions

Patenting new biotechnological inventions provides a constant challenge. In addition to its fast growth and increasingly interdisciplinary nature, both patent prosecutors and the USPTO face the ethical and public policy issues of patenting human cell-related inventions. Even though patents are only a part of an intellectual property strategy, effective and efficient patent strategies are essential to provide incentives to advance biotechnology research and growth of the industry.

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[53] *Id.*

[54] *See* Chambers, *supra* note 46, at 231.

[55] *See* Nash, *supra* note 45, at 299-300.

Patent Prosecution in Pharmacogenomics [1]

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Executive Summary

This paper presents a brief overview of intellectual property rights and the various areas in pharmacogenomics to which IP rights may be applicable. First, the basic forms of intellectual property protections and the concepts in the science and utility of pharmagenomics technology are introduced. The patentable subject matters and the issues and complications related to national and overseas patent prosecution in this relatively new field are discussed in the second half of this paper.

Pharmacogenomics is an emerging new field that attempts to correlate patterns of genetic variation to different drug response phenotypes. This technology makes it possible to target clinical trials to patient populations having the genotypes that are likely to response to the drugs and thus may reduce clinical trial costs and speed up FDA approval processes. It can also be used to identify patients that are likely to suffer adverse effect from the drugs.

Tools, compositions and methods involved in pharmacogenomics technology can be patentable subject matters. However, there are unique challenges in the prosecution and enforcement of such patents in the United States and overseas. The utility requirement may prevent the patenting of a nucleic acid sequence that is solely used as a gene probe, a primer in PCR, a chromosome marker or an antigen generator. This may be overcome by finding the function of the DNA or by linking it to a homologous DNA with known functions. Further, patentees may find it difficult to enforce pharmacogenomics patents because an infringer may be able to use the research tools and technologies overseas to produce pharmaceutical products which may be legally sold in the US. The exemption to infringement under 35 USC § 271 (e)(1) is also a potential defense for infringement. Awareness of these challenges to the pharmacogenomics patent process will lead to more skillful prosecution and better protection for such inventions.

1. Intellectual Property Overview

1.1 Introduction

Some find the concept of intellectual property hard to grasp, often because it's hard to determine the monetary worth of ideas. One simple example of the value of intellectual property is the common occurrence of expensive and high-stakes infringement lawsuits. One of the costliest examples is the decades long case of Eastman Kodak vs. Polaroid, which resulted in the destruction of Kodak's instant photography business, as well as more than $3 billion dollars in infringement damages, compensation and legal fees, and research and manufacturing costs[2]. Even lawsuits that result in settlements, such as that filed by the University of California against Genentech for the company's manufacture and sale of the growth hormone product Protropin[R], can be severe ($200 million in the case of UC vs. Genentech) punishments for the defendants[3]. That is not to mention the hundreds of thousands of dollars lost by both sides on legal and courtroom fees and on time spent by employees and management embroiled in the suit.

Although successful suits filed by small companies can result in large settlements or infringement damages from industry juggernauts, companies without the proverbial 'deep pockets' typically do not have the time and money to spend on lengthy, costly litigation. The price of resolving patent disputes can sometimes cripple a business, compared with the modest cost of building an effective IP portfolio. Thus, successful companies stand to benefit more from a strong IP portfolio to accompany equally strong and innovative research and development. Besides, with sound and successful innovation, a company can avoid being mired in litigation over a technology that it has long since improved upon.

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[2] Rivette, K. G., Kline, D. "A Hidden Weapon for High-Tech Battles." Upside Jan. 2000:165-174.

[3] Kude, Timothy, "Regents drop case against Genentech, agree to settle." *UCLA Daily Bruin online* 22 Nov. 1999. Available: http://www.dailybruin.ucla.edu/db/issues/99/11.22/news.settlement.html

From a different angle, those still questioning the value of intellectual property can look at the value derived from successful licensing of IP. The well-known Cohen-Boyer recombinant DNA patents, often credited as key catalysts of today's biotech industry, were reported to have earned $37.3 million in licensing royalties in 1997 alone[4].

