

Life Sciences Patent Eligibility “101”: *Mayo at Five*



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LIFE SCIENCES PATENT ELIGIBILITY “101”: MAYO AT FIVE

Just over five years ago, the Supreme Court began reshaping the concept of patent-eligible subject matter in the life sciences with its decision in *Mayo v Prometheus*.¹ Decisions following *Mayo* – from the Supreme Court to the district courts to the USPTO – have further changed the paradigm for determining what inventions in the life sciences field are eligible for patent protection in the United States.

The evolving jurisprudence regarding patent eligibility under 35 U.S.C. § 101 has raised questions for many in the patent bar and in the life sciences industry. At least one biopharmaceutical organization (PhRMA) has highlighted the importance of this developing area of law, explaining “[p]atents are critical for biopharmaceutical innovation given the research-intensive nature of this sector and the substantial upfront investment needed to discover and develop products that meet FDA approval requirements.”² This organization, among others in the industry, has voiced concerns that the present direction of Section 101 jurisprudence “has made it harder for companies to consistently rely on the U.S. patent system to protect their innovations,” putting the United States at a disadvantage in global markets.³

Here, we provide an overview of the state of life science patent eligibility law just over five years post-*Mayo*. First, we lay out the path leading to today’s legal framework for patent-eligible subject matter in the life sciences. Second, we examine key Federal Circuit and district court decisions to see how courts are currently treating different types of life sciences patent claims with respect to patent eligibility. And, in this context, we also discuss the USPTO’s examples of patent-eligible and ineligible claims as data points for how the USPTO has interpreted and is applying the Supreme Court’s legal framework.⁴

We conclude that patterns have started to emerge in the post-*Mayo* jurisprudence. Courts have nearly universally found “diagnostic” method claims—those that only include steps for diagnosing a disease or identifying a characteristic in a patient—to be patent ineligible. Method of treatment claims, whether with or without a diagnosis step, have fared better, but some district court decisions have found such claims ineligible or, at least, “directed to” ineligible subject matter. In the process, these courts have fueled concerns of some in the pharmaceutical industry who fear nearly all pharmaceutical method of treatment claims could be at risk because, at some level, all treatments are based on natural phenomenon.⁵ Cases involving challenged composition of matter claims have likewise skewed towards ineligibility, albeit in a

¹ *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012)

²https://www.uspto.gov/sites/default/files/documents/comments_PHRMA_Jan182017.pdf;
<http://www.corpcounsel.com/id=1202774015808/At-Stanford-Patent-Experts-Sound-Off-on-Section-101?mcode=0&curindex=0&curpage=ALL&slreturn=20170610202429>

³*Id.*;https://www.law360.com/ip/articles/939165/tech-pharma-divided-over-section-101-challenges-post-alice?nl_pk=7f45793d-94ac-4cab-82b6-68c62c2735c9&utm_source=newsletter&utm_medium=email&utm_campaign=ip.

Outside of the life sciences field, the American Intellectual Property Association has also stated its “concern[s] that recent section 101 jurisprudence has put the United States at risk of falling behind the patent system of other developed countries.” https://www.uspto.gov/sites/default/files/documents/comments_aipla_jan182017.pdf

⁴See https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf;
<https://www.gpo.gov/fdsys/pkg/FR-2014-12-16/pdf/2014-29414.pdf>

⁵See https://www.uspto.gov/sites/default/files/documents/comments_PHRMA_Jan182017.pdf at 5-6.

small number of case. Finally, and in contrast to the other categories, claims directed to laboratory techniques and methods of manufacture have, thus far, emerged generally unscathed.

BILSKI, MAYO, MYRIAD, AND ALICE, IN BRIEF

The statutory prerequisite for patent eligible subject matter is codified in 35 U.S.C. § 101, which states “[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.” In the late 1970s and early 1980s, the Supreme Court’s decisions in § 101 cases such as *Diamond v. Diehr*⁶ and *Diamond v. Chakrabarty*⁷ began a period of over three decades where courts took a broad view of what constitutes patent eligible subject matter for life science-related patents. The Federal Circuit during that period applied the machine-or-transformation test to evaluate whether a process was patent eligible. Under this test, a process was patentable if it (1) was tied to a particular machine or apparatus, or (2) transformed a particular article into a different state or thing. In the context of composition of matter claims, during this era, the USPTO regularly issued patent claims directed to isolated genetic material.⁸ The breadth of Section 101 law during this period prompted some to posture that § 101 was no longer a meaningful limitation and essentially a “dead letter.”⁹

In 2010, the Supreme Court began reshaping patent-eligibility jurisprudence in *Bilski v. Kappos*.¹⁰ There, the Supreme Court analyzed the machine-or-transformation test in the context of a patent to a business method for hedging risk. In holding the claimed invention patent ineligible, the Court rejected the machine-or-transformation test as the sole test of patent eligibility under § 101.¹¹ The Court held that the claims at issue were invalid because they were directed to the unpatentable abstract idea of hedging risk and added only token post-solution components.¹² Although not a life sciences decision, the Court believed that the machine or transformation test “would create uncertainty as to . . . advanced diagnostic medicine techniques” among other categories of technologies from the “Information Age.”¹³

In 2012, the Supreme Court’s decision in *Mayo v. Prometheus*¹⁴ further blurred the boundaries of patent eligible subject matter, this time in the context of life sciences. In *Mayo*, the Court considered claims related to the use of thiopurine drugs to treat patients with gastrointestinal autoimmune diseases. Doctors had long been treating autoimmune diseases with thiopurine drugs but had difficulty determining the ideal dose, i.e., balancing efficacy and potential side effects, because patients metabolize the drugs differently. Prometheus identified correlations between thiopurine metabolite levels in the blood and the likely resulting efficacy and side effects. Prometheus’ patents claimed methods of (1) administering thiopurine drugs, (2)

⁶ 450 U.S. 175 (1981).

⁷ 447 U.S. 303 (1980).

⁸ See <http://www.ipwatchdog.com/2010/05/04/kappos-talks-patent-reform-and-gene-patents-at-bio-convention/id=10382/>

⁹ See Peter M. Brody and Jennifer Kwon, *Social Media and Patent Eligibility*, Social Media Law & Policy Report, Bloomberg BNA (March 24, 2015).

¹⁰ 561 U.S. 593 (2010).

¹¹ *Id.* at 603-604.

¹² *Id.* at 612.

¹³ *Id.* at 605.

¹⁴ *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 566 U.S. 66 (2012).

determining the levels of thiopurine metabolites in the patient's blood, and (3) a "wherein" step describing the metabolite concentrations required to produce efficacy but avoid side effects.

The *Mayo* Court introduced a new two-step framework for determining patent eligibility. Under the *Mayo* test, courts must first determine whether claims are directed to a patent ineligible concept, i.e., laws of nature, natural phenomena, or abstract idea. If so, courts must then search for an "inventive concept" by determining whether additional elements "transform the nature of the claim" into a patent-eligible application.

Using this new analysis, the *Mayo* Court found Prometheus' patent claims ineligible. Under the first step, the Court found "Prometheus' patents set forth laws of nature – namely, relationships between concentrations of certain metabolites in the blood and the likelihood that a dosage of a thiopurine drug will prove ineffective or cause harm."¹⁵ Regarding the second step, the Court found that the recited "administering," "determining," and "wherein" steps merely inform "doctors interested in the subject about the correlations that the researchers discovered" and were not "sufficient to transform the nature of the claim."¹⁶ Importantly, the administering step "simply refers to the relevant audience, namely doctors who treat patients with certain diseases with thiopurine drugs."¹⁷ In addition, the "wherein" clause, at most, added a suggestion that those doctors consider the test results when making their treatment decisions.¹⁸ The framework set forth in *Mayo* recalibrated the starting point for patent eligible subject matter analysis, but some commentators complained that the Court had not provided enough guidance on how the test should be applied.

