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Developing a Patent Strategy

Leading Lawyers on Drafting Effective Patents, Seeking Global Protection, and Navigating the America Invents Act

2015 EDITION

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Refashioning IP Asset Protection Strategies for Biotechnology and BioPharma Clients in View of the New Legal Realities of Subject Matter Eligibility

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Introduction

In the 1970s, the biotechnology industry was in its infancy. Many academic researchers were developing faster, more efficient ways to clone and characterize gene products of interest, and companies arose to provide practical applications of the new technology for pharmaceuticals, agriculture, and industry. Since then, the industry has experienced meteoric growth worldwide, but especially in the United States. The industry has produced scores of lifesaving products and methods, although development has been, and continues to be extremely expensive. The biotechnology industry has relied on the patent system to incentivize the discovery and development of groundbreaking innovations.

For the last thirty-five years, the legal framework behind the patent system (as provided by Congress) has supported biotechnological innovation through the patenting of isolated nucleic acid and proteins, new methods of treatment and diagnosis, and engineered microorganisms, plants, and animals. More recently, continuing developments in personalized medicine are literally transforming the way many serious diseases such as cancer are treated. Advances include the discovery and use of biomarkers (genetic or phenotypic characteristics of an individual or an individual's cells that predict whether the individual has a predilection to develop a certain disease or condition or is more or less likely to benefit from a particular treatment) companion diagnostics (assays to determine whether a given therapy will be effective in a given patient), and autologous cell therapies (engineering or stimulating a patient's own cells to fight a disease or condition, and then returning the cells to the patient). These advances will not only improve the efficacy and safety of patient treatment, but also will also reduce the costs associated with innovative new treatments, because only those patients who are likely to benefit from a given treatment will receive it. These advances, however, require enormous monetary investments by biotechnology and pharmaceutical companies, which the companies will make only if there is a possibility of a return on their investment—a possibility provided by patent protection.

Congress, through three major revisions of the patent statutes, has clearly intended that biotechnological subject matter should be eligible for patenting.

Likewise, the longstanding policies and practices of the United States Patent and Trademark Office (USPTO) have promoted patent protection for biotechnological innovation. However, in the last few years, the United States Supreme Court has set a new course, severely limiting the scope of patent-eligible subject matter in ways that have hit the biotechnology and biopharma industries hard. This chapter charts how we got to this point, and provides some ideas of how patent practitioners can continue to protect their biotech clients' innovations in the new regime.[1]

Recent Supreme Court Decisions Devalue Biotech Patents and Hamper New IP Asset Protection

My practice as a registered US patent attorney focuses on procuring, protecting, and defending intellectual property (IP) rights for innovators in the biotechnology industry, with an emphasis on pharmaceuticals. The impact of biotech innovation on health care is clear, but the cost of developing new drugs and targeting them to appropriate patients is enormous. The average cost of bringing a new drug to market has been estimated to be at least $1.2 billion.[2] It does not take an advanced degree in economics to understand that a drug developer must recoup that cost and make a profit to stay in business.

Biopharmaceutical companies, from small startups to large multinational corporations, rely on intellectual property protection to provide the market exclusivity needed to drive research and development (R&D). Indeed, the birth of the biotechnology industry can be tied to a key Supreme Court decision in 1980, which held that a living organism developed through genetic engineering was eligible for a patent.[3] For more than thirty years, biotechnology companies in the United States have brought lifesaving drugs, treatment methods, and diagnostic tests to

[1] *The views expressed herein are solely those of the author and do not represent the views of her law firm or of any of its clients. This paper does not constitute legal advice, which can only be given by taking into account individual issues affecting individual clients.*

[2] PHARMACEUTICAL RESEARCH AND MANUFACTURERS OF AMERICA, 2014 BIOPHARMACEUTICAL RESEARCH INDUSTRY PROFILE 28 (2014), *available at* http://www.phrma.org/sites/default/files/pdf/2014_PhRMA_PROFILE.pdf.

[3] *Diamond v. Chakrabarty*, 447 U.S. 303 (1980); *see also* Douglas Robinson & Nina Medlock, *Diamond v. Chakrabarty: A retrospective on 25 Years of Biotech Patents*, 17 INTELL. PROP. & TECH. L.J. 12, 12 (2005).

consumers through R&D investment leveraged by intellectual property.[4] Thousands of patents claiming isolated DNA, genetically engineered organisms, antibiotics, diagnostic tests, and methods of treatment have been granted by the USPTO, and upheld by the courts.

The duty to provide a system for patent protection in the United States was bestowed upon Congress in our Constitution,[5] and during the past thirty years, lawmaker intent has clearly supported broad patent subject matter eligibility under 35 U.S.C. § 101.[6] While certain subject matter has long been considered ineligible for patenting,[7] as early as 1952 Congress noted that "anything under the sun that is made by man" was eligible for patenting.[8] Up to and including major revisions under the America Invents Act in 2011,[9] Congress has not provided any indication suggesting an intent to limit subject matter eligibility for biotechnological inventions. Moreover, in the nearly thirty-five years since the *Chakrabarty* holding, the USPTO has issued thousands of patents directed to biotechnological innovations that have driven the commercialization of many blockbuster pharmaceuticals. However, the federal courts have now decided that Congress and the USPTO had it all wrong.