While U.S. legislation such as the Bayh-Dole Act allowed for transfer of ownership of many government funded inventions from the U.S. government to the universities[5], resulting in successful licensing of almost half of university-born inventions[6],[7], the fact is that an estimated 3% of all patents are actually licensed[8]. Thus an effective IP prosecution strategy should take note of the competing demands for licensing revenue and defense from litigious competitors. On one hand well-written patents are needed to defend the core technologies a company builds upon, and on the other hand an aggressive patenting strategy is needed to map the course a company sees itself undertaking. The latter can result in licensing deals, or serve as a useful method for sidestepping unwanted litigation, by keeping far ahead of the competition.

This paper presents a brief overview of intellectual property rights and the various areas in pharmacogenomics to which IP rights may be applicable. The perfection of an IP portfolio is of interest to startups and their investors, whereas licensing agreements are of interest to manufacturers and customers. Technology transfer, including licensing and business agreements, is not covered in this paper. Instead, issues and complications related to national and overseas patent prosecution in this relatively new field will be discussed.

1.2 Patents

United States patents offer protection for any process, machine, manufacture, or composition of matter, or any improvement thereof, that is novel, useful, and non-obvious[9]. The Agreement in Trade-Related Aspects of Intellectual Property Rights (TRIPS Agreements) in 1994, a multilateral concord proposed by the council administering the WTO's intellectual property agreement[10], defines patentable matter as any invention that involves an innovative step and has a potential industrial application[11].

In theory, the purpose of intellectual property is to foster intellectual and economic growth. Patents spur innovation through the disclosure and teaching of the details of an invention to the public, and in exchange, the inventor or owner is rewarded the legal rights of ownership. The legal rights give the owner exclusive rights to capitalize on the invention, by excluding others from making or using the invention, importing the invention into the U.S., or offering the invention for sale. These ownership rights are granted for a period of 17-20 years, depending on the date of filing of the patent application.

Patents are obtained through a lengthy process that can sometimes turn out to be quite costly. In high-tech fields such as pharmacogenomics, the time between filing a patent and a first response from the U.S. patent office is typically a year and a half. This is due in part to the large volume of patent applica-

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4 Stanford Office of Technology Licensing. *Medical Staff Update* Dec. 1998. Available: http://www-med.stanford.edu/shs/update/archives/dec1998/fact.html

5 Consumer Project on Technology. *The Bayh-Dole Act.* Available: http://cptech.org/ip/health/bd

6 Campbell, Kenneth D. "TLO says government research pays off through $3 billion in taxes." *MIT Tech Talk* 15 Apr. 1998. Available: http://web.mit.edu/newsoffice/tt/1998/apr15/patents.html

7 Council on Governmental Regulations. *The Bayh-Dole Act: A Guide to the Law and Implementing Regulations*. Sept. 1999. Available: http://www.cogr.edu/bayh-dole.htm

8 Murtha, Emmet J. Interview. *Licensing Economics Review* Oct. 2001.

9 35 U.S. Code, Sect. 101, 102, 103

10 World Trade Organization. *Overview: the TRIPS Agreement*. Available: http://www.wto.org/english/tratop_e/trips_e/intel2_e.htm

11 McCabe, K.W. "The January 1999 Review of Article 27 of the TRIPS Agreement: Diverging Views of Developed and Developing Countries toward the Patentability of Biotechnology." *J. Intell. Prop. L.* **6.1** 1998: 41-67.

tions in these fields, and to the lack of expertise in the patent examiner corps. In Europe, Japan, and the Pacific, the "first to file" system applies. On the other hand, in the U.S. the "first-to-invent" system applies, but patent applications must be filed within one year of the first offer for sale of the product or public disclosure of the invention to avoid being barred under 35 U.S.C. § 102 (b). Thus it is important to keep an accurate record of dates of invention as well as offers for sale or other public disclosures.

1.3 Copyrights

Copyrights protect the original expression of an idea. By offering protection, copyright encourages the expression of original, artistic ideas into a tangible medium. Legal protection is effected instantly, when the original copyrightable subject matter is fixed into a tangible medium, e.g. on paper or in a digital storage form.

Copyrights are free and do not require months of paperwork as do patents, and they are valid for the author's lifetime plus 50 years. A longer period of validity (75-100 years) applies if the work was created for hire, which is generally the case in a business such as the biotech industry.