The year after *Mayo*, the Supreme Court revisited § 101 in *Association for Molecular Pathology v. Myriad Genetics*, this time in the context of composition claims.¹⁹ Myriad had discovered the location and nucleotide sequences of two genes associated with predisposition to breast and ovarian cancers, the BRCA1 and BRCA2 genes. The claims at issue were directed to isolated DNA with nucleotide sequences found in a typical BRCA1 or BRCA2 gene, or to isolated cDNA with the nucleotide sequences found in the exons of the a typical BRCA1 or BRCA2 gene.

The *Myriad* Court found that the claims to isolated DNA were not patent eligible, but the claims to cDNA were patent eligible.²⁰ Because these were not method claims, the Court did not apply *Mayo*, but instead framed the inquiry as deciding whether the claims covered a product of nature, and were thus patent ineligible, or claimed a new and useful composition of matter with "markedly different characteristics from any found in nature" that could enjoy patent protection.²¹ The Court found the claims to isolated DNA not patent eligible because "Myriad did not create or alter any of the genetic information encoded in the BRCA1 and BRCA2 genes. The location and order of the nucleotides existed in nature before Myriad found them."²²

¹⁵ *Id.* at 77.

¹⁶ *Id.* at 78.

¹⁷ *Id.*

¹⁸ *Id.*

¹⁹ *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013).

²⁰ *Id.* at 2111. In the underlying decision, the Federal Circuit also held certain of Myriad's diagnostic method claims involving the BRCA1 and BRCA2 genes ineligible under Section 101. Myriad did not include the method claims in its petition for certiorari, and the Supreme Court thus did not address them.

²¹ *Id.* at 2117.

²² *Id.* at 2116.

The Court held that “genes and the information they encode are not patent eligible under § 101 because they have been isolated from the surrounding genetic material.”²³ In contrast, the Court found cDNA patent eligible because its exon-only sequence, without introns, does not exist in nature and thus is “not naturally occurring.”²⁴ According to the Court, a lab technician “unquestionably creates something new when cDNA is made.”²⁵ Although it spared the cDNA claims, the Court’s decision finding DNA patent ineligible under § 101 upended decades of USPTO practice allowing such claims.

The Court did suggest that method claims related to Myriad discovery may be patent eligible. As the Court noted, there were no method claims before the Court and the case did not involve new applications of knowledge about the BRCA1 and BRCA2 genes. But, “as the first party with knowledge of the [BRCA1 and BRCA2] sequences, Myriad was in an excellent position to claim applications of that knowledge.”²⁶

The Supreme Court addressed patent eligible subject matter again in 2014 in *Alice Corp v CLS Bank*.²⁷ The *Alice* court reaffirmed the *Mayo* two-step framework in determining that patent claims directed towards a scheme for using a third party to mitigate settlement risk were drawn to a patent ineligible abstract idea.

Over the past five years, in the wake of these decisions, there has been nearly 500 decisions in federal district courts involving patent eligibility challenges under § 101. In contrast, there were only 25 decisions involving patent eligibility challenges in the prior 10 years. Noticeably, there has been a shift as to when parties are challenging patent eligibility in the past five years with more parties challenging early on in litigation through motions to dismiss. For example, in 2016, out of the 184 decisions relating to patent eligibility, 111 of those decisions were the result of dismissal motions, whereas 59 of those decisions were from motions for judgment on the pleadings and 11 were from summary judgment motions.

THE IMPACT OF *MAYO* AND *MYRIAD* ON SPECIFIC CATEGORIES OF LIFE SCIENCES PATENT CLAIMS

Following the Supreme Court’s new guidance on patent eligibility, the Federal Circuit, district courts, and USPTO have attempted to further define the contours of the § 101. Within the life sciences, courts have given varied treatment to patent claims on diagnostic methods, methods of treatment using drugs or products, laboratory techniques, and compositions of matter. We discuss the significant cases and USPTO guidance in each of those areas in turn.

“DIAGNOSTIC” METHODS CLAIMS

With the ever-growing need for healthcare in the United States, diagnostic tests are increasingly used to identify disease and aid physicians in identifying appropriate, often personalized, courses of treatment. Patent claims directed towards diagnostic methods have frequently been the focus of patent eligibility challenges within the life sciences industry since the Supreme Court’s decision in *Mayo*.

Courts have consistently found diagnostic method claims patent ineligible, often finding the claims directed to interactions within the body that the courts characterize as laws of nature or naturally occurring

²³ *Id.* at 2120.

²⁴ *Id.* at 2119.

²⁵ *Id.*

²⁶ *Id.* at 2120.

²⁷ *Alice Corp. Pty. v. CLS Bank Int’l*, 134 S. Ct. 2347 (2014).

phenomenon. In particular, the Federal Circuit has gone 4 for 4 in invalidating these types of claims. This has left some to question to what extent patent claims to diagnostic methods are patentable.²⁸ While diagnostic method claims have fared poorly in the post-*Mayo* world, most of the claims found ineligible have also been broad, and it remains an open question whether a narrowly-tailored diagnostic method claim could survive the two-part *Mayo* test.

In 2014, the Federal Circuit addressed the eligibility of additional Myriad Genetics patent claims related to the BRCA1 and BRCA2 genes in *In re BRCA1- and BRCA2- Hereditary Cancer Test Patent Litigation*.²⁹ After the Supreme Court decision, Myriad sued Ambry Genetics Corp. for infringement of numerous claims not addressed in the Supreme Court decision or in the underlying Federal Circuit decision. The two method claims at issue recited methods of identifying a mutation in a patient's BRCA1 gene by comparing the patient's BRCA sequences with wild-type BRCA sequences. The claims required that the comparison be accomplished by specific laboratory techniques, either through amplifying the subject's BRCA1 gene using a set of primers and sequencing, or by using a probe to detect certain alleles in the subject.

The Federal Circuit declined to decide whether *Mayo* was factually on point but found the claims ineligible as directed to an abstract idea under the *Mayo/Alice* test. In the first *Mayo/Alice* step, the Court found that the method claims were "directed to the patent-ineligible abstract idea of comparing BRCA sequences and determining the existence of alterations," which "require merely comparing the patient's gene with the wild-type [sequences] and identifying any differences that arise."³⁰ The court believed that the number of comparisons was unlimited and would cover "yet-undiscovered alterations" and expressed a resulting concern that "allowing a patent on the comparison step could impede a great swath of research relating to the BRCA genes, and . . . allow these basic building blocks of scientific research to be monopolized."³¹ As to the second *Mayo/Alice* step, the court found that the elements describing the way in which the sequences are compared (via probe or via amplification and sequencing) "set forth well-understood, routine and conventional activity engaged in by scientists at the time of Myriad's patent applications."³² The court held that these elements did not add "enough" to make the claims patent eligible because "nothing is added by identifying the techniques to be used in making the comparison because those comparison techniques were . . . techniques that a scientist would have thought of when instructed to compare the two sequences."³³

The Federal Circuit again found diagnostic claims ineligible under § 101 in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*³⁴ The inventors in *Ariosa* discovered that maternal blood plasma harbored a small amount of non-cellular DNA that the fetus inherited from its father ("cffDNA"). Based on this discovery, Sequenom developed a prenatal diagnostic test that used the maternal blood plasma, previously discarded as medical waste, to determine a fetus's gender and identify genetic defects, thereby avoiding the risks of previous techniques that obtained samples directly from the fetus or placenta. Sequenom's patent claimed methods of using cffDNA. For instance, claim 1 included the steps of (1) amplifying the cffDNA contained in a sample

²⁸ <https://www.gpo.gov/fdsys/pkg/FR-2016-10-17/pdf/2016-24888.pdf>

²⁹ *In re BRCA1- and BRCA2- Hereditary Cancer Test Patent Litigation*, 774 F.3d 755 (Fed. Cir. 2014).

³⁰ *Id.* at 763.

³¹ *Id.* at 764.

³² *Id.*

³³ *Id.*

³⁴ *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 788 F.3d 1371 (Fed. Cir. 2015).

of plasma from a pregnant female and (2) detecting the paternally inherited cffDNA. The remaining claims required the amplifying or detecting steps to be performed by specific techniques.

