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Message from the Editor

The Biotechnology Law Committee is proud to bring you the Summer 2012 issue of Biotech Briefing. This issue of the Biotech Briefing contains two articles. The first article, “Putting Myriad in Perspective,” authored by Professor Eileen M. Herlihy (New England Law School in Boston, Massachusetts), discusses the Myriad case on patentability of certain DNA based technologies and its similarities with early regulatory issues for recombinant DNA technologies. The second article, “Will Patents Matter in a Biosimilars Future?,” was authored by Dr. Kevin E. Noonan, Ph.D. (Partner with McDonnell Boehnen Hulbert & Berghoff LLP, Chicago, Illinois) and explores intellectual property issues facing biological drug manufacturers following enactment of the Biologics Price Competition and Innovation Act. We kindly thank our gracious authors for their contributions and we hope you enjoy this issue.

If you are interested in contributing to our Fall issue please feel free to contact me (wbleibel@lplegal.com).

—Wasim Bleibel
Biotechnology Law Committee, Vice Chair

Putting Myriad in Perspective

Eileen M. Herlihy¹

The attention of the biotechnology and pharmaceutical industries has been riveted on the Myriad case since March of 2010 when Judge Sweet of the Southern District of New York invalidated patent claims to DNA molecules associated with the BRCA1 and BRCA2 genes on the basis that they do not constitute patentable subject matter.² Although a panel of judges at the Federal Circuit later reversed Judge Sweet’s rulings on the DNA claims, the judgment was not unanimous. While all three judges agreed that the claims covering cDNA molecules related to the BRCA1/2 genes fall within the bounds of patentable subject matter,³ only two of the judges agreed that the remaining DNA claims at issue cover patentable subject matter as opposed to unpatentable “products of nature.”⁴ Moreover, each judge wrote a separate opinion,⁵ leaving an uncomfortable amount of uncertainty in the rationale underlying the holding. Now that the Supreme Court has issued its highly anticipated decision on patentable subject matter in the Prometheus case,⁶ and entered a related order in the Myriad case granting certiorari, vacating the Federal Circuit’s decision, and remanding the case,⁷ all interested parties are again holding their breath.

The Myriad case is not only highly controversial, it has generated a complex split of positions. The plaintiffs, a group of medical organizations, doctors, patients, and researchers, have taken the position that none of the DNA claims at issue are valid. It is the plaintiffs’ position that the claims do not encompass patentable subject matter under § 101 of the patent statutes because they are not “markedly different” from human genes and are therefore “products of nature.”⁸ The defendants, Myriad Genetics, Inc. and the Directors of the University of Utah Research

¹ Associate Professor of Law and Co-Director of the IP Institute, New England Law | Boston.
³ Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office, 653 F.3d 1329, 1339, 1350, 1358, 1364, 1373 (Fed. Cir. 2011).
⁴ Judges Lourie and Moore agreed that claims to “isolated” DNA molecules cover patentable subject matter (id. at 1334, 1350, 1358), while Judge Bryson dissented from that holding (id. at 1373).
⁵ Id. at 1339-58 (Judge Lourie writing the opinion for the court); Id. at 1358-73 (Judge Moore concurring in part); Id. at 1373-81 (Judge Bryson concurring in part and dissenting in part).
Foundation, the owner and licensee of the patents at issue, have taken the position that all of the DNA claims at issue are valid. The defendants assert that the claims fall within the scope of “compositions of matter” under § 101, and should not be excluded from the reach of patentable subject matter since they cover molecules that are structurally and functionally distinct from the BRCA1/2 genes as they exist in nature. 9 The U.S. Department of Justice has taken an intermediate position. It contends that the cDNA claims represent patentable subject matter because they cover genetically engineered molecules that are “human-made,” as opposed to the claims to “isolated” naturally occurring DNA which the Department of Justice views as non-patentable “products of nature.” 10 It is, of course, significant that the Department of Justice has taken a position at odds with the long-standing policy of the USPTO to treat DNA molecules as non-patentable “products of nature.” 11

While the Myriad case is the focal point of widespread controversy concerning the patentability of DNA molecules “isolated” from larger DNA molecules in the human chromosome, it is not the first time that the human manipulation of naturally occurring DNA has caught the attention of the public and created conflict among experts.

