How Fed. Circ. Is Applying Section 101 To Drug Patents

By **Mark Waddell, Ryan Hagglund and Dan Liu** (May 12, 2023, 6:25 PM EDT)

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Between 2010 and 2014, the U.S. Supreme Court issued four decisions on patent subject matter eligibility under Title 35 of the U.S. Code, Section 101 — Bilski v. Kappos,[1] Mayo Collaborative Services v. Prometheus Labs Inc.,[2] Association for Molecular Pathology v. Myriad Genetics Inc.[3] and Alice Corp v. CLS Bank International[4] — establishing its modern Section 101 jurisprudence.

In Mayo, the court in 2012 set forth a two-step test for determining eligibility, commonly known as the Mayo/Alice framework. Step one inquires whether the patent is "directed to" an ineligible subject matter: a law of nature, a natural phenomenon or an abstract idea.[5]

If so, step two evaluates whether the patent claims any "inventive concept" to transform the patent ineligible subject matter into patent eligible application of that subject matter.[6]

In Myriad Genetics, the court in 2013 applied a different framework looking to whether a claimed composition had "markedly different characteristics" from those found in nature for determining whether a composition claim is directed to a natural phenomenon.[7]

This article reviews the U.S. Court of Appeals for the Federal Circuit's recent applications of the Mayo, Myriad and Alice decisions to life sciences patents. It also discusses practical implications for claim drafting and enforcement as practitioners and parties strategize when facing Section 101 issues.

Composition and Formulation Claims

In its Feb. 13 ChromaDex Inc. v. Elysium Health Inc. decision, the Federal Circuit **applied** the "markedly different characteristics" framework and found that the claimed formulation of nicotinamide riboside, or NR, which is a form of vitamin B3, was directed to a natural phenomenon and therefore unpatentable under Section 101.[8]

The representative claim in ChromaDex recites:

[A] composition comprising isolated nicotinamide riboside in combination with one or more of tryptophan, nicotinic acid, or nicotinamide, wherein said combination is in admixture with a carrier comprising a sugar, [a list of additional carriers], wherein said composition is formulated for oral administration and increases NAD+ biosynthesis upon oral administration.[9]

It was undisputed that natural milk contains NR, tryptophan, and lactose — a sugar — and that "the tryptophan in milk treats NAD+ deficiencies."[10]

Thus, the Federal Circuit found that "the only difference between at least one embodiment within the scope of the claims and natural milk is that the NR in the former is isolated."[11]

The Federal Circuit thus concluded that "the Supreme Court's decisions in Myriad and

Diamond v. Chakrabarty appl[ied]."[12]

In those cases, the court applied the "markedly different characteristics" test to determine whether a claimed composition was directed to a natural phenomenon.

In the 1980 Chakrabarty decision, the Supreme Court found a genetically engineered bacterium that broke down crude oil components patentable because it exhibited "markedly different characteristics from any [bacteria] found in nature and ha[d] the potential for significant utility."[13]

In contrast, the Supreme Court in Myriad found that claims reciting a naturally occurring DNA segment were not patent eligible because Myriad "found an important and useful gene, but separating that gene from its surrounding genetic material is not an act of invention."[14]

Applying these principles, the Federal Circuit in ChromaDex found that, like the DNA segment in Myriad, "the act of isolating the NR compared to how NR naturally exists in milk is not sufficient, on its own, to confer patent eligibility" and that the compositions did not have markedly different characteristics from milk.[15]

ChromaDex argued marked differences because "NR is found in milk in only trace amounts" and NR in milk is not bioavailable and does not enhance NAD+ biosynthesis.[16] The court rejected that argument, finding that the claims "do not require any specific quantity of isolated NR."[17] Nor do the claims require "that the NR, specifically, increase NAD+ biosynthesis."[18]

The only therapeutic effect required by the claims is to increase NAD+ biosynthesis, which milk does, although due to tryptophan rather than the trace amounts of NR.[19]

While the claims covered embodiments that are structurally different from milk, they were invalid because they were "broad enough to encompass a product of nature."[20]

Method Claims

Under Mayo/Alice, the Federal Circuit has "consistently held diagnostic claims unpatentable as directed to ineligible subject matter."[21]