The Federal Circuit found these claims ineligible applying the two-step *Mayo/Alice* framework. On the first step, the court found that the “existence of cffDNA in maternal blood is a natural phenomenon” and that the claimed methods started with cffDNA taken from maternal plasma and ended with paternally inherited cffDNA.³⁵ Because it “begins and ends with a natural phenomenon,” the court found that each claim was “directed to matter that is naturally occurring.”³⁶ On the second step, the court found that the additional elements of the claimed methods did not amount to “an inventive concept that transform[ed] the natural phenomenon of cffDNA into a patentable invention.”³⁷ The court found the additional steps of preparing, amplifying, and detecting paternally-derived cffDNA, including polymerase chain reaction (PCR) techniques, to be “well-understood, conventional and routine” steps, appended to a natural phenomenon.³⁸ “Because the method steps were well-understood, conventional and routine, the method of detecting paternally inherited cffDNA is not new and useful. The only subject matter new and useful as of the date of the application was the discovery of the presence of cffDNA in maternal plasma or serum.”³⁹

Notably, Judges Linn (in concurrence), Dyk, and Lourie (both in denying rehearing en banc) all suggested that they did not agree that the *Sequenom* claims should be patent ineligible but felt bound to reach that decision based on *Mayo*.⁴⁰ As Judge Lurie explained, he “felt that claims should not be patent-ineligible on the ground that they set forth natural laws or abstractions” because “it is unsound to have a rule that takes inventions of this nature out of the realm of patent-eligibility on grounds that they only claim a natural phenomenon plus conventional steps.”⁴¹

Last year, in *Genetic Tech. Ltd. v. Merial LLC*, the Federal Circuit found patent claims to a method for amplifying and analyzing correlations between different regions of DNA ineligible under §101.⁴² The inventor there discovered that coding regions of a gene may be linked to non-coding regions located either within that gene or elsewhere in the genome. As a result, the inventor realized that the alleles of a particular gene could be detected by looking at the non-coding regions known to be linked with the gene, instead of looking directly at the coding regions. The representative claims considered by the Federal Circuit comprised two steps: (1) amplifying non-coding region DNA known to be linked to coding region DNA and (2) analyzing the amplified non-coding DNA to detect the coding region allele of interest.

The Federal Circuit found the claims ineligible under the Supreme Court’s two-step *Mayo/Alice* test. First, the Federal Circuit found that the claims were directed to a “law of nature”: the linkage between non-coding and coding sequences and the tendency of such non-coding DNA sequences to be representative of the linked coding sequences.⁴³ The court found that “just as the relationship at issue in *Mayo* was entirely a consequence of the body’s natural processes for metabolizing thiopurine, so too is the correlation here

³⁵ *Id.* at 1376.

³⁶ *Id.*

³⁷ *Id.*

³⁸ *Id.* at 1377.

³⁹ *Id.*

⁴⁰ *Id.* at 1380; *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*, 809 F.3d 1282 (Fed. Cir. 2015)

⁴¹ *Ariosa*, 809 F.3d at 1287.

⁴² *Genetic Technologies Ltd. v. Merial LLC*, 818 F.3d 1369 (Fed. Cir. 2016).

⁴³ *Id.* at 1374-1375.

(between variations in the non-coding regions and allele presences in the coding regions) a consequence of the naturally occurring linkages in the DNA sequence.”⁴⁴ Second, the court found that the steps of amplifying DNA and analyzing the amplified sequence were well known in the art at the time of filing and did not constitute an “inventive concept.”⁴⁵ In so holding, the Federal Circuit rejected Genetic Tech.’s argument that, even if the detecting alleles by the amplification process was well known, no one had ever amplified “non-coding regions” to detect “coding regions.”⁴⁶ The Federal Circuit reasoned that even if detection of an allele in a non-coding region was a new concept, it was not an “inventive concept” as it was a “mental process” that could be performed entirely in the human mind.⁴⁷

The Federal Circuit most recently found claims related to methods for assessing risk of cardiovascular disease ineligible under § 101 in *The Cleveland Clinic Foundation v. True Health Diagnostics*.⁴⁸ The inventors in *Cleveland Clinic* developed a way to correlate the amount of myeloperoxidase (MPO) in a body fluid sample with the subject’s risk of developing cardiovascular disease. The claims recited methods for characterizing a subject’s risk for cardiovascular disease by determining level of MPO in a bodily sample and comparing that with the MPO levels in persons not having cardiovascular disease. The dependent claims limited the way MPO is detected (such as by flow cytometry) and how the MPO values in the control subjects are evaluated.⁴⁹

Applying step one of the *Mayo/Alice* analysis, the Federal Circuit noted that the patents’ specifications instruct that the inventions are “based on the discovery that patients with cardiovascular disease have significantly greater levels of leukocyte and [MPO].”⁵⁰ Analogizing to *Ariosa*, the court noted that the patent discussed detection of MPO and other MPO-related products, which are naturally occurring, and did not purport to alter MPO levels in any way.⁵¹ The court found that “just like *Ariosa*, the method starts and ends with naturally occurring phenomena with no meaningful non-routine steps in between—the presence of MPO in a bodily sample is correlated to its relationship to cardiovascular disease. The claims are therefore directed to a natural law.”⁵²

Applying step two of the *Mayo/Alice* analysis, the Federal Circuit found that “the claims, whether considered limitation-by-limitation or as a whole, do not sufficiently transform the natural existence of MPO in a bodily sample and its correlation to cardiovascular risk into a patentable invention. The process steps here merely tell those ‘interested in the subject about the correlations that the researchers discovered.”⁵³ The court specifically reasoned that the inventors did not claim to have invented any of the recited methods for detecting MPO in bodily samples, nor to have derived any new statistical methods to arrive at the control

⁴⁴ *Id.* at 1375.

⁴⁵ *Id.* at 1376.

⁴⁶ *Id.* at 1377.

⁴⁷ *Id.* at 1378.

⁴⁸ *The Cleveland Clinic Foundation et al. v. True Health Diagnostics, LLC*, 859 F.3d 1352 (Fed. Cir. June 16, 2017)

⁴⁹ *Id.* at *2.

⁵⁰ *Id.* at 1361.

⁵¹ *Id.*

⁵² *Id.*

⁵³ *Id.* at 1362.

levels of MPO used to assess a subject's disease risk. In short, the claims failed step two because they did not recite the use of any new detection or analytical techniques.⁵⁴

In a recent case, the District of Massachusetts joined the Federal Circuit in largely rejecting diagnostic claims under § 101 post-*Mayo*. In *Athena Diagnostics, Inc. v. Mayo Collaborative Services*,⁵⁵ the court initially denied a motion to dismiss on § 101 grounds, but later granted a renewed motion to dismiss for a patent related to diagnosis of Myasthenia Gravis, a chronic autoimmune disorder. The inventors there purported to discover that, in a certain percentage of patients, Myasthenia Gravis is caused by IgG antibodies attacking the muscle specific tyrosine kinase ("MuSK"), a receptor located on the surface of neuromuscular junctions. The patents claimed a method for diagnosing Myasthenia Gravis by detecting antibodies to MuSK in bodily fluid. Dependent claims required that the antibodies be detected by attaching a radioactive label to MuSK (or a fragment thereof), introducing the radiolabeled MuSK to a sample of body fluid, immunoprecipitating any antibody/MuSK complexes, and monitoring for the radiolabel in any of the complexes. The presence of the radiolabel in the complexes indicates that the patient suffers from Myasthenia Gravis.⁵⁶

Applying the now familiar two-part *Mayo/Alice* framework, the court found that step one was satisfied because the claims were directed to a patent ineligible law of nature, namely that some patients with Myasthenia Gravis have MuSK antibodies in their body fluid. The court found that "[t]he focus of the claims of the invention is the interaction of the [radioactive label] and the bodily fluid, an interaction which is naturally occurring."⁵⁷ The court reasoned that, like *Mayo*, a man-made substance (there, thiopurine drugs; here, a radioactive-labeled MuSK fragment) was administered and a byproduct was observed (there, thiopurine metabolites; here, antibody/MuSK complexes).⁵⁸ With respect to step two, the court initially found that discovery was needed to determine whether Athena's method "uses standard techniques in the art, or whether it is sufficiently inventive to be patentable under the second step of *Mayo*."⁵⁹ But, after discovery, the court found step two satisfied because the iodination and immunoprecipitation techniques disclosed in the patent were standard in the art.⁶⁰ The court rejected plaintiffs' argument that application of iodination and immunoprecipitation techniques to proteins was novel and detecting MuSK with an appropriate label used was a complex, non-routine process at the time of the patent because "[n]one of the complexity to which Plaintiffs cite is described or claimed in the patent."⁶¹ Further, the court explained that the claim's inclusion of a man-made molecule, the radiolabeled MUSK, was unavailing because the claims themselves were directed to "a process for detecting autoantibodies, not a process for creating the [radiolabeled] MuSK."⁶²

⁵⁴ *Id.* (citing *Mayo*, 566 U.S. at 78.)