1.4 Trade Secrets

Trade secrets are any technical or business information that give a company a competitive advantage. There is no formal filing procedure to register trade secrets. The secret need not be completely novel or exclusive; it simply must have a derived or potential economic value from being unknown by others. Additionally, reasonable efforts must be made to keep the information secret, e.g. through the use of inexpensive Non-Disclosure Agreements (NDA). Legal protection under trade secret no longer applies when the information is publicly disseminated.

1.5 Trademarks

Trademarks refer to the distinctive signature mark, name, or symbol that can be used to protect the company, product, or service. The trademark must not be descriptive or generic. Legal protection is not offered to the technology, rather to the company good will and quality associated with the use of the recognized name or symbol. Trademarks provide exclusive rights within a region or nation and as long as used commercially, they may be renewed indefinitely. Compared to patents, they are obtained within a moderate time period (usually under two years) and typically at a cost under $5K per registered mark.

1.6 IP Strategy

The IP rights are protected under various federal and state laws. Without protection, intellectual property falls into the public domain and may be used by any party without license. A sound management strategy would be to systematically build a portfolio consisting of different IP rights, with the aim of protecting the various aspects of the company's technology and commercial interests.

IP rights protect the commercial interests of a company at the various stages of design, manufacturing, and product operation. At the design and development stage, copyrights and trade secrets can be immediately enforced. Novel apparatus and methods can then be patented, a process that takes about three years and requires the investment of some funds. Once a product or service is developed, issued patents and trademarks protect the technology and associated names and symbols.

While copyright and trade secret protection are obtained easily, patents, trademarks, and maskworks require applicant action and response within critical filing deadlines. Generally, the first to patent will have the best chance of winning the broadest patents.

2. Pharmacogenomics

2.1 Issues

Pharmacogenomics stems from a related field, pharmacogenetics, and the two terms are often used interchangeably. Pharmacogenetics is the decades-old study of differences in drug absorption, metabolism, elimination or response and then examines a few candidate genes for variations underlying the observed phenotypes. In contrast, pharmacogenomics casts a wider net to capture complicated patterns of genetic variation and attempts to correlate these patterns to different drug response phenotypes[12]. The challenge is to identify genetic differences that influence drug metabolism and response, and to correlate that data with drug efficacy and safety information. The goal is to weave all this information together into something that has enough predictive value to be used reliably.

Single nucleotide polymorphisms (SNPs pronounced "snips") are the most prevalent genetic variations in the human genome. They are single base pair differences that occur in 1% of the human population[13] on average every 1.91 kb. The human SNP map shows 1.42 million differences, a majority of which occur in coding regions[14]. Pharmacogenomics is the study of how these sequence differences affects the ways in which people respond to drugs. Variations in the disease-causing genes, drug targets or the enzymes that metabolize drugs influence the drug's potency and efficacy. Also, genetic differences between patients explain why some patients but not others suffer from harmful drug side effects.

2.2 Challenges

Currently, costs limit the widespread use of pharmacogenomics. For instance, it costs approximately one dollar to identify one SNP in a patient sample[15]. It is estimated that it will require the screening of 100,000 SNPs per patient to construct an accurate picture of a patient's response to a drug; this translates to 100,000 dollars per patient. For this technology to become practicable, the cost must be reduced to a penny per SNP. Further, narrowing down a large number of genetic variations to a number that is amenable to application in a clinical trial would also prove useful. In this regard, computation methods to categorize and prioritize SNPs or haplotyping, the identification of closely associated polymorphisms that tend to occur in clusters, are being developed[16].

Other limitations in the progress of pharmacogenomics include tools used for collecting, archiving, organizing and interpreting the huge amount of data generated in a pharmacogenomics study so that data from diverse experiments can be compared. Also, drug dosage and treatment schedules need to be standardized in order to accurately compare patient data[17]. Successful interpretation of data also requires comparison of enormous quantities of data such as the publicly available databases, Pharmacogenetics and Pharmacogenomics Knowledge Base (PharmGKB) and the SNP Consortium[18].

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[12] Constans, E. "Making Medicine Personal" *The Scientist* **16**.**19** 2002: 44-50

[13] Henry, C.E. "Pharmacogenomics" *Chemical and Engineering News* **79.33** 2001: 37-42.

[14] The Internation SNP Map Working Group "A Map of Human Genome Sequence Variation Containing 1.42 million Single Nucleotide Polymorphisms" *Nature* **409** 2001: 928-933

[15] See ref. 13.

[16] See ref. 12.