Early Regulation of Recombinant DNA Research

Another category of human manipulation of naturally occurring DNA that initially caused widespread controversy and public concern is recombinant DNA technology. This technology encompasses the formation of new DNA molecules by cutting segments of DNA out of larger naturally occurring DNA molecules and splicing them together or splicing them with synthetic DNA segments. 12

In 1975, when the technology was in its infancy, a group of concerned scientists met at the Asilomar Conference Center in California to discuss possible hazards associated with the new research. 13 One of the fears discussed was the possibility that the research could yield new pathogenic microorganisms that would be uncontrollable. 14 The scientists’ discussions concerning the safety of the so-called gene-splicing prompted the NIH to consider and ultimately adopt guidelines for conducting experiments involving the powerful new techniques. 15 In addition to the regulatory action taken by the NIH, which applied to experiments conducted with NIH grants, 16 some local and state governments took steps to regulate, or even ban, this research. 17

Cambridge, Massachusetts was one of the cities that took action. In June of 1976, before the NIH published its first set of guidelines, then Mayor Vellucci called the Cambridge City Council together to consider the possible dangers surrounding the technology, which was the object of intense investigation at both Harvard University and the Massachusetts Institute of Technology. 18 A resolution for a “good faith” moratorium on recombinant DNA experimentation was passed by the City Council, to take effect during the course of a local investigation and evaluation of the public safety impact of the research. 19 A panel of eight citizens, all unfamiliar with the technology, was chosen to serve as the Cambridge Experimentation Review Board. 20 This board

10 Brief for the United States As Amicus Curiae In Support Of Neither Party at 14-27, Ass’n for Molecular Pathology, 653 F.3d 1329 (Fed. Cir. 2011) (No. 2010-1406).
12 For a good description of recombinant DNA techniques and the early debate over the possible risks of this research see Clifford A. Grobstein, The Recombinant DNA Debate, SCI. AM. 22 (July 1977). See also Baker & Clough, The

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heard the arguments of those in favor of and those opposed to allowing the experimentation to continue, and engaged in research and reading into the problem on their own. After listening to the predictions of many leading scientists, including a host of Nobel laureates and a representative from the NIH, the panel unanimously agreed that most of the recombinant DNA experimentation should be allowed to proceed subject to regulations based upon the NIH guidelines. An ordinance was subsequently passed incorporating the committee’s recommendations.  

Similar scenarios played out in other locations, and in the end recombinant DNA research was generally allowed to proceed, subject to safety regulations. It is now taken for granted. In retrospect, it is easy to come to the conclusion that the right balance was struck between protecting the health and safety of the public and allowing scientists to pursue this research, which has proven to be extremely valuable. At the time the crucial decisions were made, however, it was far more difficult to gauge their ultimate impact.

The overall outcome in the case of recombinant DNA research represented an accommodation that avoided sweeping categorical bans on the research. There is certainly some irony today in the fact that the very research that was originally the subject of controversy in the area of human manipulation of naturally occurring DNA is focused on whether less drastic manipulation should receive the incentive of a patent.

The Petition for Certiorari in Myriad

In their Petition for a Writ of Certiorari, the plaintiffs in the Myriad case sought a sweeping ban on the patenting of DNA molecules derived from human genes. The first question presented in their petition states simply and categorically: “Are human genes patentable?”  

The plaintiffs argue that the answer to this question should be no because so-called gene patents cover “products and laws of nature and abstract ideas.”  They also argue that such patents stifle scientific and medical inquiry and prevent patients from obtaining access to their own “genetic information.”  

In seeking a reversal of the Federal Circuit’s decision in Myriad, the plaintiffs focus in their petition on arguments involving structure and function, and cite the divergent views expressed by the district court judge and each of the three Federal Circuit judges who previously decided the case.

With respect to structure, the plaintiffs minimize the legal significance of any structural differences between the isolated DNA molecules covered by the claims at issue and the BRCA1/2 genes as they exist in the human body, and also dispute that any such difference exists. The plaintiffs argue that, in order to meet the requirements of Supreme Court precedent on patentable subject matter, a composition of matter must be more than just structurally different from a naturally occurring substance, it must have “a distinctive name, character [and] use’ and ‘markedly different characteristics from any found in nature.”  They reject the analysis of Judge Lourie, who wrote for the Federal Circuit in its now vacated Myriad decision. Judge Lourie reasoned that the “isolated” DNA molecules covered by the claims fall within the scope of § 101 because they are distinct chemical molecules, formed by breaking covalent bonds in larger DNA molecules that are naturally present in human chromosomes. In addition to their arguments on the proper legal standard, the plaintiffs also allege that the claimed DNA molecules are not even structurally different from naturally occurring molecules, since

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21 Thomas A. Balmer, Recombinant DNA: Legal Responses to a New Biohazard, 7 ENVTL L. 293, 300-304 (1977) (original version of ordinance passed in February of 1977).  