⁵⁵ *Athena Diagnostics, Inc. v. Mayo Collaborative Servs.*, Civil Action No. 15-cv-40075-IT, 2016 WL 4491832 (D. Mass. Aug. 25, 2016).

⁵⁶ *Id.* at *1.

⁵⁷ *Id.*

⁵⁸ *Id.* at *4.

⁵⁹ *Id.* at *5.

⁶⁰ *Athena Diagnostics, Inc. v. Mayo Collaborative Servs.*, Civil Action No. 15-cv-400075-IT, 2017 WL 3336275 (D. Mass. Aug. 4, 2017).

⁶¹ *Id.*

⁶² *Id.*

In addition to court decisions, the USPTO has provided Subject Matter Eligibility Guidance on the eligibility of diagnostic claims post-*Mayo* that may have raised more questions than it provided answers. In Example 29 of its Section 101 guidance, the USPTO analyzed several example claims directed to methods for detecting and diagnosing a hypothetical disease called “julitis.”⁶³ The first claim recited a method for detecting a julitis antibody called “JUL-1” in a patient by screening for the antibody in a sample of the patient’s plasma:

1. A method of detecting JUL-1 in a patient, said method comprising:
 - a. obtaining a plasma sample from a human patient; and
 - b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody.⁶⁴

The second claim added a step of “diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected.”⁶⁵ Otherwise, claim 30 contained the exact same language as claim 1, with the exception of reciting a method of “*diagnosing* julitis” in the preamble, instead of “detecting JUL-1”:

2. A method of diagnosing julitis in a patient, said method comprising:
 - a. obtaining a plasma sample from a human patient;
 - b. detecting whether JUL-1 is present in the plasma sample by contacting the plasma sample with an anti-JUL-1 antibody and detecting binding between JUL-1 and the antibody; and
 - c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected.⁶⁶

Despite the similarities between claim 29 and claim 30, the USPTO came to different conclusions on the eligibility of the claims. According to the USPTO, claim 29 would be patent-eligible, but claim 30 would not be, even though it adds an additional limitation.⁶⁷ According to the USPTO, Claim 29 was not directed to a law of nature and was thus patentable pursuant to Step 1 of the *Mayo/Alice* test.⁶⁸ On the other hand, the addition of a diagnosis step in claim 30 introduced reliance on a natural law—the “correlation or relationship between the presence of JUL-1 in a patient’s plasma and the presence of julitis in the patient.”⁶⁹ Thus, claim 30 was not patentable because it fell under the judicial exception for claims directed to natural laws, and the claim’s “additional elements fail[ed] to transform the exception into a patent-eligible application of that exception.”⁷⁰ Public comments have been critical of this example.⁷¹

⁶³ https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf at 10-11.

⁶⁴ *Id.*

⁶⁵ *Id.*

⁶⁶ *Id.*

⁶⁷ *Id.* at 11-12.

⁶⁸ *Id.* at 11.

⁶⁹ *Id.* at 11-12.

⁷⁰ *Id.* at 12.

⁷¹ See https://www.uspto.gov/sites/default/files/documents/comments_PHRMA_Jan182017.pdf at 4 (“Examples such as this one, where one claim is patentable but another almost identical claim is not, re-enforces the arbitrary nature of the Mayo two-step test, as discussed further below.”).

The USPTO guidance also includes a hypothetical claim reciting a method of genetic screening from *In re BRCA1- and BRCA2*, with the added steps of (1) hybridizing a wild-type probe to the isolated gene sample, and (2) detecting the hybridization product through scanning near-field optical microscopy. Under Step 2 of the *Mayo/Alice* test, the USPTO indicated that this claim would be patent eligible because the application of scanning near-field optical microscopy to detect DNA hybridization was novel and unconventional. Therefore, the addition of this detection step “yield[ed] a claim as a whole that is significantly more than the judicial exception itself,” and “recites patent eligible subject matter.”⁷²

METHOD OF TREATMENT CLAIMS

While purely diagnostic claims have not fared well since *Mayo*, claims that include a treatment or administration step have received more mixed treatment. For purposes of this article, we include in this category claims fairly characterized as “personal medicine” claims, i.e., claims that include a diagnosis step, such as diagnosing a condition or characteristic, followed by an action step, such as administering a drug to treat the condition or changing the dose of a drug based on the characteristic. We also include more traditional method of treatment claims that do not include a diagnosis step.

The Supreme Court and Federal Circuit have both made statements suggesting that methods of treating disease should not be found patent ineligible. See *Myriad*, 133 S. Ct. at 2120 (inventors that make discoveries are “in an excellent position to claim applications of that knowledge”); *CellzDirect*, 827 F.3d at 1049 (rejecting ineligibility argument because “If that were so, we would find patent ineligible methods of, say . . . treating cancer with chemotherapy (as directed to cancer cell’s inability to survive chemotherapy), or treating headaches with aspirin (as directed to the body’s natural response to aspirin).”

Despite those reassurances, as discussed below, some courts have found claims including treatment steps to be “directed to” patent ineligible subject matter under the first step of *Mayo* (*Bristol-Myers Squibb, Vanda*), and in other cases, found a method of treatment claim patent ineligible (*Endo, Boehringer Ingelheim*).

After *Mayo* was decided but before *Alice*, the Western District of Texas found a method for administering a “hangover cure” made from glucaric acid patent eligible under § 101 in *Applied Food Sciences v. Monster Beverage Corp.*⁷³ The independent claim at issue comprised steps of “administering to a human recipient a therapeutically effective amount of an active agent wherein said agent is glucarate or a pharmaceutically acceptable salt, or enantiomer thereof or a derivative thereof selected from a group consisting of d-glucaro-1,4-lactone, d-glucuronolactone, d-glucaro-6,3-lactone, d-glucuronic acid gamma lactone, and d-glucurone and said administering occurring in temporal proximity to the consumption of said ethanol by said human recipient.”⁷⁴ In a short analysis, the court found the claims patent eligible without explicitly applying the two-step *Mayo* test. In so holding, the court rejected Defendant’s arguments the claims were ineligible because they relied on the inherent properties of glucaric acid, which occurs naturally in orange juice and broccoli.⁷⁵ The court reasoned that the claims were eligible because “[a] patent may be issuable for a

⁷² https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf at 26.

⁷³ *Applied Food Sciences v. Monster Beverage Corp.*, Civil Action No. W-13-CV-195, 2013 WL 12092492 (W.D. Tex. Dec. 13, 2013.)

⁷⁴ 2013 WL 12092492, at *1.