For example, in a 2019 decision in Athena Diagnostics Inc. v. Mayo Collaborative Services Inc., it held that claims reciting methods for diagnosing a neurological disorder by detecting autoantibodies to a membrane protein were invalid "because the claimed advance was only in the discovery of a natural law, and that the additional recited steps only apply conventional techniques to detect that natural law."[22]

In contrast, the Federal Circuit has, as it mentions in the Athena decision, "held that method of treatment claims are patent-eligible."[23] In the 2018 Vanda Pharmaceuticals Inc. v. West-Ward Pharmaceuticals International Ltd., decision, the Federal Circuit found that method of using iloperidone at the specific dosage ranges to treat schizophrenia based on a patient's genotype was not directed to a law of nature.[24]

The Vanda court distinguished Mayo because the claims "recite more than the natural relationship between CYP2D6 metabolizer genotype and the risk of QTc prolongation. Instead, they recite a method of treating patients based on this relationship that makes iloperidone safer by lowering the risk of QTc prolongation."[25]

These cases illustrate the Federal Circuit's distinction between claims reciting a natural law and claims reciting an application of a natural law. The court in Athena said a diagnostic claim that recites "a natural cause of an ailment and well-known means of observing it" is patent-ineligible because it "only encompasses the natural law itself."[26]

In contrast, the court in Athena said, a treatment claim that recites "a new treatment for an ailment, albeit using a natural law, is not claiming the natural law" and therefore patent-eligible.[27]

The Federal Circuit has also held that claims reciting a method for preserving hepatocytes that can survive multiple freeze-thaw cycles[28] and a method for preparing cell-free fetal DNA are patent eligible.[29] The court recognized that these claims are directed to a new and useful application of a natural phenomenon rather than simply observing it.[30]

Takeaways

The "markedly different characteristics" framework likely controls composition claims while the two-step Mayo/Alice analysis applies to method claims.

The Federal Circuit in ChromaDex noted that the Supreme Court in Myriad never applied the two-step Mayo/Alice framework to the claimed compositions despite deciding that case after Mayo.[31] Indeed, in the 2014 In re: BRCA1-and BRCA2 case, the court analyzed composition claims under Myriad and method claims under Mayo/Alice.[32]

This suggests that the "inventive concept" analysis may not be applicable at least to some composition claims. This approach makes sense where a claim does not recite any steps.

The ChromaDex court found that, if an analysis under the Mayo/Alice framework were necessary, the claims did not recite an inventive step because "[the claims] are directed to nothing more than compositions that increase NAD+ biosynthesis, which is the very natural principle that renders the claims patent-ineligible."[33]

The step 2 inventive-concept requirement is very difficult to meet.

Courts have made clear that the inventive concept inquiry, the Federal Circuit said in its 2016 Genetic Technologis Ltd. v. Merial LLC decision, "cannot be furnished by the unpatentable law of nature (or natural phenomenon or abstract idea) itself."[34]

Most life sciences patents only recite routine and conventional steps, such as amplifying, analyzing, comparing, detecting, isolating and measuring, which would not represent an "inventive concept" that transforms an unpatentable law of nature into a patent-eligible application of it.

The Federal Circuit has never found a life sciences patent to meet the step two "inventive concept" requirement after determining that it is directed to ineligible subject matter in step one.[35]

Accordingly, life science patents are most likely to survive a challenge where the patent is found not to be directed to ineligible subject matter in which case step two is not reached.[36]

The key to step one of the Mayo/Alice inquiry is the term "directed to."

The Mayo court noted that "all inventions at some level embody, use, reflect, rest upon or apply laws of nature, natural phenomena, or abstract ideas."[37]

Thus the court said in its 2016 Rapid Litigation Management Inc. v. Cellzdirect Inc. decision, "it is not enough to merely identify a patent-ineligible concept underlying the claim; [the court] must determine whether that patent-ineligible concept is what the claim is 'directed to.'"[38]

In this analysis, the Federal Circuit considers, as in Athena, "whether the claimed advance improves upon a technological process or merely an ineligible concept, based on both the written description and the claims."[39]

For example, In Rapid Litigation v. Cellzdirect, the Federal Circuit found that claims covering a method for preparing hepatocytes capable of surviving multiple freeze-thaw cycles were patent-eligible because they recited "a new and improved way of preserving hepatocyte cells for later use ... not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles."[40]

The court explained that "[t]he claimed advance harnessed a natural law to produce a technological improvement."[41]

Meanwhile, the 2020 American Axle and Manufacturing Inc. v. Neapco Holdings Inc. decision has yet to have an impact on life science patents.