22 All three Federal Circuit Judges in the Myriad case found the claims to cDNA molecules to be patentable since the molecules encompass a different DNA sequence than that in a naturally occurring gene. Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office, 653 F.3d 1329, 1350, 1358, 1364, 1373 (Fed. Cir. 2011). Recombinant DNA technology results in a DNA sequence that differs from that occurring in nature. See supra text accompanying note 12. See also Diamond v. Chakrabarty, 447 U.S. 303 (1980) (holding that a novel genetically engineered bacterium created using genetic technology falls within the scope of patentable subject matter).
covalent bonds are broken in nature. Plaintiffs state “[t]he standard process of isolation does not result in DNA fragments that do not exist naturally in the body.”

With respect to function, the plaintiffs focus on the biological characteristics of DNA. The plaintiffs point out that DNA conveys information through the natural sequence of nucleotides that provides a “blueprint” for protein synthesis, and that this “blueprint” is the “essential characteristic” of DNA. Since the “isolated” DNA of the claims retain a sequence that can code for a protein, the plaintiffs argue that the claimed “isolated” DNA molecules do not have a distinctive use as compared to the “blueprint” of the naturally occurring DNA. The plaintiffs reject the analysis of Judge Moore, who concurred in the Federal Circuit’s majority judgment in Myriad. Judge Moore noted that “isolated” DNA molecules that contain only a segment of the sequence in a human gene have distinct uses as primers or probes. The plaintiffs reject this analysis, arguing that the small segments are unpatentable “phenomenon of nature,” and that none of the claims at issue are limited in their scope to such uses.

Now that the Supreme Court has vacated the decision of the Federal Circuit and remanded the case, the outcome in the next phase will be determined by the Federal Circuit’s interpretation of the Supreme Court’s recent decision in Prometheus.

While the Petition for Certiorari in the Myriad case only relates to DNA molecule claims, which are composition of matter claims, the patentable subject matter issues the Supreme Court addressed in Prometheus concern method claims. In particular, the claims at issue in Prometheus relate to methods for calibrating the proper dosage of thiopurine drugs for the treatment of autoimmune diseases based upon the natural correlations between the concentration of certain metabolites of the drugs in a patient’s blood and the likelihood that the drug dosage will be harmful or ineffective.

In a unanimous decision, the Supreme Court held that claims at issue in Prometheus are invalid since they effectively claim underlying laws of nature. In some portions of the opinion, the Court criticizes certain claim drafting efforts that it views as expressly designed to “monopolize the law of nature itself,” by essentially stating a law of nature and effectively adding “apply it.” In other portions of the opinion, the Court more broadly criticizes claims that add no more than steps covering “well-understood, routine, conventional activity previously engaged in by researchers in the field” to natural laws. The Court does, however, twice quote its own precedent which states that “a novel and useful structure created with the aid of knowledge of scientific truth” may be patentable.

It is difficult to predict how the Federal Circuit will apply the statements in Prometheus to the DNA claims in Myriad.

A Perspective on Myriad

The human manipulation of naturally occurring DNA is an area that is fraught with controversies. Two of these relate to regulation and patenting. While the specific issues confronted in the past surrounding the regulation of recombinant DNA research are not the same as those currently at issue surrounding the scope of patentable subject matter in the area of so-called gene-patents, there are some common threads in the controversies that are worth consideration.

First, whether the issues involve decisions on banning or putting up regulatory barriers, as they did in the early days of recombinant DNA research, or potentially taking away patent incentives, as they do in the Myriad case, their resolution influences the progress of science and technology. As a result, decisions in these areas should not be made lightly and need to be made in a deliberate manner. In the case of the early regulation of recombinant DNA research, decisions were made following the vetting of the known facts and potential hazards by scientists, in meetings such as the one held in