⁷⁵ *Id.* at *1-2.

method or process of using a naturally occurring phenomena in a new and innovative manner,” and “[i]n the present case, the '863 patent covers a new use, or process, of a known substance.”⁷⁶

In 2015, Judge Andrews from the District of Delaware held ineligible under § 101 claims to a method of treating pain with oxymorphone in renally impaired patients in *Endo Pharmaceuticals, Inc. et al. v. Actavis Inc., et al.*⁷⁷ The inventors in this case discovered that the bioavailability of oxymorphone was increased in renally impaired patients such that more renally impaired individuals needed less drug to provide pain relief. The claims, as characterized by the court, told “doctors to take an existing pharmaceutical compound for treating pain and 1) measure the creatinine clearance rate of the patient using an existing method, 2) use an unpatentable law of nature to assess the bioavailability of oxymorphone in light of the patient's creatinine clearance rate, 3) reconsider drug dosage in light of the law, and 4) administer that dosage.”⁷⁸

The court found these claims analogous to the claims evaluated by the Supreme Court in *Mayo* and ineligible under the Supreme Court's two-step test. Regarding step one, the court found that “the subject matter of the invention is the connection between the severity of renal impairment and the bioavailability of oxymorphone, or, in other words, the reaction of the human body of a renally impaired individual to oxymorphone, which is unquestionably a natural law.”⁷⁹ Regarding step two, as was the case in *Mayo*, the Court found “neither formulation provides any sort of inventive concept to suggest that more than just the natural law is being claimed.”⁸⁰ Notably, Judge Andrews rejected Endo's argument that the claims were different than *Mayo*, and patent eligible, because “the claim at issue in *Mayo* did not require that anyone act upon or apply the method in a tangible way, while claim 1 of the '737 patent actually requires that the lower dose be administered.”⁸¹ Judge Andrews found that, even though the claim required the doctor to orally administer a lower dose based on the level of renal impairment, the patent did no more than tell doctors to apply the natural law.⁸² As to policy, Judge Andrews believed the decision was not “so far-reaching that it would invalidate all pharmaceutical method-of-treatment patents that employ an existing pharmaceutical compound. Patentees can still avoid invalidation under § 101 by demonstrating an inventive leap beyond merely claiming a law of nature.”^{83,84}

A year later in *Bristol-Myers Squibb Co. v. Merck & Co.*, Judge Sleet denied a motion to dismiss based on § 101 but found that a method of treatment claim, without any diagnostic limitation, satisfied step one of the *Mayo/Alice* test.⁸⁵ The claims at issue were directed to treating cancer by administering compositions with an anti-PD-1 human antibody in solution and were asserted against Merck's Keytruda®, used for the treatment of patients with melanoma. Specifically, claim 1 of the patent-at-issue claimed:

⁷⁶ *Id.* at *3.

⁷⁷ *Endo Pharmaceuticals, Inc. et al. v. Actavis Inc., et al.*, Civil Action No. 14-1381-RGA, 2015 WL 7253674 (D. Del. Nov. 17, 2015).

⁷⁸ 2015 WL 7253674, at *2.

⁷⁹ 2015 WL 7253674, at *3.

⁸⁰ *Id.*

⁸¹ *Id.* at *1, *3

⁸² *Id.* at *3-*4.

⁸³ 2015 WL 7253674, at *4.

⁸⁴ Judge Andrews subsequently entered a Partial Final Judgement on the invalidated claims, and Endo filed a notice of appeal to the Federal Circuit. As of the date of this article, Endo's appeal is still pending before the Federal Circuit.

⁸⁵ *Bristol-Myers Squibb Co. v. Merck & Co.*, Civil Action No. 15-572-GMS, 2016 WL 1698385 (D. Del. Mar. 29, 2016).

A method of treating a metastatic melanoma comprising intravenously administering an effective amount of a composition comprising a human or humanized anti-PD-1 monoclonal antibody and a solubilizer in a solution to a human with the metastatic melanoma, wherein the administration of the composition treats the metastatic melanoma in the human.

The antibody solution worked by blocking a pathway in the body that suppressed the immune system, called the PD-1 pathway. With this pathway blocked, a patient's T cells were free to attack and remove the cancer from the body.

The Court applied the *Mayo* test and found step one satisfied but that step two required discovery. The court found the step one satisfied because the claims "touch upon" a natural phenomenon:

First, the court concludes that, contrary to Bristol-Myers contention, the '994 patent touches upon a natural phenomenon by using T cells to activate the immune system. The '994 patent relies on the known scientific fact that blocking activation of the PD-1 pathway causes this effect in the body, which enables the patient's T cells to perform their normal biological activity of removing cancer cells. This interaction is a natural phenomenon.⁸⁶

On step two, the court framed the question as "do the patent claims add enough to their statements of the correlations to allow the processes they describe to qualify as patent-eligible processes that apply natural laws?"⁸⁷ The court found this question was "a complicated factual determination that the court could better resolve after discovery."⁸⁸

Later the same year, Judge Sleet upheld method claims relating to Vanda Pharmaceutical's Fanapt® product used for the treatment of schizophrenia in *Vanda Pharmaceuticals, Inc. v. Roxane Labs, Inc.*⁸⁹ The patent at issue related to a method for treating patients with different amounts of iloperidone depending on how the patient metabolized the drug. Similar to the claims found ineligible *Endo*, the claims in *Vanda* were directed to multiple steps including, first, a determination step to identify whether the patient is a CYP2D6 poor metabolizer via a genotyping assay and, second, an administration step where iloperidone is administered to a patient in a certain amount depending on whether the patient was determined to be a CYP2D6 poor metabolizer.⁹⁰

Applying the *Mayo/Alice* two-part test, the court found the first step satisfied because the claims "depend upon laws of nature," namely "the relationship between iloperidone, CYP2DA metabolism, and QTc prolongation."⁹¹ But, with respect to step two, the court found Roxane had "not proven by clear and convincing evidence that the precise test and the discovered results were routine or conventional" as was found in *Mayo*.⁹² Rather, the court reasoned that the patent at issue "does not apply to all patients, but only a specific patient population based upon their genetic composition," that "[t]he dosage steps requires

⁸⁶ 2016 WL 1698385, at *1 n.2.

⁸⁷ *Id.* (quoting *Mayo*, 132 S. Ct. at 1297).

⁸⁸ The parties stipulated to dismissal before trial began, on January 20, 2017.

⁸⁹ *Vanda Pharmaceuticals Inc. v. Roxane Laboratories, Inc.*, Civil Action No. 13-1973, 14-757, 2016 WL 4490701 (D. Del. Aug. 25, 2016)

⁹⁰ *Id.* at *2.

⁹¹ *Id.* at *11.

⁹² *Id.*

applying genetic tests in a highly specified way,” and that “the process of using this genetic test to inform the dosage adjustment recited in the claims was not routine or conventional and amounted to more than a mere instruction to apply a natural relationship.”⁹³

Later in 2016, the District of New Jersey, at the motion to dismiss stage, found ineligible under § 101 claims reciting a method for treating metabolic diseases in *Boehringer Ingelheim Pharma, Inc. v. HEC Pharma Co., Ltd.*⁹⁴ The patent generally related to treatments of metabolic diseases using DPP-IV inhibitors. The use of certain DPP-IV inhibitors to treat metabolic diseases was known, but the patent disclosed DPP-IV inhibitors that purported to improve upon conventional DPP-IV inhibitors. These improved inhibitors provide a better side effect profile for patients with renal impairments because they are mainly excreted via the liver, not the kidneys. Claim 1 of the patent disclosed:

1. A method for treating and/or preventing metabolic diseases in a patient for whom metformin therapy is inappropriate due to at least one contraindication against metformin comprising orally administering to the patient a DPP-IV inhibitor wherein the contraindication is selected from the group consisting of: renal disease, renal impairment or renal dysfunction, unstable or acute congestive heart failure, acute or chronic metabolic acidosis, and hereditary galactose intolerance.

The court found that that Step 1 of the *Mayo/Alice* analysis was satisfied. The court acknowledged that the “end result [of the claimed methods] is to treat a targeted patient population with a DPP-IV inhibitor.”⁹⁵ Despite that, the court found the patent was directed to an abstract idea because the “improvement over the conventional DPP-IV inhibitors is that the DPP-IV inhibitors disclosed in the ’156 patent are mainly excreted via the liver, and only to a minor extent via the kidney, in order to treat the targeted patient population.”⁹⁶ The court further reasoned that the patent was directed to ineligible subject matter because the improvement “is performed at the anatomical level of the human body, where a series of reactions in the human body process DPP-IV inhibitor under the natural biological process.”⁹⁷ The court further found that the claimed “act of administering the DPP-IV inhibitor to the target patient population” was “an abstract idea” because it did “not require any prior determination that natural body levels have changed or altered before performing the step of administering.”⁹⁸

The court also found step 2 satisfied. According to the court, the claims did not add enough to transform the abstract idea into patent eligible subject matter for three reasons: (1) the problems with using conventional DPP-IV inhibitors to treat metabolic diseases were “well known and well-understood in the scientific community,” (2) the steps of claim 1 did “not amount to significantly more than an abstract idea of providing an instruction for a medical care professional who is treating the targeted patient population,” and (3) the additional features recited in other claims were well known and conventional because they either

⁹³ *Id.* *Vanda* is currently on appeal to the Federal Circuit.