In the past three years the United States Supreme Court has called the previous thirty-plus years of subject matter eligibility for biotechnological innovation into doubt. First, in 2012, the Court decided in *Mayo Collaborative Services v. Prometheus Laboratories Incorporated* that therapeutic methods relating to "natural laws" are not patent eligible without an amorphous and ill-defined "something more."[10] The claims in *Mayo* involved a method for determining

[4] The development of such life-saving drugs is not limited to biotechnology companies in the United States. *See infra* notes 56–59.
[5] U.S. CONST. art. I, § 8, cl. 8.
[6] The Patent Statute states that: "[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." 35 U.S.C. § 101.
[7] Excluded subject matter includes laws of nature, natural phenomena, and abstract ideas. *See Diamond*, 447 U.S. at 309.
[8] S. REP. NO. 1979, 82d Cong., 2d Sess., at 5 (1952); H.R. REP. NO. 1923, 82d Cong., 2d Sess., at 6 (1952) (Senate and House Committee Reports accompanying the 1952 Patent Act).
[9] *See* Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (codified in various sections of 35 U.S.C.).
[10] *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1294–1302 (2012).

whether to adjust a patient's treatment based on a determination of the level of a metabolite in the patient's system:

> A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:
>
> a) *administering* a drug providing 6-thioguanine to a subject having said immune-mediated gastrointestinal disorder; and
> b) *determining* the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, *wherein* the level of 6-thioguanine less than about 230 pmol per $8x10^8$ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and *wherein* the level of 6-thioguanine greater than about 400 pmol per $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.[11]

The unanimous Supreme Court decided that the correlation between 6-thioguanine levels and therapeutic efficacy or toxicity was a "natural law" ineligible for patenting. The Court concluded that the "administering" and "determining" steps amounted to mere routine "pre-solution" activity. The "wherein" clauses, according to the Court, served merely to inform the doctor of the natural law, and to suggest a course of action.[12]

What if the course of action was more than a suggestion? Such a claim might have subject matter eligibility, but in view of a 2014 Supreme Court opinion, might not be enforceable. A claim in a related patent assigned to Prometheus Laboratories, Inc., which required actual treatment as opposed to merely suggesting it, was not part of the case, and remains valid.[13]

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[11] *Id*. at 1295 (emphases added).
[12] *Id*. at 1297.
[13] U.S. Patent No. 6,987,097 (filed Nov. 6, 2003) (claim 1: "A method for optimizing therapeutic efficacy in a subject in need thereof, said subject receiving a drug providing 6-thioguanine, said method comprising: (a) *determining* a level of 6-thioguanine in said subject; and (b) *increasing* the subsequent dose of said drug when said level of 6-thioguanine is less than a member selected from the group consisting of about 230, 240, 250, 260, 280, and 300 pmol per 8 x 108 red blood cells.") (emphasis added).

However, such a claim might be difficult or impossible to enforce because the steps of the claim would likely be carried out by two unrelated parties (for example, a clinical laboratory and a physician). Thus, no single party would directly infringe the claim. The Supreme Court recently held induced infringement of a method claim requires an initial determination of direct infringement.[14] In view of the Federal Circuit's precedent in *Muniauction*[15] that direct infringement requires all steps of a claim to be carried out by a single party, or parties that are clearly in privity with each other, a "divided infringement" claim may be unenforceable.

Then, in 2014, the Court followed up with a decision holding that isolated DNA is a "product of nature," and is thus ineligible for patenting.[16] In a case involving patents owned by Myriad Genetics, covering the BRCA1/2 genetic tests for susceptibility to breast and/or ovarian cancer, the unanimous Court held that claiming "isolated DNA" is not enough to confer patent eligibility,[17] but claiming cDNA (a DNA molecule created in the laboratory from a messenger RNA) might confer eligibility if the original genomic DNA contained introns.[18] The Court further pointed out that a claim reciting even small changes to the nucleotide sequence would likely confer eligibility.[19] Justice Thomas, writing for the Court, emphasized the narrow scope of the holding: "[w]e merely hold that genes and the information they encode are not patent eligible under §101 simply because they have been isolated from the surrounding genetic material."[20]

The USPTO Response to *Mayo* and *Myriad*

After a patent application is originally filed, the USPTO examines the application and determines whether to initially reject or grant the application. In response to important changes in patent law, the USPTO often issues guidelines to help patent examiners navigate the changes and make

[14] *Limelight Networks, Inc. v. Akamai Techs., Inc.*, 134 S. Ct. 2111, 2113 & 2118–19 (2014).
[15] *Muniauction, Inc. v. Thomson Corp.*, 532 F.3d 1318, 1329-30 (Fed. Cir. 2008). *Limelight* was remanded to the Federal Circuit, presumably for a reconsideration of the *Muniauction* holding. *See Limelight Networks, Inc.*, 134 S. Ct. at 2113.
[16] *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2019 (2013).
[17] *Id.* at 2116–19.
[18] *Id.* at 2119.
[19] *Id*. at 2119–20.
[20] *Id.* at 2120.