[17] See ref. 12

[18] Eisenberg, R. S. "Will Pharmacogenomics Alter the Role of Patents in Drug Development" *Pharmacogenomics* **3.5** 2002: 571-574

2.3 Uses

The primary goal of pharmacogenomics is to reduce the time and cost of drug development. Choosing patient candidates for a clinical trial based on pharmacogenomic knowledge and the patients' genotype is hoped to eliminate sub-populations for whom drugs are predicted to be ineffective. This would justify smaller and fewer trials, likely generate more consistent trial results, and make it easier to gain FDA approval[19].

Another goal of pharmacogenomics is to identify patients who are likely to suffer drug related adverse events. A 1998 study of hospitalized patients published in the Journal of the American Medical Association reported that in 1994, there were more than 2.2 million adverse drug reactions and 100,000 drug-related deaths, making adverse drug reactions one of the leading causes of hospitalization and death in the United States. Moreover, the ability to pre-test patients may have prevented certain high profile drug withdrawals, including the former Warner-Lambert Rezulin (troglitazone) and Glaxo Wellcome's Lotronex (alosetron)[20].

Pharmacogenomics can be used to identify how quickly a patient will metabolize a drug and, therefore, ensure appropriate dosing. Up to 30% patients do not respond optimally to certain drugs, which can often be addressed by merely changing the dose. If these problems were identified and remedied early in clinical trials, results would be more convincing and, therefore, approval would be faster and less costly[21].

Pharmacogenomics will allow the differentiation of a company's product from others in the marketplace (e.g. by identifying patient's by genotype who will respond to product X and not to product Y). One further benefit to patients is that pharmacogenomic knowledge will also allow identification of those patients in the population who will derive no clinical benefit from a prospective treatment. A look at data from clinical trials in 14 major drug categories reveals that this "non-responder" subset may be 20-75% of the general population. Additionally, pharmacogenomic knowledge from association studies (SNP to disease links) will allow for preventative screening and preventative treatment.

Drug patent holders in pharmaceutical industry have many incentives to use pharmacogenomic knowledge to develop genotyping diagnostic tests to be used with a drug. They have a vested interest in having shorter, less expensive clinical trials, identifying patients who are expected to have adverse drug reactions and those requiring tailored dosages of a drug. However, the anticipated loss of sales revenue by identification of the "non-responders" serves as a strict disincentive for the development of genotyping diagnostic tests.

3. Protectable Applications in Pharmacogenomics

3.1 Tools

The tools available to researchers involved in pharmacogenomics studies are viewed as patentable. These include reagents, kits, chips, microarrays, instrumentation, devices used for genetic tests, algorithms for searching and sequence alignments and database technology. Certain proteins may also fall under the tool category if they can be used as probes to identify other biomolecules or small molecules.

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[19] Overend-Freeman, E. "Maximizing R&D Productivity: Getting More Bang for Your R&D Buck" Datamonitor Report.

[20] See ref. 19.

[21] See ref. 19.

3.2 Composition

The composition of isolated nucleic acid sequence, isolated protein and small molecules can be claimed. A patent application has to comply with the requirements for utility, novelty and non-obviousness. Further, the patent application must also comply with requirements for written description, enablement and best mode. For example, one has not shown utility if one claims a nucleic acid sequence that may be used as a gene probe, a primer in PCR, a chromosome marker or an antigen generator since such utility is applicable to virtually any nucleic acid sequence. However, if the function of the gene is known and its utility is understood then claiming the DNA, as a gene probe, would be valid. Further, if the gene function is known and the utility is accepted then a homologous DNA sequence would comply with the utility requirements and could be claimed. Even if a portion of this homologous gene was previously published as an expressed sequence tag (EST), the patenting of this homologous gene still complies with the novelty requirement. While a single nucleotide polymorphism or a nucleic acid sequence containing such a variation can not be claimed, if such a variation proved useful as a marker for a disease state or for drug metabolism, the composition could be claimed. The written description requirement is the greatest hurdle for patenting of composition in inventions. In an age where "describing a method of preparing a cDNA or even describing the protein that the cDNA encodes. …does not necessarily describe the cDNA itself," one can be sure that the written description requirement is very strictly enforced[22].