⁹⁴ *Boehringer Ingelheim Pharma, Inc. v. HEC Pharma Co., Ltd.*, Civil Action No. 15-cv-5982 (PGS)(TJB), 2016 WL 7177704 (D.N.J. Dec. 8, 2016).

⁹⁵ 2016 WL 7177704, at *8.

⁹⁶ 2016 WL 7177704, at *9.

⁹⁷ 2016 WL 7177704, at *9.

⁹⁸ 2016 WL 7177704, at *9.

limited the use or dose of the DPP-IV inhibitors to specific diseases or described known methods for structurally modifying the conventional DPP-IV inhibitors to achieve better pharmacological properties.⁹⁹

Of particular note, is the court's treatment of method claims reciting the administration of a specific Boehringer Ingelheim DPP-IV inhibitor. Specifically, claims 24 and 25 of the '156 patent both recite:

A method of treating 2 diabetes mellitus in a patient for whom metformin therapy is inappropriate due to at least one contraindication against metformin comprising orally administering to the patient 1-[(4-methyl-quinazolin-2-yl)-methyl]-3-methyl-7-(2-butyn-1-yl)-8-(3-(R)-amino-piperidin-1-yl)-xanthine, . . .

Despite claiming a method of treatment using a specific DPP-IV inhibitor, the court viewed claims 24 and 25 as similar to claim 1 in that they all are "(i) method claims for treating a metabolic disease, such as type 2 diabetes; (ii) in a patient for whom metformin therapy is inappropriate because of a contraindication; (iii) by orally administering a DPP-IV inhibitor to the patient; and (iv) wherein the contraindication being, for example, renal disease, renal impairment, heart failure, etc."¹⁰⁰ Ultimately, the court found that claims 24 and 25 were directed to patent ineligible subject matter under § 101 because "at its core, claims 24 and 25 simply recite a single instruction of administering a drug to a targeted patient population, which is an abstract idea."^{101, 102}

Most recently, in *Natural Alternatives International, Inc. v. Allmax Nutrition, Inc.*, the Southern District of California granted the defendant's motion to dismiss, finding that four asserted patents claimed ineligible subject matter under § 101.¹⁰³ One of the four patents claimed methods of increasing the amount of beta-alanylhistidine in human tissue by administering a dietary supplement including beta-alanine. The claims specifically recited "a method of regulating hydronium ion concentrations in a human tissue" with a first step of "providing an amount of beta-alanine to blood or blood plasma effective to increase beta-alanylhistidine dipeptide synthesis in the human tissue" and second step of "exposing the tissue to the blood or blood plasma, whereby the concentration of beta-alanylhistidine is increased in the human tissue."¹⁰⁴

The Court found these claims ineligible under the two-part *Mayo/Alice* test. The court found the first step satisfied because "the principle that ingesting beta-alanine, a natural substance, will increase carnosine concentration in tissue and, thereby, aid in regulating the hydronium ion concentration in the tissue" was a law of nature.¹⁰⁵ Regarding step two, the court found that the additional elements contained in the claim did not "disclose an inventive concept sufficient to transformed the claimed law of nature into a patent-eligible application."¹⁰⁶ The court reasoned that the claims did not require beta-alanine from non-natural

⁹⁹ 2016 WL 7177704, at *10-12.

¹⁰⁰ 2016 WL 7177704, at *12.

¹⁰¹ 2016 WL 7177704, at *13.

¹⁰² Although the court found the claims of this patent invalid, the case continued on other asserted patents. Plaintiffs moved to sever the claims related to the ineligible patent so that a final judgment of invalidity could be entered and they could appeal. But, on April 17, 2017, the court denied plaintiffs' motion.

¹⁰³ *Natural Alternatives International, Inc. v. Allmax Nutrition, Inc.*, Case No.: 16-cv-01764-H-AGS, 2017 WL 2733923 (SD Cal. June 26, 2017)

¹⁰⁴ *Id.* at *11.

¹⁰⁵ *Id.*

¹⁰⁶ *Id.*

sources and, thus, the claims encompassed “natural methods of exposing beta-alanine to human tissue.”¹⁰⁷ Even if plaintiff were correct that the patent disclosed a new and useful method of using a natural product for increasing the amount of carnosine in muscles, the Court found that “insufficient to render the claims at issue patent eligible.”¹⁰⁸

The USPTO’s Subject Matter Eligibility Guidance suggests that adding administering step may make claims patent eligible. Continuing on the “julitis” examples discussed earlier, the guidance includes two additional claims that are the same as example claim 30, except that they each add step of administering vitamin D or anti-tumor necrosis factor (TNF) antibodies to the patient.

5. A method of diagnosing and treating julitis in a patient, said method comprising:
 - a. obtaining a plasma sample from a human patient;
 - b. detecting whether JUL-1 is present in the plasma sample;
 - c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected; and
 - d. administering an effective amount of topical vitamin D to the diagnosed patient.

6. A method of diagnosing and treating julitis in a patient, said method comprising:
 - a. obtaining a plasma sample from a human patient;
 - b. detecting whether JUL-1 is present in the plasma sample;
 - c. diagnosing the patient with julitis when the presence of JUL-1 in the plasma sample is detected; and
 - d. administering an effective amount of anti-tumor necrosis factor (TNF) antibodies to the diagnosed patient.

According to the USPTO, both of these claims are patentable given certain assumptions. The USPTO’s examples assume that the administration of vitamin D to treat julitis was not “widely prevalent in the field at the time the invention was made and the application was filed” and was thus “an unconventional step that is more than a mere instruction to ‘apply’ the [natural] correlation.”¹⁰⁹ Alternatively, the use of anti-TNF antibodies to treat julitis was well-understood and conventional, but the combination of all the steps together was not “routine and conventional.” In the USPTO’s hypothetical, doctors frequently misdiagnosed julitis as rosacea using conventional diagnostic techniques. The combination of steps here was “transformative” because it “ensure[d] that patients who have julitis will be accurately diagnosed (due to the detection of JUL-1 in their plasma) and properly treated with anti-TNF antibodies, as opposed to being misdiagnosed as having rosacea as was previously commonplace.”

LABORATORY/MANUFACTURING TECHNIQUE CLAIMS

In light of the courts’ treatment of diagnostic claims and method of treatment claims, one might assume laboratory and manufacturing technique claims might also have faced a bumpy road on patent eligibility since *Mayo*. To the contrary, these types of claims have found greater success in being found patent eligible.

¹⁰⁷ *Id.*

¹⁰⁸ *Id.* at *12.

¹⁰⁹ https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf at 14.