appropriate changes to examination procedure. Examiners are generally expected to rely on examination guidelines provided by the USPTO when making patentability determinations, even though such guidelines do not have the force of law.[21]

Since USPTO examination is the first level of scrutiny for any patent claim, the USPTO's reaction to *Mayo* and *Myriad* is particularly important. Initially, the USPTO reacted (or, according to many stakeholders, overreacted) to these decisions by issuing examination guidelines that went far beyond precluding patents on isolated DNA and methods relating to laws of nature.[22] The Initial Guidance applied to *any* composition of matter or method claims relating to one or more of the "judicial exceptions" (for example, laws of nature, natural principles, natural phenomena, or natural products). According to the Initial Guidance, an examiner determined whether a given claim involved a judicial exception, and if so, make the presumption that the claim was ineligible under 35 United States Code, Section 101 *unless* "the claim as a whole recited something *significantly different* than the judicial exception(s)," based on a twelve-factor balancing test.[23] The generality of the factors made their interpretation by USPTO examiners inconsistent and confusing, since the factors were not based on factual determinations, but instead required examiners to resort to intuition. Importantly, since subject matter eligibility is a threshold issue, examiners were asked to determine whether elements or steps in a claim were "well understood, purely conventional, or routine" *before* doing a search and conducting an analysis of novelty and non-obviousness.[24]

In response to substantial backlash from the patent community following release of the Initial Guidance, the USPTO went back to the drawing board. On December 16, 2014, the Office issued the 2014 Interim Guidance on Patent Subject Matter Eligibility under 35 U.S.C. § 101.[25]

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[21] *See Syntex (U.S.A.) Inc. v. U.S. Patent & Trademark Office,* 882 F.2d 1570, 1571 n. 3 (Fed. Cir. 1989).

[22] ANDREW H. HIRSHFELD, 2014 PROCEDURE FOR SUBJECT MATTER ELIGIBILITY ANALYSIS OF CLAIMS RECITING OR INVOLVING LAWS OF NATURE/NATURAL PRINCIPLES, NATURAL PHENOMENA, AND/OR NATURAL PRODUCTS (2014), *available at* http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf (hereinafter Initial Guidance).

[23] *Id.* at 3 (emphasis in original).

[24] *Id.* at 4.

[25] *See* 2014 Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74618 (Dec. 16, 2014) (to be codified at 37 C.F.R. pt. 1), *available at* http://www.gpo.gov/fdsys/pkg/FR-

Several aspects of the Revised Guidance are different from the Initial Guidance. The analysis begins with an inquiry as to whether the claim is "directed to a law of nature, a natural phenomenon or an abstract idea," rather than whether the claim merely "involves" a judicial exception.[26] As part of this analysis, the examiner is instructed to compare isolated elements of the claim suspected of being, e.g., a law of nature or a natural phenomenon to its actual counterpart in nature, to identify "markedly different" characteristics based on structure, function, and/ or properties.[27] If any such "marked difference" is found, the claim is directed to eligible subject matter and the analysis is complete. If markedly different characteristics cannot be identified, further analysis is made as to whether the claim as a whole recites "additional elements that amount to significantly more than the judicial exception."[28] Instead of the burdensome twelve-factor balancing test of the Initial Guidance, the USPTO has provided a broad spectrum of practical and tangible examples of both eligible and ineligible claims.

The Revised Guidance clearly defines the terms "directed to" and "markedly different." The "directed to" analysis largely turns on whether the claim, if allowed, would "tie up the judicial exception," such that it would pre-empt others in the field from using the law of nature, natural phenomenon or abstract idea. Moreover, the Revised Guidance provides that "[m]arkedly different characteristics can be expressed as the product's structure, function, and/or other properties," noting that "even a small change can result in markedly different characteristics from the product's naturally occurring counterpart … a product that is purified or isolated, for example, will be eligible when there is a resultant change in characteristics sufficient to show a marked difference from the product's naturally occurring counterpart."[29] The Initial Guidance required that differences be structural. Further distinguishing it from the Initial Guidance, the Revised Guidance instructs examiners to apply the "markedly different" analysis to only the nature-based elements in the claim, and when a claim recites a

2014-12-16/pdf/2014-29414.pdf (hereinafter Revised Guidance). "Interim," in that further revisions are expected after the period for public comment transpires on March 16, 2015.

[26] *Id.* at 74621.

