Who Will Finance Drug Development if Natural Products Are No Longer Patentable?

By Tamsen Valoir

Many natural products that have been discovered and purified from their natural state have been patented over the decades. These products include adrenaline, insulin, and Vitamin B12. This article discusses these early natural product patents, recent court decisions pertaining to the patentability of natural products, and the trend toward courts invalidating claims.

Early Natural Product Patents

Adrenaline

Adrenaline is probably the first human hormone patented in 1906 in its purified form. Adrenaline, also known as epinephrine, has saved countless lives and is still in use today. Indeed, many people carry an Epipen and can testify to its life-saving effect in the event of anaphylaxis.

It is important to remember that the original adrenaline patent did not cover adrenaline in its natural form as found in a human being or animal. That could not be patented because it was not new. Instead, the patent only covered the purified form of the hormone, which at that time was new. In fact, Judge Learned Hand noted that the inventor “was the first to make it available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.” Thus, Learned Hand recognized that adrenaline in an animal’s glandular tissue virtually had no therapeutic use due to the low concentration and impurities, whereas the purified adrenaline had therapeutic (and commercial) value.

Insulin

Insulin is another good example of a life-saving natural product. It was first patented when Banting partially purified it from dog pancreas and has saved countless lives since. One could treat diabetes by eating raw pancreas, but that is not very practical in the event of diabetic coma. Thus, the discovery of at least partially purified insulin was a great therapeutic benefit to patients.

Vitamin B12

Vitamin B12 is another natural compound patented in purified form. Prior to the patent, anemia was treated by eating raw liver, and thus the discovery of purified B12 was a great medical advance over consuming large quantities of raw liver.

Recent Court Decisions

Association of Molecular Pathology v. Myriad Genetics, Inc.

Even today, a significant percentage of small molecule drugs are natural products. Indeed, in a review of new drugs covering 30 years, authors David Newman and Gordon Cragg showed that roughly 30 percent to 40 percent of new drugs each year are either natural products or directly derived therefrom.

Yet in the recent U.S. Supreme Court case of Association of Molecular Pathology v. Myriad Genetics, Inc., the Supreme Court held that natural products are not patentable stating: “[W]e hold that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated.”

Of course, the naturally occurring DNA segments were not actually patented, but rather only the “isolated” DNA was patented. In other words, DNA that had been “uncovered” from the three billion or so bases of the genome, as well as from all of the proteins making up the chromatin structure in a chromosome.
The Supreme Court recognized that isolating the DNA from its normal chromatin and cellular environment meant the claimed product was in fact no longer a natural product. Nonetheless, they opined that merely purifying the DNA was not enough to confer patentability, stating: “[Myriad] found an important and useful gene, but … ground-breaking, innovative, or even brilliant discovery does not by itself satisfy the §101 inquiry.”

Arguably, this holding is in direct conflict with the U.S. Constitution. Since the birth of our nation, the Constitution has provided for patents for discoveries. Article 1, Section 8 of the Constitution of the United States of America, gives Congress the power “To promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive right to their respective writings and discoveries…”

In reliance on this power, the Legislature provided for the patentability of discoveries in the original 1790 Patent Act. Although there were intervening amendments and changes, the 1952 Patent Act still provided for patents on discoveries and it stated:

Whoever 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.

This language is still in the statute today. In fact, the definition of “invention” even includes discoveries.

The definition of a “discovery” is “something found, invented or uncovered.” Yet, “uncovering” a gene just isn’t enough anymore according to the Supreme Court. Regardless of the dubious constitutional grounds of the Supreme Court’s holding that discoveries are not patentable, the U.S. Patent Office has no choice but to follow Supreme Court precedent, and is applying the Supreme Court’s holding to all natural products, rejecting claims to natural products under Section 101.

**Mayo Collaborative Services v. Prometheus Laboratories, Inc.**

The difficulty is compounded when the Patent Office applies the Supreme Court’s earlier analysis from *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, in which a unanimous Supreme Court held that methods of treatment optimization claims were ineligible for patent protection on the basis that the claims recited a law of nature.

The claims at issue in the Mayo case related to optimizing drug dosage levels by determining the levels of a metabolite of that drug. Certain drugs, such as 6-mercaptopurine (6-MP), are converted to 6-thioguanine (6-TG) in the body, and the inventors discovered how much 6-TG is too much, thus indicating a need to lower the dosage of 6-MP.

Claim 1 is illustrative:

1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:

   (a) administering a drug providing [6-TG] to a subject having said immune-mediated gastrointestinal disorder; and

   (b) determining the level of [6-TG] in said subject having said immune-mediated gastrointestinal disorder,

   wherein the level of [6-TG] less than about 230 pmol per 8×10⁸ red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of [6-TG] greater than about 400 pmol per 8×10⁸ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Thus, the claim requires two active steps. First “administering” a drug, and second “determining” the level of metabolite. The “wherein” clauses merely identify an optimal dosage level. However, no active step of changing the dosage was affirmatively recited in the claim.