In American Axle, a divided Federal Circuit panel held that claims reciting methods of manufacturing an automobile shaft with liners tuned to reduce two types of vibrations were invalid as directed to a law of nature.[42]

Although related to a mechanical technology, many believe that American Axle expanded Section 101 and could support invaliding claims historically deemed patent-eligible.[43]

For example, a method of treatment patent can be interpreted as "claiming a result" of an operation of a natural law — the body's biological response to a drug. The Federal Circuit has decided at least three life sciences Section 101 cases since denying rehearing en banc in American Axle, but none has cited or applied American Axle.[44] Thus, the impact of American Axle remains to be seen.

Claim Drafting Tips

Several claim drafting lessons can be learned from ChromaDex and other Section 101 decisions. First, if a claim encompasses an embodiment that is a product of nature or is not markedly different from a product of nature, that claim is likely directed to patent-ineligible subject matter even if it also encompasses other embodiments that are not products of nature. Thus, it is prudent to draft narrower dependent claims targeting more specific embodiments.

Second, it's important to claim characteristics of the composition that are different from products of nature. The patent in ChromaDex only claims "a composition comprising isolated [NR] ... wherein said composition is formulated for … increased NAD+ biosynthesis" but did not require any specific amount of NR or any increase in NAD+ biosynthesis that is markedly different from milk.

In contrast, the Federal Circuit in its 2019 Natural Alternatives International Inc. v. Creative Compounds LLC decision upheld the patentability of claims comprising beta-alanine, finding although the claimed formulations "incorporate natural products, but they have different characteristics and can be used in a manner that natural beta-alanine cannot."[45]

Specifically, the claims required the beta-alanine in a specific dosage form — "between about 0.4 grams to 16 grams" — and with a specific characteristics — "to effectively increase athletic performance."[46] Accordingly, tying unnatural characteristics to the claimed composition is crucial to distinguish it from a product of nature.

Third, one consideration for patent ineligibility of laws of nature or natural phenomena is preemption, i.e., inhibition of future innovation or subsequent development.[47]

The claims in Mayo "tell a treating doctor to measure metabolite levels and to consider the resulting measurements in light of the statistical relationships they describe."[48]

Those claims would "tie up the doctor's subsequent treatment decision whether that treatment does, or does not, change in light of the inference he has drawn using the correlations" and "inhibit the development of more refined treatment recommendations."[49]

In contrast, the claims in Vanda "are directed to a specific method of treatment for specific patients using a specific compound at specific doses to achieve a specific outcome" and thus "do not 'tie up the doctor's subsequent treatment decision.'"[50]

Indeed, claims reciting steps to achieve a desired outcome or produce a desired product have been found to be directed to patent-eligible subject matter.[51]

The state of Section 101 law remains fluid and to some degree uncertain. The Federal Circuit continues to try to figure out the contours of Section 101 but has issued decisions that are, what the dissenting judges in American Axle termed "diverse and unpredictable."[52]

The uncertainty and unpredictability have posed significant challenges to all parties involved, and particularly to patent drafting as claims may face challenges that are not anticipated during prosecution. Thus, it is prudent to conduct a case-by-case analysis and have claims of various scopes.

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[1] 561 U.S. 593 (2010).

[2] 566 U.S. 66 (2012).

[3] 569 U.S. 576 (2013).

[4] 573 U.S. 208 (2014).

[5] Id. at 217.

[6] Id. at 217-18.

[7] 569 U.S. at 590-91.

[8] 59 F.4th 1280, 1284-85 (Fed. Cir. 2023). 2023) (petition for panel rehearing and rehearing en banc
denied (ChromaDex, Inc. v. Elysium Health, Inc., Case No. 22-1116, Doc. No. 54. (Fed. Cir. May 10, 2023))).

[9] Id. at 1281.

[10] Id. at 1282-83.

[11] Id. at 1284.

[12] Id. at 1284.

[13] 447 U.S. 303, 305, 310 (1980).

[14] Id. at 591.

[15] ChromaDex, 59 F.4th at 1284.

[16] Id. at 1285.

[17] Id.