[27] *Id.*

[28] *Id.*

[29] *Id.* at 74623.

combination of two or more natural products, to consider the combination, not each element individually.[30]

When a claim is determined to be "directed to a judicial exception" in the first part of the analysis, the examiner is then instructed to determine whether other elements recited in the claim add "significantly more" to the exception. This second part of the analysis asks whether the recited elements of the claim "considered both individually and as an ordered combination," add something significantly more than the judicial exception itself. The USPTO explicitly refers to this step as "a search for an 'inventive concept…, additional features to ensure that the claim describes a process or product that applies the exception in a meaningful way, such that it is more than a drafting effort designed to monopolize the exception."[31]

In theory, under the Revised Guidance the number of rejections for lack of subject matter eligibility should drop significantly. Moreover, the Revised Guidance sensibly instructs examiners to fully examine every claim, *e.g.,* for novelty, non-obviousness, enablement, and written description, even if a subject matter eligibility rejection has been made.[32]

In a separate "Nature-based Products" document available on the USPTO website,[33] the USPTO provides additional sample analyses for subject matter eligibility. Several of these are similar to examples provided in the Initial Guidance, but in many cases the examples reach the opposite conclusion. Notably, gunpowder is once again patent-eligible subject matter.[34] Purified proteins are deemed patent eligible if, for example, the purified protein has a different crystal structure, or possesses properties that are different from those of the impure protein.[35] Moreover, claims directed to antibodies possessing specific CDR sequences are patent eligible because, "unless the Examiner can show that this particular murine antibody exists in nature, this mere possibility does not bar the

[30] Revised Guidance, 79 Fed. Reg. at 74623.
[31] *Id.* at 74624.
[32] *Id.* at 74625.
[33] UNITED STATES PATENT AND TRADEMARK OFFICE, NATURE-BASED PRODUCTS (2014), *available at* http://www.uspto.gov/patents/law/exam/mdc_examples_nature-based_products.pdf.
[34] *Id.* at 1.
[35] *Id*. at 4–7.

eligibility of this claim."[36] According to this example, the burden appears to be on the examiner to prove that an antibody possessing the CDR sequences actually exists in nature.

The Revised Guidance and its supporting documents are surprisingly devoid of any diagnostic assay examples. Unconfirmed reports indicate that a future example set will be made available following decisions in various cases pending at the Federal Circuit.[37]

One of these cases, again involving BRCA1/2 patents owned by Myriad Genetics, was decided just one day after the publication of the 2014 Guidance.[38] In *Ambry Genetics*, a three-judge Federal Circuit panel held that six claims from three of Myriad's patents were ineligible for patenting as a matter of law, even though the issue before the panel was whether the district court correctly denied Myriad's request for a preliminary injunction.[39]

Two of the six claims were directed to diagnostic methods, namely methods for screening germline DNA from human subjects for alterations in the BRCA1 gene. Both claims recited the step of comparing a sample of a subject's DNA to that of the wild-type BRCA1 gene. The comparison in one claim is through detection of hybridization of the subject's sample to a DNA probe, and the comparison in the other claim is through DNA amplification and sequencing.[40] The panel determined that the "comparing" step was an abstract mental process, noting that the broad claims did not recite any specific purpose for the screening, and did not specify any particular alterations to be detected.[41] Hybridization, amplification, and sequencing were determined to be "well-understood, routine and conventional activity engaged in by scientists at the time…," actions that, according to the panel, were insufficient to render the claims as a whole patent-eligible.[42] In dictum, the panel inferred that limitations reciting specific alterations, or reciting

[36] *Id.* at 11–13.
[37] *See, e.g., Ariosa Diagnostics, Inc v. Sequenom, Inc.*, Fed. Cir. Appeal No. 2014-1139 (argued on November 7, 2014).
[38] *See Univ. of Utah Res. Found. v. Ambry Genetics Corp.*, No. 2:13-0064, at *1 (Fed. Cir. Dec. 17, 2014).
[39] *Id.* at *3.
[40] *Id.* at *10–11.
[41] *Id.* at *15.
[42] *Id.* at *17.

specific purposes such as "detection of risk of breast or ovarian cancer," might have affected their analysis.[43]

Four of the six claims recited compositions of matter, namely sets of DNA primers, small pieces of DNA that have sequences complementary to the human BRCA1 gene, for use in amplification and sequencing.[44] The panel concluded that the primers had the same structure as naturally occurring DNA,[45] and that they served the same function, "utiliz[ing] the innate ability of DNA to bind to itself."[46] Therefore the panel held the primer claims to be patent-ineligible.

The *Ambry Genetics* decision, as well as other decisions expected soon may result in modifications to the Revised Guidance, injecting even more uncertainty into how claims directed to biotechnological inventions will be examined at the USPTO.

Strategies to Protect Biotechnology Innovation after *Mayo*, *Limelight*, and *Myriad*

The *Mayo*, *Myriad*, and *Limelight* decisions have effectively devalued thousands of granted patents in the biotechnology industry. While the Revised Guidance provides examiners with considerably more leeway in evaluating claims, protection of new biotech innovations will be challenging, particularly in the areas of biomarkers, diagnostics, and personalized medicine. For example, a 2012 survey of about 1,000 granted US patents directed to methods of treatment and diagnosis found that 78.6 percent of the independent claims likely would have been found ineligible for patenting based on the *Mayo* holding.[47] Moreover, a recent survey of 1,000 patent applications directed to biotechnology inventions found that 40 percent had received a rejection under 35 United States Code, Section 101 due to subject matter that is