In fact, the drugs and the metabolite were both known, and assays for determining 6-TG had long been in use, even with inflammatory bowel diseases such as Crohn’s disease. Thus, the claim should have been invalidated under the usual anticipation or obviousness analysis.

However, the Supreme Court declined to analyze the claim under traditional prior art precedent.
instead taking the opportunity to create new law on patent eligibility under Section 101 of the patent statute. Unfortunately, the Supreme Court's analysis of the patent eligibility introduced novelty and non-obviousness concepts into the 101 analysis.

To put the matter more succinctly, the claims inform a relevant audience about certain laws of nature; any additional steps consist of well understood, routine, conventional activity already engaged in by the scientific community; and those steps, when viewed as a whole, add nothing significant beyond the sum of their parts taken separately.22

Many have criticized this portion of the analysis in particular because it appears to conflate patent eligibility under Section 101 with novelty and non-obviousness requirements under Sections 102 and 103. Indeed, more than one commentator has noted that any law student would receive a failing grade for an analysis that imports novelty and non-obviousness criteria into a patent eligibility analysis.23

Yet apparently, the Supreme Court apparently intentionally conflated these different concepts: "We recognize that, in evaluating the significance of additional steps, the § 101 patent-eligibility inquiry and, say, the § 102 novelty inquiry might sometimes overlap."24

In addition, the Supreme Court seems to have unraveled decades of patent jurisprudence and brought the "synergism" requirement back into the patentability analysis, albeit under Section 101 instead of the prior Section 103 analysis.25 To even be eligible for patents, the invention as a whole must add something "significant beyond the sum of their parts taken separately."

The damage potential of an eligibility test that conflates Section 102 and Section 103 issues with Section 101 issues and has a synergy requirement is very high. If we do not consider any routine, conventional steps as imparting anything significant more than the sum of the parts to a claim, what can be patentable in a well developed industry that merely applies routine, conventional steps in new applications? Most patents rely on applying routine, conventional steps in new ways, and thus can be invalidated as not even eligible under the Mayo analysis.

**Ariosa Diagnostics, Inc. v. Sequenom, Inc.**

The potential for damage has now been fully realized in *Ariosa Diagnostics, Inc. v. Sequenom, Inc.*26 Ariosa filed a declaratory judgment action against Sequenom, arguing that the claims of U.S. Patent No. 6,258,540 were not even patent eligible. The patents at issue related to diagnostic tests for fetal abnormalities, such as trisomy 21 or "Down's Syndrome." The test used cell free maternal fluids, rather than fetal fluids. This was an important advance because it reduced the need for invasive sampling methods, such as amniocentesis. Any woman who has ever undergone this painful needle biopsy procedure certainly would agree that testing maternal blood instead was an important improvement.

Claim 1 is exemplary:

1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.27

Ariosa filed a declaratory judgment action of invalidity against Sequenom on these claims, and the district court denied Sequenom's motion for preliminary injunction, based on a substantial question of invalidity under Section 101.

The U.S. Court of Appeals for the Federal Circuit applied the Mayo analysis, as follows:

First, we determine whether the claims at issue are directed to a patent ineligible concept. If the answer is yes, then we next consider the elements of each claim both individually and "as an ordered combination" to determine whether additional elements "transform the nature of the claim" into a patent-eligible application. The Supreme Court has described the second step of this analysis as a search for an "inventive concept"—that is, an element or combination of elements that is "sufficient to ensure that the patent in practice amounts to significantly more
than a patent upon the [ineligible concept] itself."  

It was undisputed in the record that the fetal DNA in the cell free maternal fluids was a natural phenomenon, and it also was undisputed that Sequenom did not create or alter any of these fetal DNAs. Thus, the Federal Circuit concluded that the claim was "directed to matter that was naturally occurring."  

In the second step, the Federal Circuit found that the amplifying and detecting steps were conventional at the time of filing. Indeed, the specification described sample preparation as using "standard techniques" and amplification was also "standard." Further, during prosecution, the patentee described the detecting steps as "routine." Thus, the Federal Circuit concluded that "the practice of the method claims does not result in an inventive concept that transforms the natural phenomenon of [cell free fetal] DNA into a patentable invention." Therefore, the claim was not patent eligible:  

[I]n this case, appending routine, conventional steps to a natural phenomenon, specified at a high level of generality, is not enough to supply an inventive concept. Where claims of a method patent are directed to an application that starts and ends with a naturally occurring phenomenon, the patent fails to disclose patent eligible subject matter if the methods themselves are conventional, routine and well understood applications in the art. The claims of the '540 patent at issue in this appeal are not directed to patent eligible subject matter and are, therefore, invalid.  