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30 Petition for a Writ of Certiorari, supra note 23, at 15-16.  
31 Id. at 5.  
32 Id. at 27-28.  
33 Id. at 28.  
34 Ass’n for Molecular Pathology, 653 F.3d at 1365-66.  
35 Petition for a Writ of Certiorari, supra note 23, at 29.  
36 Id. at 6-7 & n.2.  
38 Id. at 1294-95.  
39 Id. at 1297; see also id. at 1294.  
40 Id. at 1294.  
41 Id.; see also id. at 1291-92.  
42 Id. at 1294, 1301 (quoting Mackay Radio & Telegraph Co. v. Radio Corp. of America, 306 U.S. 86, 94 (1939)).
Asilomar, and by citizens, in hearings such as the ones held in Cambridge, Massachusetts. The regulatory conclusions reached reflected an orderly process rather than a fearful backlash against the research. The results have proven to be sound. Similarly, in the area of patent law, decisions concerning whether and to what extent claims to DNA molecules derived from human genes constitute patentable subject matter should not be made in reaction to public perceptions. Rather, the decisions need to be made in light of legal precedent. The Supreme Court has recently addressed this point in *Prometheus*. Noting the different opinions of various researchers and medical experts on public policy issues related to patent incentives, the Court stated that it hesitated to depart from “established general legal rules” and would refrain from deciding public policy issues which could be taken up by Congress. 43

Second, just as outright bans of recombinant DNA research were avoided on the regulatory front, with beneficial results, the Supreme Court has appropriately avoided categorical bans in the area of patentable subject matter. In *Chakrabarty*, the Court refused to categorically exclude living organisms from the scope of patentable subject matter, 44 and in *Bilski* the Court refused to adopt an exclusion for business method patents. 45 In *Prometheus*, the Court was careful to note at several points that it was deciding the case based upon the specific claims at issue. 46

Third, as was seen with the regulation of recombinant DNA research, important decisions need to be made about the scope of patentable subject matter for DNA claims before the future landscape can be accurately predicted. In the case of recombinant DNA research, we now have some historical perspective, and the decisions made in the past appear to have been sound. The decisions yet to be made in the area of DNA patenting in the *Myriad* case will hopefully prove to be sound as well.

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the requirements and procedures for approving biosimilars that are specified broadly by Congress in subsection (k). The agency has recently issued proposed guidelines, and although somewhat disappointing in scope these guidelines set out the general approach the agency intends to take. Biosimilar drug manufacturers have the choice of applying for approval under the biosimilars provisions (§ 351(k) of the Public Health Service Act, codified at 42 U.S.C. § 262(k)) or under full-blown Biologic License Applications under § 351(a) of the Public Health Service Act, codified at 42 U.S.C. § 262(a). Although FDA’s draft guidelines do not provide detailed recommendations with regard to interchangeability, agency guidelines will also affect the likelihood that the biosimilar applicant will attempt to qualify for interchangeability (which requires a higher standard of “similarity” under the statute). How the FDA implements the Act will also influence whether there will be incentives for producing so-called “bio-betters,” i.e., biologic molecules having differences in structure and different (preferably improved) biological properties.

The principle benefits of obtaining approval of a biologic drug under the PHS Act are twelve years of exclusivity that bars approval of biosimilar applications relying on the innovator’s reference drug product, and a four year delay from licensure of the reference drug product to when the agency will accept a biosimilar application. (The Obama administration has repeatedly attempted to reduce the 12-year exclusivity period to seven years, but has thus far been unsuccessful.) The exclusivity period is important because it is likely that at least some patents on biologic drugs may expire before the regulatory exclusivity does. This eventually could make patenting much less valuable for biologic drugs than for conventional small molecule drugs, which under the Hatch-Waxman Act have but five years of market exclusivity and for which patents provide valuable protection against generic competition.

The litigation provisions of the law, on the other hand, depend on the existence of patents to protect biologic drugs after expiration of the twelve-year data exclusivity period. Superficially, these provisions are modeled on the Hatch-Waxman regime, insofar the statute guides how patent infringement litigation will proceed. Superficially is where the resemblance to Hatch-Waxman ends, of course; a significant difference is the absence of an "Orange Book" defining what patents are to be the subject of litigation. In its stead is a complex negotiation protocol by which the parties decide which patents will be the subject of infringement litigation triggered by the filing of a biosimilar application. There has been speculation that the statute was intended to discourage litigation and its labyrinthine, almost Byzantine provisions support this view. It is likely to take at least five years to almost a decade before there is any case law developed enough to test the effectiveness of these provisions.