[43] *Univ. of Utah Res. Foundation*, No. 2:13-0064, at *15.
[44] *Id.* at *6.
[45] *Id.* at *7.
[46] *Id.* at *9.
[47] Elizabeth J. Haanes & Jaume M. Cànaves, *Stealing Fire: A Retrospective Survey of Biotech Patent Claims in the Wake of Mayo v. Prometheus*, 30 NATURE BIOTECHNOLOGY 758, 759 (2012).

allegedly ineligible for patenting under *Mayo* or *Myriad*.[48] The Revised Guidance is just that—guidance for patent examiners—and the USPTO in various public presentations has distinguished examiner guidelines from laws or regulations. Patent practitioners in the biotech space will be carefully monitoring the course of §101 rejections at the USPTO under the Revised Guidance and any upcoming modifications. For the time being, though, the likelihood of receiving claim rejections for lack of subject matter eligibility remains high.

What should patent applicants do? While large corporations might have the resources and time to fight the USPTO rejections through appeal at the Patent Trial and Appeal Board (PTAB) and eventually to the federal courts, such battles may not be financially realistic for academic institutions or startup or mid-level companies, where much of the innovation is taking place. Even without an appeal, drafting a fairly complex biotechnological patent application and prosecuting through issuance can cost upwards of $50,000 to $80,000, over the span of two to three years. Appealing to the PTAB and eventually to the Federal Circuit could easily cost five to ten times as much, and add three to five years to the process, with no assurance of success. As a result, many of tomorrow's lifesaving drugs and treatment methods may be left on the lab bench.

As is the case with most Supreme Court opinions, the *Mayo*, *Limelight*, and *Myriad* decisions are broad brushstrokes. For example, *Mayo* notes that a claim requires "something more" in addition to a recited "natural law," but exactly how much more remains an open question. Likewise, whether the Federal Circuit will reconsider the *Muniauction* decision on direct infringement in view of the Supreme Court's *Limelight* holding is an open question. Furthermore, despite Justice Thomas's statement that the *Myriad* decision is narrowly directed to "isolated DNA," the patent office has extended the holding to any claims that possibly read on "naturally occurring" substances. Patent practitioners cannot precisely advise clients until the case law is filled in with more specific decisions, or Congress

[48] MATTHEW B. MCFARLANE, TARA GUFFREY SHARP AND JOHN T. AQUINO, STOPPED AT THE THRESHOLD: THE PRACTICAL IMPACT OF THE SUPREME COURT'S *MAYO* AND *MYRIAD* DECISIONS ON BIOTECHNOLOGY PATENT PRACTICES S-16 (2014).

makes legislative changes to more precisely define patentable subject matter. All of this will take time. As a result, drafting and prosecution of patent applications with claims that might be interpreted to be directed to "judicial exceptions" will become increasingly complex and expensive.

Prosecution Strategies for Already Pending Applications

For the time being, for applications that have received a rejection under 35 U.S.C. § 101 for claims drawn to ineligible subject matter, waiting temporarily to see how the Revised Guidance will be amended and applied may be the best strategy. USPTO examiners applied the Initial Guidance very inconsistently, which is not surprising due to the fact that the Initial Guidance provided very little in the way of guidance. Responding to inconsistent rejections made under the Initial Guidance could muddy the record with arguments that may or may not comport with the Revised Guidance, or subsequent legal precedents. Examiners may agree to issue new, non-final office actions in view of the Revised Guidance, even if a final rejection had been issued. Therefore, try to contact the examiner before responding to a rejection made under the Initial Guidance.

However, subject matter eligibility rejections will continue, even under the Revised Guidance. Until the USPTO and the courts provide additional interpretations of *Myriad* and *Mayo*, as patent practitioners we must use a crystal ball and try to develop and implement myriad strategies that can be adapted to any number of possible scenarios. We cannot pick a single course of action and follow it. We must attempt to anticipate all the possible ways the Supreme Court holdings might be interpreted by the USPTO and courts, and adapt our applications and claims accordingly. With new applications we can devise and provide new types of disclosure to support the various scenarios, but for already filed applications, the options are much more limited.

As the USPTO has pointed out in many public presentations following the *Mayo* and *Myriad* cases, "the name of the game is the claim."[49] If the

[49] June Cohan, Legal Advisor with the USPTO's Office of Patent Legal Administration, Speech at the 2014 BIO IP & Diagnostics Symposium in Alexandria, VA (Sept. 26, 2014).

wording of a claim reads on a naturally occurring substance or recites a step that reads on a natural law, the claim will be rejected as being ineligible for patenting. In a notable recent example, a claim to a cloned mammal, based on the famous sheep "Dolly," was found to be ineligible for patenting because the claim covered a product of nature indistinguishable from the donor. The rejection was affirmed by the Federal Circuit.[50] An exemplary claim at issue recited: "A live-born clone of a pre-existing, nonembryonic, donor mammal, wherein the mammal is selected from cattle, sheep, pigs, and goats."[51] The applicants argued that a cloned mammal such as Dolly the sheep would have phenotypic differences from the donor due to environmental differences, and would definitely have genotypic differences, *e.g.,* different mitochondrial DNA, as the mitochondria would be provided by an enucleated oocyte into which the donor somatic cell nucleus was implanted.[52] The Federal Circuit did not disagree with these arguments, but pointed out neither of the stated differences were recited limitations in the claims.[53] If the specification had provided support, precise limitations could have been added to intermediate claims, and would not limit the scope in any commercially significant way. However, unless support for claims of intermediate scope was available in the specification, the applicant would either be out of luck, or would need to narrow the claims drastically, such that they could be easily designed around, reducing the value of the patent.