3.3 Methods

Patenting methods that aid in the acquisition of pharmacogenomic data such as screening and genotyping methods is standard practice. Further, methods used in the diagnosis and treatment of subjects based on pharmacogenomic knowledge are also patentable. Interestingly, methods for management of complex data from pharmacogenomic studies such as a method for integrating clinical, diagnostic, genomic and therapeutic data is patentable. Finally, methods for pharmacogenomics-based clinical trial design meet the criteria for patentability.

4. Challenges to Patent Process in Pharmacogenomics

As already touched upon, there exist some challenges that are specific to the pharmacogenomics patent process. The main issues for obtaining commercially relevant patent protection in pharmacogenomics are utility, enablement and written description. However, the challenges in enforcing pharmacogenomics patents may prove to be the larger problem in the patent process.

Groups involved in developing pharmacogenomic research tools and methods should be aware of the *Housey* decision passed by the district court of Delaware. In accordance with this decision one can elude US protection on patented screening methods by performing the research work outside the United States. Once the screening is completed and a useful product is found, the *Housey* decision permits the information to be brought back into the United States for further testing and development into a commercial product[23].

The research exemption is designed to protect actions performed "for amusement, to satisfy idle curiosity, and for strictly philosophical inquiry". As seen in the case of *Madey vs. Duke University* the experimental use defense is not valid if the activity furthered the "legitimate business objectives" of the alleged infringer whether or not a profit was made. This defense is "very narrow and strictly limited"[24].

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[22] Warburg et al. "Patentability and Maximum Protection of Intellectual Property in Proteomics and Genomics" *Pharmacogenomics* **4.1** 2003: 81-90.

[23] *Id*.

[24] *Id*.

The exemption to infringement under 35 USC 271 (e)(1) provides that it is not an act of infringement to use a patented invention solely for uses "reasonably related" to the generation of information likely to be relevant to FDA approval of a product. This exemption may be applied in the case of business methods, devices, research tool and even chemical entities. Unlike the research exemption, this exemption has been interpreted broadly and judged as non-infringement in favor of the defendant in the *Bristol-Meyers Squibb vs. Rhone-Poulenc Rorer* case[25]. The scope of the 35 USC exceptions was reigned in by an opinion from the Court of Appeals for the Federal Circuit in the case of *Integra vs. Merck*. In this case the use of patented research tool in drug discovery was deemed as infringement as pre-clinical work is not included in the safe harbor of 35 USC 271 (e)(1)[26].

The EPO also has specific laws pertaining to biotechnology patents, described in the EU Biotechnology Directive of July 1998, and the European Patent Convention (EPC) of 1999. For instance, Article 53(a) of the EPC states that "European patents shall not be granted in respect of… inventions the publication or exploitation of which would be contrary to 'ordre public' or morality"[27], and Rule 23d (d) excludes "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"[28]. Thus, patents that cover genetically modified animals, for example, that do not specify or imply medical benefits can be rejected by the EPO or challenged in an Opposition, a procedure in which any person may oppose granting a European patent within nine months from publication.

Finally, the notable rule pertaining specifically to biotechnology patents in both the US and Europe is that of utility. Under amended guidelines issued in January 2001 by the USPTO, patentable subject matter is that which has specific, substantial, and credible utility. The addition of the substantiality requirement means that patent claims that require considerable research by a person of ordinary skill in the art in order to determine the function of a molecule are likely to be rejected. The motivation for the requirement is to reduce claims that expand the scope of the invention beyond the functions and utility described in the specifications. In its most simplified interpretation, the utility rule demands that each claim pertain to products that have a clear use and benefit to human society.

The challenges to pharmacogenomics patents are still evolving. Because of their direct application to biological life on earth, pharmacogenomics and genomics patents are subject to intense scrutiny by the various patent offices. As the technology develops, however, one impedance to the biotech patent process, namely the need for more cross-technically educated patent examiners and counsel, will eventually become less of a burden. Knowledge of the challenges to the pharmacogenomics patent process will lead to more skillful prosecution and more rapid innovation overall.

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[25] *Id*.

[26] Maebius, S. B. and Warburg, R. J. "Court upholds infringement of research tool patents, but discounts damages" *Pharmacogenomics* **4.4** 2003: 369-370.

[27] European Patent Convention: Part II Ch.I Article 53(a).

[28] Implementing Regulations to the Convention on the Grant of European Patents: Part II Ch. IV Rule 23d(d).

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