[18] Id. at n.4.

[19] Id.

[20] Id.

[21] Illumina, Inc. v. Ariosa Diagnostics, Inc., Case No. 19-1419, Doc. No. 64 at 8 (Fed. Cir. Aug. 3, 2020).

[22] Athena Diagnostics, Inc. v. Mayo Collaborative Serv;s., LLC, 915 F.3d 743, 751 (Fed. Cir. 2019)

[23] Id. at 9.

[24] 887 F.3d 1117, 1136 (Fed. Cir. 2018).

[25] Id.

[26] Athena, 915 F.3d at 752-53.

[27] Id. at 753.

[28] Rapid Litig. Mgmt. Ltd. v. CellzDirect, Inc., 827 F.3d 1042, 1050 (Fed. Cir. 2016).

[29] Illumina, Doc. No. 64 at 10.

[30] CellzDirect, 827 F.3d at 1048-50; Illumina, Doc. No. 64 at 10-12.

[31] ChromaDex, 59 F.4th at 1285.

[32] Compare In re BRCA1-and BRCA2, 774 F.3d 755, 759-61 (Fed. Cir. 2014), with id. at 761-65.

[33] ChromaDex, 59 F.4th at 1285-86.

[34] Genetic Techs. Ltd. v. Merial L.L.C., 818 F.3d 1369, 1376 (Fed. Cir. 2016) (citing Mayo, 566 U.S. at 77).

[35] See e.g. Cleveland Clinic Found. v. True Health Diagnostics LLC, 859 F.3d 1352 (Fed. Cir. 2017); Roche Molecular Sys. v. Cepheid, 905 F.3d 1363 (Fed. Cir. 2018); Cleveland Clinic Found. v. True Health Diagnostics LLC, 760 F. App'x 1013 (Fed. Cir. 2019); Athena, 915 F.3d 743.

[36] See Vanda, 887 F.3d at 1134.

[37] 566 U.S. at 71.

[38] CellzDirect, 827 F.3d at 1050; see also Enfish, LLC v. Microsoft Corp., 822 F.3d 1327, 1335 (Fed. Cir. 2016) (recognizing that "a substantial class of claims are not directed to a patent-ineligible concept.").

[39] Athena, 915 F.3d at 750 (Fed. Cir. 2019).

[40] CellzDirect., 827 F.3d at 1048.

[41] Athena, 915 F.3d at 751 (citing CellzDirect, 827 F.3d at 1048-1049).

[42] 967 F.3d 1285, 1289, 1299 (Fed. Cir. 2019).

[43] See, e.g., Am. Axle, 967 F.3d at 1304 (Moore, J., dissenting); Am. Axle & Mfg. v. Neapco Holdings LLC, 966 F.3d at 1357 (Newman, J., dissenting), 1361 (Stoll, J., dissenting); David Ludwig and Ted Mathias, Fed. Circ. Ruling May Affect Eligibility Of Life Sciences Patents, Law360 (November 21, 2019), available at https://www.law360.com/articles/1221967/fed-circ-ruling-may-affect-eligibility-of-life-sciences-patents; Laura Smalley, Life Sciences Patents After American Axle — Grave Danger or Temporary Uncertainty?, IPWatchdog (OCTOBER 4, 2022), available at https://ipwatchdog.com/2022/10/04/life-sciences-patents-american-axle-grave-danger-temporary-uncertainty/id=151854/; Life Sciences Litigation Update - January 2023, available at https://www.jdsupra.com/legalnews/life-sciences-litigation-update-january-1530642/.

[44] See Illumina, Doc. No. 64; Caredx, Inc. v. Natera, Inc., 40 F.4th 1371, 1372 (Fed. Cir. 2022); ChromaDex, 59 F.4th at 1280.

[45] 918 F.3d 1338, 1348-49 (Fed. Cir. 2019).

[46] Id.

[47] See Mayo, 566 U.S. at 86.

[48] Id.

[49] Id. at 86-87.

[50] 887 F.3d at 1135-1136.

[51] See e.g., CellzDirect, 827 F.3d at 1042; Vanda, 887 F.3d at 1117; Natural Alternatives, 918 F.3d at 1338; Illumina, Doc. No. 64.

[52] See Am. Axle, 966 F.3d at 1357 (Newman, J., dissenting).