In arriving at appropriate claim language during prosecution, it is always a good strategy to plan examiner interviews early and often. Interviews can be a negotiation, and lots of different ideas and proposals can be discussed, without putting extensive details on the record. Examiners are feeling their way through the new legal precedents just as practitioners are, and in many cases examiners will welcome new ideas and explanations. For complex technologies, consider bringing an inventor to the interview to explain the technology. Examiners have considerable technical expertise, and in many cases appreciate not having to talk solely to a lawyer. Make certain, however, that the inventor is prepared, and understands what to say, and

[50] *See In re Roslin Inst.,* 750 F.3d 1333 (Fed. Cir. 2014).
[51] *Id.* at 1335.
[52] *Id.* at 1336-37.
[53] *Id.*

more importantly, what not to say. I have found it easiest to have the examiner and the examiner's supervisor present if at all possible, since the more senior USPTO personnel will likely be the decision makers once a written response is filed. Also, face-to-face interviews at the USPTO are typically more effective than telephone interviews. Do not take interview practice lightly—practitioners need to be extremely well prepared for the interview. Indeed, for important applications, it is not a bad idea to have a "moot" practice run prior to the actual interview. Always do a practice interview if you are bringing an inventor or other non-lawyer representative of the client. Find colleagues who can review the record and act as the examiner, and tease out any weaknesses in your arguments before you talk to the actual examiner. Finally, keep in mind that examiners are not bound by statements and agreements made during the interview—it is always good to follow up with a written response as soon as possible after the interview, while it is still fresh in the examiner's mind, and before the examiner changes his or her mind!

Drafting Strategies for New Applications

Many patent prosecutors have been caught off guard with respect to existing applications, as have the owners of granted patents obtained prior to the *Mayo*, *Limelight*, and *Myriad* decisions. The drafting conventions of the past may not be adequate in a post-*Mayo* and post-*Myriad* world. Luckily, neither the USPTO nor the US courts require literal basis in the specification for particular claim language, so for pending applications, eligible claim language can potentially be crafted even if it is not literally present in the specification as filed. In the past, terms such as "isolated" served as terms of art, signifying the claim specifically excluded naturally occurring substances.[54] At least for now, resorting to such terms will not be sufficient. Terms such as "purified," "recombinant," "contained in a vector," "synthetic," or "non-naturally-occurring" may or may not pass muster, depending on how (or whether) the terms are defined in the patent's specification, or how the USPTO and courts choose to interpret the terms. Given the current uncertainties in the law, it makes sense to have a palette of terminology available to meet changing expectations. Likewise, it appears from the *Mayo* opinion that method claims including a specific

[54] *See, e.g., Ass'n for Molecular Pathology v. USPTO*, 653 F.3d 1329, 1350–54 (2011).

action (post-solution activity) as a result of a recited "natural law" might be subject matter eligible.[55] However, care must be taken to write a claim that can be directly infringed by a single party. For example, a clinical laboratory could "advise" or "instruct" a health care provider to administer a certain therapy in view of characteristics of the patient (drug levels, the presence of a biomarker, or gene expression levels), or a health care provider could "submit" patient samples to a clinical laboratory for measurement of a certain parameter, and then treat the patient based on the results.

Unfortunately, many of the claiming conventions that biotechnology patent practitioners have successfully relied upon for the last thirty years to claim biotechnological products and processes are out the window in the United States. We can and will devise new types of claims, one or more of which might protect biotechnology innovations. For now, however, we do not know exactly how to proceed, so any and all possibilities should be considered. At the same time, the existing strategies cannot be abandoned entirely, because the requirements for patent eligibility in other important jurisdictions have not changed. For example, "isolated DNA" remains statutory subject matter for patenting in Europe,[56] Canada,[57] Japan,[58] and Australia.[59] As one possible strategy to address requirements in different jurisdictions, I define "isolated," as in "an isolated polynucleotide," broadly to include anything that has been removed from its natural milieu (which still confers subject matter eligibility outside the US), but note that "non-naturally occurring" substances are a subset of "isolated" substances. "Non-naturally occurring," in turn, can be defined to explicitly exclude those substances that are considered "naturally occurring," such as genomic