Judge Lynn said it best in his concurrence noting that "But for the sweeping language in the Supreme Court’s Mayo opinion, I see no reason, in policy or statute, why this breakthrough invention should be deemed patent ineligible."  

Further, although requesting the Court rehear the case en banc, the Federal Circuit denied the petition, and courts and the Patent Office are free to use Myriad and Mayo jurisprudence to block any natural product patent from issuing, or to invalidate existing patents. Ariosa has filed a Petition for certiorari to the Supreme Court, and it is anticipated that the Court will take the case.  

**Courts Are Invalidating Claims**  
In the interim, based on this dramatic change in Section 101 jurisprudence, courts are invalidating claims for lack of patent eligibility. Robert Sachs has canvassed Federal Circuit cases, and shows that more than 90 percent of claims are being invalidated. (See Exhibit 1.) The PTAB is mostly invalidating claims (almost 90 percent), as well. (See Exhibit 2.) District courts also have been active, although almost a quarter of claims have survived. (See Exhibit 3.)

### Exhibit 1

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It is not just a few biotech or diagnostic patents at issue here, but broad swaths of medical innovation, including vaccines, protein drugs, the next antibiotics, even new small molecule drugs with natural origins.

Teixobactin is one example. This is a new small molecule antibiotic that is active against gram-positive bacteria, and is heralded as the first new class of antibiotic in 30 years. Although a U.S. patent was filed, it was rejected by the Patent Office as not eligible for patent under the new eligibility doctrine. Eventually, the applicants cancelled all drug claims, and instead a patent issued on a method of use. A child case was filed to further pursue drug claims, although at this time, these are rejected under Section 101.

While not as broad a patent protection as one would like, the method claims do have value. Or do they? Actually, one could easily invalidate the method claims under a Mayo-style analysis. Ignore the drug Teixobactin because it is a natural product. Administering antibiotics to treat infection have been around since penicillin was first developed for therapeutic use in the 1940s, therefore the method steps are routine and conventional. Thus, the patent offers nothing more than a patent ineligible concept and the instruction to "use it," and is therefore not eligible.

Lest one dismiss such results as highly unlikely, be aware that a presumption of validity no longer applies to patents being challenged on a Section 101 basis. Judge Rich said it best when he famously noted that:

The laws of physics and chemistry in accordance with which all inventions perform do not permit of the judicially imagined magic accordingly to which $2 + 2 = 5$. Wherever such a spurious test prevails all patents are invalid. And there are those who think that is heaven.

**Conclusion**

It remains to be seen what happens to innovation in the United States in this patent hostile environment. But rest assured that even if this new antibiotic is never developed in the United States, wealthy Americans can travel and purchase approved drugs in other countries, and poor Americans can purify the antibiotic from soil themselves without risking patent infringement.

**Notes**

1. See, U.S. Pat. No. 730176 ("A substance possessing the herein-described physiological characteristics and reactions of the suprarenal glands in a stable and concentrated form, and practically free from inert and associated gland-tissue.").
2. Id.
3. Parke-Davis & Co. v. H. K. Mulford Co., 189 F.95, 103 (C.C.S.D.N.Y. 1911) (Judge Learned Hand upholding the adrenaline patent U.S. Pat. No. 730176 and stating "But, even if it were merely an extracted product without change, there is no rule that such products are not patentable. Takamine was the first to make it available for any use by removing it from the other gland-tissue in which it was found, and, while it is of course possible logically to call this a purification of the principle, it became for every practical purpose a new thing commercially and therapeutically. That was a good ground for a patent.").
4. See, U.S. Pat. No. 1469994, Extract obtainable from the mammalian pancreas or from the related glands in fishes, useful in the treatment of diabetes mellitus, and a method of preparing it. Claim 1: "A substance prepared from fresh pancreatic or related glands containing in concentrated form the extractive from the ductless portion of the glands sufficiently free from injurious substances for repeated administration and having a physiological characteristics of causing a reduction in blood sugar useful for the treatment of diabetes mellitus."
5. See also, Parke-Davis & Co., 189 F at 103 (holding (arguably in dicta that purified adrenalin is patentable subject matter).
7. U.S. Pat. No. 2563794 ("The compound vitamin B12 an organic substance containing cobalt, together with carbon, nitrogen, hydrogen, oxygen, and phosphorus, said compound being a red crystalline substance soluble in water, methyl and ethyl alcohol and phenol, and insoluble in acetone, ether and chloroform, and exhibiting strong absorption maxima at about 2780 Å 3610 Å and 5500 Å, and an L. L. D. activity of about 11,000,000 L. L. D. units per milligram."). See also Merck & Co. v. Olin Mathieson Chem. Corp., 253 F2d 156 (4th Cir. 1958) (upholding Vitamin B12 patent U.S. Pat. No. 2703302 and stating “The patentees have given us for the first time a medicine which can be used successfully in the treatment of pernicious anemia, a medicine which avoids the dangers and disadvantages of the liver extracts, the only remedies available prior to this
invention, a medicine subject to accurate standardization and which can be produced in large quantities and inexpensively, a medicine which is valuable for other purposes, as well as for the treatment of pernicious anemia. It did not exist in nature in the form in which the patentees produced it and was produced by them only after lengthy experiments. Nothing in the prior art either anticipated or suggested it.