In 2016, the Federal Circuit found claims to laboratory techniques eligible under § 101 in *Rapid Litigation Management, Ltd. v. CellzDirect, Inc.*¹¹⁰ The patent at issue in *CellzDirect* involved a process for cryopreserving hepatocytes such that some fraction of hepatocytes are capable of surviving multiple freeze-thaw cycles.¹¹¹ Conventional wisdom was that hepatocytes could only be frozen once and techniques based on that belief resulted in poor yields after the first thaw and inability to pool hepatocytes from multiple donors. The inventors discovered that some hepatocytes could survive multiple freeze-thaw cycles. The claims were directed to a method of producing a preparation of cryopreserved hepatocytes that includes steps of freezing, thawing, selecting hepatocytes capable of surviving a second freeze, and refreezing.¹¹²

In applying the two-part framework, the Federal Circuit found that these method claims were patent eligible subject matter. Regarding step one, the court found that they were not directed to a natural phenomenon because the claims were directed to a better way of preserving hepatocytes, not the ability of some hepatocytes to survive multiple freeze-thaw cycles.¹¹³ The court explained that “[t]he inventors certainly discovered the cell’s ability to survive multiple freeze-thaw cycles, but that is not where they stopped, nor is it what they patented. . . . The end result of the ’929 patent claims is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles. Rather, the claims are directed to a new and useful method of preserving hepatocyte cells.”¹¹⁴ The court determined that step two did not need to be reached but, regardless, determined it would not be satisfied if considered. The court reasoned that individual steps of freezing and thawing were “well known” and routine if viewed in isolation, but the claimed process of “preserving hepatocytes by repeating those steps was itself far from routine or conventional.”¹¹⁵

A year later, the District of Massachusetts found method of manufacturing claims patent eligible in *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.* (D. Mass 2017).¹¹⁶ Momenta’s patents were directed to manufacturing quality control processes used to ensure that each batch of the drug enoxaparin includes characteristics of the branded pharmaceutical product, Lovenox, an anticoagulant used to prevent blood clots.¹¹⁷ The claims were specifically directed to a method for analyzing an enoxaparin sample for the presence or amount of a non-naturally occurring sugar, including an exhaustive digestion of enoxaparin step, a separation step, a comparison step, and a determination step.¹¹⁸

The Court recognized the *Mayo* two-step test as the appropriate standard for analyzing these laboratory claims under § 101. But, without much elaboration, the court determined that Momenta’s patent “is directed to a new and useful method of ensuring the quality of enoxaparin,” not a patent ineligible concept, and rejected Amphastar’s arguments that the first step involved a law of nature and the third and fourth steps involved “comparisons of abstract ideas.”¹¹⁹

¹¹⁰ *Rapid Litigation Mgmt, Ltd. v. CellzDirect, Inc.*, 827 F.3d 1042 (Fed. Cir. 2016)

¹¹¹ *Id.* at 1045.

¹¹² *Id.* at 1046.

¹¹³ *Id.* at 1048-49.

¹¹⁴ *Id.* at 1048.

¹¹⁵ *Id.* at 1052.

¹¹⁶ *Momenta Pharmaceuticals, Inc. v. Amphastar Pharmaceuticals, Inc.*, Civil Action No. 11-11681-NMG, 2017 WL 2623167 (D. Mass. June 16, 2017). The case settled shortly after the Federal Circuit decision.

¹¹⁷ *Id.* at *1.

¹¹⁸ *Id.* at *3.

¹¹⁹ *Id.* There has been no final judgment entered in the *Momenta* case as of the filing of this article.

The USPTO's Subject Matter Eligibility Guidance provides an example of a method of manufacturing claim that the office views as patent eligible. Example 33 is a method of making free fatty acids and glycerol:

1. A process for obtaining free fatty acids and glycerol from fat comprising:
 - mixing substantially equal quantities of fat and water in a closed vessel; and
 - heating the mixture to an elevated temperature of at least 600 degrees Fahrenheit under sufficient pressure to prevent the formation of steam in the closed vessel; and
 - maintaining the elevated temperature for at least 10 minutes so that the fat and water react with each other to form free fatty acids and glycerol.¹²⁰

Here, according to the USPTO, the combination of the steps as a whole “clearly amount[ed] to significantly more than any potential recited exception.”¹²¹ The USPTO's analysis did not offer many other facts to support this finding, except that “the claim as a whole effects a transformation of the fat and water into different chemicals, *i.e.*, from fat and water into the fatty acids and glycerol, by means of specific and unconventional steps.”¹²² Thus, while this manufacturing technique claim is considered patentable like the claims in *Momenta* and *CellzDirect*, the USPTO's reasoning is not entirely clear.

COMPOSITION CLAIMS

In the post-*Mayo* landscape, there have been a limited number of court decisions analyzing challenged composition of matter claims under § 101. The key takeaway from those cases is that a claimed composition will not be patent eligible unless the subject of the claims has “markedly different” characteristics from that which is naturally occurring. According to the Federal Circuit, it is not enough to separate a naturally occurring product from its surroundings, nor does it matter if the composition was actually created by man or pulled from nature. Instead, the composition must be markedly different, whether structurally or functionally, from that found in nature.

The Federal Circuit's first decision on composition claims after the Supreme Court's 2013 *Myriad* decision, *In re Roslin Institute (Edinburgh)*, related to the first mammal ever cloned from an adult somatic cell: Dolly the Sheep.¹²³ The Federal Circuit affirmed the Patent Trial and Appeal Board's (“Board”) final decision and rejection of all of Roslin's pending claims in U.S. Patent Application No. 09/225,233 as patent ineligible under §101. The claims were directed to the cloned mammal, for example, pending claim 155 recited: “A live-born clone of a pre-existing, non-embryonic, donor mammal, wherein the mammal is selected from cattle, sheep, pigs, and goats.” The Board found that while “the claimed clones may be called a composition of matter or a manufacture as required by § 101, . . . the claimed subject matter was ineligible for patent protection under § 101 because it constituted a natural phenomenon that did not possess markedly different characteristics than any found in nature.”¹²⁴

¹²⁰ https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf at 30-31.

¹²¹ *Id.* at 31.

¹²² *Id.*

¹²³ *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333 (Fed. Cir. 2014).

¹²⁴ *Id.* at 1335 (internal citations omitted).

Although it discussed *Mayo*, the court did not apply the two-part test from that case. Instead, the court determined whether the claimed subject matter “possess[es] markedly different characteristics from any found in nature.”¹²⁵ The court found Roslin’s “chief innovation was the preservation of the donor DNA such that the clone is an exact copy of the mammal from which the somatic cell was taken.”¹²⁶ But it was that very precision, the fact that “Dolly herself is an exact genetic replica of another sheep,” that led to the court’s conclusion that the claimed clones were ineligible under § 101 because they did not “possess markedly different characteristics from any [farm animals] found in nature.”¹²⁷ The court rejected Roslin’s arguments distinguishing its clones and their donor mammals based on phenotypic differences, differences in mitochondrial DNA, and time-delay.¹²⁸ Regarding phenotypic differences, i.e., differences resulting from the interaction of the organism’s genotype with its environment, the Court noted that such differences were unclaimed. Even if they were, however, the court found “these phenotypic differences do not confer eligibility on their claimed subject matter.”¹²⁹ Regarding mitochondrial DNA, the Court similarly noted that such aspects were unclaimed and that “[t]here is nothing in the claims, or even the specification, that suggests that the clones are distinct in any relevant way from the donor animals of which they are copies.”¹³⁰ Notably, the court made clear that “having the same nuclear DNA as the donor mammal may not necessarily result in patent ineligibility in every case.”¹³¹ Regarding time delay, the court was unconvinced that time-delay differentiated the cloned mammal from the donor mammal as time-delay is a characteristic of any copy of an original.¹³²

Only months later, the Federal Circuit was again tasked with evaluating composition claims in light of § 101 in the appeal from Myriad’s follow on suit against Ambyr Genetics, *In re BRCA1- and BRCA2- Hereditary Cancer Test Patent Litigation*, discussed earlier.¹³³ The composition claims in that case were directed to “pair[s] of single stranded DNA primers,” which are “short, synthetic, single-stranded DNA molecule[s] that bind[] specifically to . . . intended target nucleotide sequence[s].”¹³⁴

The Federal Circuit analyzed the primer claims under the lens of the Supreme Court’s 2013 *Myriad* case. Under that precedent, the court indicated that a “DNA structure with a function similar to that found in nature can only be patent eligible as a composition of matter if it has a unique structure, different from anything found in nature.” The court held the claimed primer pairs ineligible under this standard because they “necessarily contain the identical sequence of the BRCA sequence directly opposite to the strand to which they are designed to bind” and are “structurally identical to the ends of DNA strands found in nature.”¹³⁵ In so holding, the court rejected the argument that the primer pairs were patent eligible because they were synthetically created because “neither naturally occurring compositions of matter, nor synthetically created

¹²⁵ *Id.* at 1336.

¹²⁶ *Id.*

¹²⁷ *Id.*

¹²⁸ *Id.* at 1338-1339.

¹²⁹ *Id.* at 1338.

¹³⁰ *Id.* at 1339.