[55] *See Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1293–94 (2012).
[56] *The European Patent Convention: Rule 27*, EUROPEAN PATENT OFFICE, http://www.epo.org/law-practice/legal-texts/html/epc/2013/e/r27.html (last visited Feb. 6, 2015) ("Biotechnological inventions shall also be patentable if they concern: (a) biological material which is isolated from its natural environment or produced by means of a technical process even if it previously occurred in nature.").
[57] *Monsanto Canada Inc v. Schmeiser*, [2004] 1 S.C.R. 902 (Can.) (genes, once isolated or developed, and single cells containing these genes, are patentable).
[58] JAPAN PATENT OFFICE, EXAMINATION GUIDELINES FOR PATENT AND UTILITY MODEL IN JAPAN pt. II, § 1.1, *available at* http://www.jpo.go.jp/tetuzuki_e/t_tokkyo_e/Guidelines/2_1.pdf ("if things in nature such as chemical substances or microorganisms have been isolated artificially from their surroundings, then those are creations and considered to be a statutory invention.").
[59] *See D'Arcy v. Myriad Genetics Inc.*, [2014] FCAFC 115 (2014) (claims to isolated DNA are statutory subject matter in Australia).

DNA. An appropriate definition consistent with the subject matter of the application, and as many specific examples of non-naturally occurring species as possible, should be provided. By providing disclosure in the specification to allow a claim to read on *only* those substances that are considered to be non-naturally occurring, and providing a sufficient number of species to demonstrate "possession" of the subgenus of non-naturally occurring substances,[60] the USPTO and the courts might find such a claim to be eligible for patenting.

We can draft new patent applications to incorporate disclosure that can provide support for any number of claiming strategies, and with a bit of creativity and careful scrutiny of pending applications, we can devise claims that will protect our clients' innovations. For already granted patents, especially where no child applications remain pending, finding solutions to allow enforcement and/or licensing of the patent are more circumscribed. In some instances, the claims may be open to various different interpretations that may provide subject matter eligibility. In other instances, e.g., where no related applications remain pending, practitioners may want to recommend the possibility of filing for reissue of the patent.[61]

Additional Strategies to Protect Biotechnological Innovations—Not too Narrow, Not too Broad, Just Right

When drafting claims for biotechnological inventions, practitioners traditionally have tried to draft the broadest set of claims possible to benefit from the expansive protective scope of their clients' inventive contributions. Those practitioners have likewise drafted exceptionally broad specifications to support such claims. To support extremely broad claims, some biotechnology applications might include laundry lists reciting every possible species within any recited genus, such as hundreds of polypeptide fragments, every dosage of a therapeutic that might eventually be used in the clinic, or every possible formulation for the therapeutic, all before any research has been done on any of these variables. While we do not want to overly limit the scope of protection our clients are entitled to, in many cases overly broad claims and

[60] *See Regents of the Univ. of Cal. v. Eli Lilly & Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997).
[61] "A patentee may file for reissue of a granted patent if the patent is "deemed wholly or partly inoperative or invalid, by reason of a defective specification or drawing, or by reason of the patentee claiming more or less than he had a right to claim in the patent." 35 U.S.C. § 251.

supporting disclosures can be detrimental in the long run. It is imperative for patent practitioners to understand the business objectives of their clients, and carefully fashion patent strategy to promote those objectives. The scope of applications cannot be too broad or too narrow, but must be just right—and should provide ample flexibility in the specification to go in a different direction upon further development of the law.

For instance, exceptionally broad claims often inadvertently encompass, or read on the "judicial exceptions" as discussed earlier. For example, a method claim that includes a correlation of a clinical outcome to a biomarker found in a patient, no matter how that biomarker is measured, might be rejected, because existence of the biomarker could be determined without any specific human intervention.[62] Likewise, a broad claim to an isolated substance such as a nucleic acid, protein, or antibody, could be interpreted to cover naturally occurring instances of that substance, even if no naturally occurring instances are actually known. The Revised Guidance does appear to put more of a burden on the examiner to prove that a claim reads on a naturally occurring substance, but it remains to be seen how the guidance will be applied, and whether the PTAB and the courts will agree.

Aside from subject matter eligibility, exceptionally broad claims can inadvertently read on the prior art, and exceptionally broad disclosures can inadvertently create prior art that could preclude patents to future refinements of an invention—patents that could enjoy a longer patent term. In the pharmaceutical space, bringing a drug to market is a lengthy prospect given the time it takes to complete clinical trials. Indeed, by the time of product release, patents granted from earlier-filed applications may be close to expiration. Thus, strategies to extend patent exclusivity for marketed drugs can be extremely important. Biotechnology innovation often starts as generalities which are then refined and improved on in subsequent rounds of R&D. For example, an initial discovery might identify a target molecule in cancer cells, and show that inactivation of that target molecule can control growth of the cancer cells. Typically, a

[62] *See Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289, 1303 (2012) ("And the [metabolite measurement] step could be satisfied without transforming the blood, should science develop a totally different system for determining metabolite levels that did not involve such a transformation.").

patent application would be filed related to the initial discovery. A subsequent discovery, three to five years later, might identify specific target antagonists that can inactivate the target molecule with unexpectedly high potency. A new patent application could then be filed on the specific target antagonists, buying three to five years of additional patent term for a potential product, but only if the claims in the later-filed application are novel and nonobvious over the earlier filing. Those extra three to five years of patent term could be worth millions or even billions of dollars for a blockbuster drug. To give the later filings the best possible chance of success, the earlier patent application filings should be drafted concisely, to avoid creating prior art for possible later discoveries. While a more circumscribed earlier filing will limit the claim breadth that can be obtained in that filing, the tradeoff is likely well worth the business risk for the client, and can be explained in that context. The life cycle of a biopharmaceutical can easily extend well beyond the expiration date of an earlier-filed patent.