9. David J. Newman & Gordon M. Cragg, “Natural Products As Sources of New Drugs over the 30 Years from 1981 to 2010,” J. Natural Prod. 75:311-335 (2012). See e.g., Fig. 5.

10. Ass’n of Molecular Pathology v. Myriad Genetics, Inc., 569 U.S. at _, slip opinion at 1 [hereinafter Myriad Slip Op.].

11. See e.g., U.S. Pat. No. 5747282 (“1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.”).

12. Myriad Slip Op. at 14 (“Nor are Myriad’s claims saved by the fact that isolating DNA from the human genome severs chemical bonds and thereby creates a non-naturally occurring molecule.”).


14. Patent Act of 1790, Ch. 7, 1 Stat. 109-112 (April 10, 1790) (providing that where “he, she, or they, hath or have invented or discovered any useful art, manufacture, engine, machine, or device, or any improvement therein not before known or used, and praying that a patent may be granted therefor”).


16. 35 U.S.C. § 100 (“The term “invention” means invention or discovery.”).


18. No law of nature was at issue in the claims, only a natural correlation, but most practitioners politely rephrase this part of the Court’s holding.

19. U.S. Pat. No. 6,355,623. There was an additional patent and additional claims at issue, but for simplicity only a single claim is discussed.

20. Cuffari C, et al., 6-Mercaptopurine metabolism in Crohn’s disease: correlation with efficacy and toxicity, Gut. 1996 Sep; 39(3):401-406 (“blood was obtained prior to daily administration of 6-MP in 25 adolescent Crohn’s disease patients...[and] 6-thioguanine (6-TG) and 6-methyl-mercaptopurine (6-MMP) were measured...”).

21. The Court specifically rejected using a 102/103 approach. Mayo Slip Op. at p.22 (“These considerations lead us to decline the Government’s invitation to substitute §§102, 103, and 112 inquiries for the better established inquiry under §101.”).


23. See e.g., http://www.ipwatchdog.com/2012/03/20/supreme­court-mayo-v-prometheus/id=22920/ (“If a student were to write such nonsense in a patent law paper or on a patent law final exam they would receive little, if any, credit.”).


25. The “Flash of Genius” test for patentability was formalized in Cuno Eng’g v. Automatic Devices, 314 U.S. 84 (1941) which held that the inventive act had to come into the mind of an inventor in a “flash of genius” and not as a result of tinkering. “The new device, however useful it may be, must reveal the flash of creative genius, not merely the skill of the calling. If it fails, it has not established its right to a private grant on the public domain.” Id. at 91. The flash of genius test was rejected by Congress in its 1952 revision of the patent statute when 35 U.S.C. § 103 was amended to state the new standard of non-obviousness: “Patentability shall not be negated by the manner in which the invention was made.” Efforts to stamp out the “synergism” or “flash of genius” requirement continued, however, even after the 1952 revision. See e.g., Chore Time Equipment Inc. v. Cumberland Corp., 713 F.2d 774, 781 (Fed. Cir. 1983) (“A requirement that an invention reflect ‘synergism’ or achieve a ‘synergistic result,’ before it may be held patentable appears nowhere in the statute.... References to synergism as a patentability requirement are, therefore, unnecessary and confusing.”) (citations omitted).


27. Again, there were many more claims at issue, but for simplicity we only discuss one representative claim.

28. Ariosa, 788 F.3d at 1375.

29. Id. at 1376.

30. Id.

31. Id. at 1375.

32. Id. at 1377.

33. Id. at 1375.

34. Id. at 1376.

35. Id. at 1377.

36. Id. at 1381.
38. Petition for Rehearing was denied on Dec. 2, 2015, and thus the 90 day deadline for filing cert was March 2, 2016. However, the deadline was extended to April 1, 2016.
42. See, Office Action, dated Jan. 15, 2016 rejected drug claims under Section 101 in case 14/789,819.
43. Ultramercial, Inc. v. Hulu, LLC, 772 F.3d 709, 720-721 (Fed. Cir. 2014) (“Although the Supreme Court has taken up several Section 101 cases in recent years, it has never mentioned—much less applied—any presumption of eligibility. The reasonable inference, therefore, is that while a presumption of validity attaches in many contexts, no equivalent presumption of eligibility applies in the section 101 calculus.”) (citation omitted).