¹³¹ *Id.*

¹³² *Id.*

¹³³ *In re BRCA1- and BRCA2- Hereditary Cancer Test Patent Litigation*, 774 F.3d 755 (Fed. Cir. 2014).

¹³⁴ *Id.* at 758.

¹³⁵ *Id.* at 760.

compositions that are structurally identical to the naturally occurring compositions, are patent eligible.”¹³⁶ The court also rejected Myriad’s arguments that the primer pairs were not naturally occurring because single-stranded DNA cannot be found in the human body because “separating [DNA] from its surrounding genetic material is not an act of invention.” The court last considered and rejected Myriad’s position that the extracted primers “have a fundamentally different function than when they are part of the DNA strand,” explaining that the natural DNA performed a similar function to bind to complementary nucleotide sequences.¹³⁷ The court did not address Myriad’s arguments that the claimed “pair” of primers did not exist in nature.

Most recently, in *Natural Alternatives International, Inc. v. Allmax Nutrition, Inc.*, the Southern District of California granted the defendant’s motion to dismiss, finding that four asserted patents claimed ineligible subject matter under § 101.¹³⁸ Three of the four asserted patents had similar claims directed towards dietary compositions. For example, claim 34 of the ’947 patent claimed:

A human dietary supplement for increasing human muscle tissue strength comprising a mixture of creatine, a carbohydrate and free amino acid beta-alanine that is not part of a dipeptide, polypeptide or an oligopeptide, wherein the human dietary supplement does not contain a free amino acid L-histidine, wherein the free amino acid beta-alanine is in an amount that is from 0.4 g to 16.0 g per daily dose, wherein the amount increases the muscle tissue strength in the human, and wherein the human dietary supplement is formulated for one or more doses per day for at least 14 days.

The court applied the two-part *Mayo* test and found the claims ineligible. The court found step one satisfied because the claims were “directed to excluded subject matter, specifically the natural phenomena of beta-alanine, creatine, and carbohydrates.”¹³⁹ Regarding step two, the court relied on *Funk Bros.*,¹⁴⁰ to find that “mixing beta-alanine, a natural phenomenon, with a carbohydrate and creatine, two other natural phenomena, and placing that mixture in a human dietary supplement, a conventional activity, is insufficient to render claim 34 patent eligible.”¹⁴¹

As with the other categories of claims, USPTO’s Subject Matter Eligibility Guidance provides the USPTO’s view on the patent eligibility of certain composition of matter claims. As with *Roslin* and *In re BRCA*, the USPTO’s analysis focuses on whether compositions derived from natural products have markedly different structural or functional properties from their naturally occurring counterparts. Example 28 includes four claims of particular relevance:

1. A vaccine comprising live attenuated Pigeon flu virus.
3. A vaccine comprising: Peptide F; and a pharmaceutically acceptable carrier.

¹³⁶ *Id.*

¹³⁷ *Id.*

¹³⁸ *Natural Alternatives International, Inc. v. Allmax Nutrition, Inc.*, Case No.: 16-cv-01764-H-AGS, 2017 WL 2733923 (SD Cal. June 26, 2017)

¹³⁹ *Id.* at *9.

¹⁴⁰ *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948).

¹⁴¹ *Id.*

4. A vaccine comprising: Peptide F; and a pharmaceutically acceptable carrier selected from the group consisting of a cream, emulsion, gel, liposome, nanoparticle, or ointment.
5. A vaccine comprising: Peptide F; and an immune-effective amount of an aluminum salt adjuvant.¹⁴²

Under the USPTO's analysis, Claim 1 is eligible because, like the cDNA in *Myriad*, the claimed composition had different characteristics than its naturally occurring counterpart.¹⁴³ Specifically, in the USPTO's Example, the nucleotide sequence of the virus covered by claim 1 was mutated to create a less-virulent, safer version of the virus for administration to humans, i.e., "attenuated."¹⁴⁴ This conferred a structural difference (different nucleotide sequences) and functional difference (reduced virulence) in the claimed virus as compared with its naturally occurring counterpart.¹⁴⁵ Thus, the claimed virus had "markedly different characteristics from what exists in nature, [so] it [was] not a 'product of nature' exception."¹⁴⁶

The USPTO views claim 3 as ineligible.¹⁴⁷ Since "Peptide F" was naturally occurring in the USPTO's hypothetical and water likewise occurs naturally, the eligibility of the claimed composition depended on whether the "mixture of these two naturally occurring components . . . changes the structure, function, or other properties of the peptide or water."¹⁴⁸ In the USPTO's example, it did not.¹⁴⁹ Even though the mixture of water and Peptide F was "novel and [did] not occur in nature," the claim was non-patentable because "the claimed mixture as a whole [did] not display markedly different characteristics compared to the naturally occurring counterparts."¹⁵⁰ Some in the pharmaceutical industry have criticized this example.¹⁵¹

In the USPTO's view, the additional elements of cream or aluminum salt adjuvant mixed with Peptide F, recited in claims 4 and 5, resulted in patent-eligible subject matter under the USPTO's analysis.¹⁵² For claim 4, the USPTO explained that cream is derived by emulsifying naturally occurring cottonseed oil and water, and the emulsification process alters the mixture's structural and physical properties.¹⁵³ Specifically, the emulsified mixture has a semi-solid form at room temperature as compared to the liquid forms of water and oil, and adheres to skin longer, "thus permitting a sufficient amount of peptide to transfer from the

¹⁴² https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf at 2-3.

¹⁴³ *Id.* at 3.

¹⁴⁴ *Id.* at 1.

¹⁴⁵ *Id.* at 3.

¹⁴⁶ *Id.*

¹⁴⁷ *Id.* at 4-5.

¹⁴⁸ *Id.* at 5.

¹⁴⁹ *Id.*

¹⁵⁰ *Id.*

¹⁵¹ In particular, the Pharmaceutical Research and Manufacturers of America, an organization of pharmaceutical and biotechnology corporations, criticized the USPTO's finding of ineligibility for Example 28 for "improperly discount[ing] the value of the claimed vaccine," and not taking into consideration that "a vaccine does not arise from well understood, routine, conventional activity, but rather represents significantly more than the patent ineligible concepts of a peptide and a carrier such as water that produce an immunogenic response."

https://www.uspto.gov/sites/default/files/documents/comments_PHRMA_Jan182017.pdf at 3-4.

¹⁵² https://www.uspto.gov/sites/default/files/documents/mdc_examples_nature-based_products.pdf at 5-7.

¹⁵³ *Id.* at 6.

cream into the patient's tissues where it will then stimulate an immune response."¹⁵⁴ Claim 4 is patentable as a result of these differences between the mixture of cream and Peptide F, and the mixture's naturally-occurring counterparts of water, oil, and Peptide F.¹⁵⁵ The aluminum salt adjuvant disclosed in claim 5 similarly altered the properties of the resulting composition, making it eligible under § 101.¹⁵⁶ In the USPTO's example, Peptide F had poor immunogenicity and the aluminum adjuvant salt had no immunogenicity.¹⁵⁷ But, the combination of the two had high immunogenicity.¹⁵⁸ Given this "marked difference in functional characteristics [greatly enhanced immunogenicity] as compared to the natural counterparts, [] the mixture [was] not a 'product of nature' exception."¹⁵⁹

CONCLUSION

The four Supreme Court decisions in the last decade, *Bilski*, *Mayo*, *Myriad*, and *Alice*, have dramatically shifted the landscape of patent eligibility jurisprudence. In the wake of those cases, the courts and USPTO have struggled to apply the Supreme Court's new eligibility framework fairly and consistently. The life sciences has been one of the two industries most affected by this changing and developing area of patent law.

While the law is still developing in this area, the Federal Circuit and district court decisions to date have consistently found "diagnostic" patent claims patent ineligible. And, despite statements from the Supreme Court and Federal Circuit suggesting method of treatment claims are more likely patent eligible, some district court are putting the eligibility of such claims in jeopardy.

¹⁵⁴ *Id.*

¹⁵⁵ *Id.*

¹⁵⁶ *Id.* at 7.

¹⁵⁷ *Id.*

¹⁵⁸ *Id.*

¹⁵⁹ *Id.*