There is an alternative, however, that may tend to change unpredictably the course of biosimilar development. That alternative is for biologic drug innovators to eschew patenting altogether and thus avoid the possibility of protracted patent infringement litigation under the statute. There are a number of vulnerabilities to patents that claim biologic drugs that are not shared with small molecule drugs and that may make such an approach attractive. Most of these vulnerabilities stem from the greater complexity of biologic drugs; as shown below, biologic drugs have two- to three-orders of magnitude more atoms than small molecule drugs. In addition, biologic drugs are made (generally) in genetically engineered cells that impose their own variabilities (in post-translation modifications such as glycosylation, for example) on the structures of such drugs and the processes used to make them. Further, the complexity makes the scope of patent protection

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52 See Patient Protection and Affordable Care Act, Pub. L. No. 111-148, § 7002.
53 42 U.S.C. § 262(k).
54 42 U.S.C. § 262(a).
55 See 42 U.S.C. § 262(k)(7)
on biologic drugs to be less certain than for small molecules, since even small differences in structure (such as the single methylene group that distinguishes valine from isoleucine) may have unpredictable effects on biologic drug structure, biological activity and immunogenicity. Limitations on claim scope, possibilities of successful “design arounds” and the limited scope available for infringement by equivalents, as well as the uncertainties associated with amino acid sequence and other variants, make biologic drugs different from conventional small molecule drugs, which have been protected by patents under the Hatch-Waxman regime. As a consequence, broad coverage for even structurally similar species of the same biologic drug is infrequently granted, and even when obtained may be of dubious provenance and reliability. As an example, claims to peptides and proteins are typically granted based on the amino acid sequence of the protein, and the Patent and Trademark Office (and the Federal Circuit) has taken the position that any variation in that sequence be expressly disclosed. Rarely does an applicant take the time to perform any extensive structure/function relationship studies on such recombinant proteins, and thus literal infringement using an amino acid sequence variant will be restricted to exact copies of the molecule.

But this very complexity might be a source of an advantage for a biologic drug innovator not to pursue patent protection. In that case, the incentives for the innovator would be to provide as little information as required by the FDA for biologic drug approval and to protect key manufacturing information as trade secrets. Although much of this information will need to be disclosed to FDA to obtain approval and meet inspection requirements, FDA generally cannot disclose this trade secret information to the public.60 That lack of disclosure could provide clear obstacles to a biosimilar manufacturer that might be a disincentive against trying to readily (i.e., predictably) produce a biosimilar version of a biologic drug. The benefits of this approach for biologic drug innovators are evident: producing obstacles to the biosimilar applicant (for whom it would be even more difficult to produce a biosimilar drug) as well as avoiding biosimilars litigation under the statute. But there is another conventional purpose for biologic drug patenting: protecting startup companies early in the development cycle. In this regard, patents continue to serve their purpose of providing exclusivity for further development stages, and in prohibiting larger, better-funded companies from expropriating early-stage technology. Patents also satisfy the requirements imposed on universities under the Bayh-Dole Act, and enable federally funded grantees to reap the benefits of licensing their technology.61 These advantages are unlikely to change even for biologic drugs. But the expected de-emphasis on patent protection for later-stage development (including regulatory approval) can be expected to change the relative importance of patents overall. Such de-emphasis will also change where the valuation in biologic drugs may lie, because there will be a relatively greater advantage in optimizing cell lines and other process parameters (which even today rarely benefit from patenting) than in patents on the biologic drugs per se. That doesn’t mean that patents will be any less important for startups, of course. But thirty years of deal-making and negotiating behavior between small companies and their larger brethren will be affected, and probably not in a way that will inure to the benefit of the startups. While patents will remain essential to early-stage companies, their diminished value to larger partners (and the

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60 See, e.g., 21 C.F.R. § 20.61.

concomitantly greater value of the contributions of such companies) should also diminish the valuation of such deals.

The counter-argument is that startups will play an even more important role in providing the next generation of new potential "blockbuster" drugs, something is short supply from big pharma over the past few years. Whether due to inherent flaws in the "waiting for a blockbuster" drug development model or because the "low-hanging fruit" of small molecule drug development has been expended (or more likely because the diseases of aging garnering the most attention today are particularly intractable to pharmaceutical intervention, i.e., you can’t put eating right and regular exercise into pill form), the prospects for startups (particularly university-generated startups) may be rosier than might be expected even if patents become less important in protecting biologic drugs. This is because biologic drugs are more likely to be specifically targeted to a patient population or disease subtype and thus provide more effective treatment options, due to a better understanding of underlying biological causes and consequences of disease.

It is unlikely that Congress intended any of these results. It is equally unlikely that the promised benefits of biosimilar availability (and the expected massive cost savings, especially to the government) will be achieved were innovators to eschew patenting. But this is yet another consequence of (mis)applying our experience with small molecule drugs and the Hatch-Waxman regime to biosimilars, and another example of the past not reliably informing the future.