Fashioning Alternative IP Asset Strategies to Promote Client Objectives

In some cases, companies may choose to forego patent protection altogether. Often the innovation behind biotechnological inventions can involve as much "art" as "science." For example, developing the perfect cell culture medium and conditions to maximize product yield, or the perfect combination of amino acid substitutions in an antibody sequence to maximize activity. In such instances, companies may try to protect their inventions as trade secrets as opposed to filing patent applications. When patenting is necessary, such as in situations where the technology could be easily reverse engineered, or when the technology must be disclosed to a regulatory agency such as the FDA, obtaining patents in critical areas such as biomarkers, diagnostics, and personalized medicine, at least in the short run, will become much more difficult and expensive. As practitioners, we can develop updated drafting strategies, and can advise our clients that obtaining a few good patents may be a better strategy than trying to get a patent on every minor improvement. The tendency to want to file applications early to allow for publishing may need to be rethought. Filing early can mean that a disclosure will be broader and more prophetic, but in some business situations, such early filings are important, for example,

where disclosure of the technology to potential investors is anticipated. Patent practitioners must strive to understand their clients' business objectives, and develop IP strategies that work for those objectives.

Conclusion

The US judiciary has become increasingly active in shaping patent law, in some instances obscuring Congress's initial intent. In the case of subject matter eligibility, the only recourse may be for Congress to act. One possibility would be for Congress to revise 35 United States Code, Section 101 to better define the statutory subject matter eligible for patenting. If Congress instead allows the courts to narrowly circumscribe subject matter eligibility, to promote continued innovation in biotechnology, they may need to come up with a new way to provide biotechnology companies with at least some measure of exclusivity for their innovations. Otherwise, the innovations may wither and die, and lifesaving drugs, diagnostics, and therapies may never make it to market.

As a recent cancer survivor, this has become personal for me. New, innovative methods of testing gene expression allowed my health care team to personalize and streamline my treatment. I received the treatment I needed—no more, no less. The technology behind the methods required years of testing and validation on thousands of samples prior to regulatory approval. The expense of such research would be prohibitive without the ability to recoup the investment. Traditional cancer therapy is much more like a sledgehammer than a scalpel. One of my doctors told me about a recent study in a population of patients who were originally thought to derive no benefit from a particularly aggressive form of chemotherapy. The study showed that 25 percent of the patients in that population *did* benefit from the therapy. Problematically, the study did not provide any way of identifying which patients fell into that 25 percent. She said in view of the study, she had no choice now but to recommend the therapy to 100 percent of patients in that category, even when only a quarter of them would actually benefit. The technologies exist to identify that 25 percent of patients, but if biotechnology companies have no incentive to invest millions of dollars in research and development—an incentive provided through patent protection—the research will never come to fruition. It is that simple.

Stakeholders in the biotechnology industry can and do have a voice. The outcry following the release of the Initial USPTO Guidance is a clear example. The USPTO was clearly listening, and they continue to solicit feedback from practitioners. Similarly, Congress will be listening.

Meanwhile, IP attorneys are left attempting to help our biotech and pharmaceutical clients protect their IP assets in the best ways possible. To do this, it is important to:

- know your clients' businesses;
- understand the technology you are trying to patent to the level that you can find the "sweet spot" in scope—not too narrow, not too broad;
- give your clients honest and thoughtful advice, even if it is not what they want to hear;
- critically read the case law. Often the abridged summaries on law blogs are not the only analysis, or even the best analysis. In prosecution, you cannot formulate good arguments if you do not understand the underlying law; and
- become involved. The recent public outcry over the USPTO's Initial Guidance shows that the public has a voice. If concerned practitioners had not raised their voices, nothing would have changed.

Key Takeaways

- Until the courts provide additional guidance, develop and implement myriad strategies that can be adapted to any number of possible scenarios. Anticipate possible ways the Supreme Court holdings might be interpreted by the USPTO and courts, and alter applications and claims accordingly.
- Do not rely on the drafting conventions of the past, which may not provide the support needed for claims in a post-*Mayo* and post-*Myriad* world. For example, in the US resorting to term "isolated," to distinguish DNA and proteins from their naturally occurring counterparts, will not be sufficient.
- Provide disclosure in your specifications to "carve out" naturally occurring substances, thus allowing a claim to only those substances that are non-naturally occurring.

- In certain business contexts, rethink the tendency of filing applications too early.

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Acknowledgment: *I am extremely grateful to my partners, David Jinkins and Matthew Braunel, for a critical review of the manuscript and for being wonderful colleagues. Finally, a big thanks to Justin Mulligan for masterful cite checking and Blue Book formatting.*

Dedication: *This chapter is dedicated to my beloved husband, Cecil Chen, whose love and support drive everything that I do.*

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