Bloomberg BNA

Life Sciences Law & Industry Report™

Patenting Purified Natural Products by Specific Activity: Eligibility and Enablement

BY CHENGHUA LUO AND JORGE GOLDSTEIN

Introduction

Purified natural products have contributed to the progress of humanity for centuries. Many antibiotics and anticancer drugs are purified natural compounds, or are derived therefrom.[1] Purification of natural antibiotics greatly enriches the compounds and focuses their utilities, making possible their therapeutic use. The importance of finding new antibiotics cannot be overstated; the absence of newly developed antibiotics is exacerbating the medical problems associated with the appearance of ever more antibiotic-resistant bacterial strains. The search for new antibiotics is thus a critical issue for our time. However, investments in the research on, and development of, useful natural materials such as new antibiotics, especially in the commercial realm, depend on a simple proposition: the existence of good patent protection. This proposition has recently come under a cloud.

Three Supreme Court decisions, handed down between 2012 and 2014, *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*;[2] *Association for Molecular Pathology v. Myriad Genetics, Inc.*;[3] and *Alice Corp. Pty. Ltd. v. CLS Bank International*,[4] have changed the landscape of patent-eligible subject matter under 35 U.S.C. § 101 of the patent statute (the ''Supreme Court Triad''). While *Myriad* dealt with the eligibility of isolated genes, *Mayo* dealt with drug correlations, and *Alice* dealt with algorithms for controlling financial risk, these decisions have one thing in common: They have severely retrenched the broad interpretation of the statute that the U.S. Patent and Trademark Office (''USPTO'') and the U.S. Court of Appeals for the Federal Circuit (''Federal Circuit'') had given us over the last 35 years. The Triad has had, and is having, a profound impact on what is eligible for patent and what—among matter that was previously thought eligible—no longer is. Purified natural products such as antibiotics are foremost on the list of concerns.

The Federal Circuit has followed the Supreme Court in retreating from its earlier, ever expanding views. In May 2014, the Federal Circuit in *In re Roslin Institute*[5] held that an artificially cloned animal derived from a pre-existing non-embryonic donor mammal is not eligible for patent protection because the clone as claimed is ''an exact genetic replica of another sheep and does not possess 'markedly different characteristics' from any [farm animals] found in nature.'' And, if the patent bar thought that *Alice* was going to be limited to eligibility evaluations of computer implemented algorithms as abstract ideas, it was quickly disabused of that notion in late 2014, when the Federal Circuit handed down *In Re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation*.[6] The Court there merged the concepts of ineligibility of isolated gene sequences from *Myriad* with the abstract idea-based two-step analyses from *Alice*. In analyzing if a claim to a pair of primers especially designed to amplify (by polymerase chain reaction or ''PCR'') an exon of a BRCA gene was or was

[1] Newman, D. J. and Gragg, G. M., Natural Products as Sources of New Drugs over the 30 Years from 1981 to 2010, 75 J. of Nat. Prod. 311-335 (2012).

Chenghua Luo and Jorge Goldstein are attorneys with Sterne, Kessler, Goldstein and Fox, PLLC, Washington; http://www.SKGF.com.

The opinions expressed herein are the authors' and not those of their firm or its clients.

[2] *Mayo Collaborative Services v. Prometheus Laboratories, Inc.*, 132 S. Ct. 1289 (2012).

[3] *Association for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013).

[4] *Alice Corp. Pty. Ltd. v. CLS Bank Int'l*, 134 S. Ct. 2347 (2014).

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

[6] *In Re BRCA1- and BRCA2-Based Hereditary Cancer Test Patent Litigation*, 774 F.3d 755 (Fed. Cir. 2014).

 ISSN 1935-7257

not eligible, the Federal Circuit used the *Alice* test to conclude that, ''without more'' in the claim, such a pair is just a combination of two patent-ineligible natural gene fragments. Clearly, the recitation of the special design of the primer pair as functionally useful for amplification of a BRCA exon was not a markedly new use or property for eligibility.

More or less in step with these decisions, on Dec. 16, 2014, the USPTO published the ''2014 Interim Guidance on Patent Subject Matter Eligibility'' (''IGE'').[7] These are a series of guidelines for use by Office personnel in determining subject matter eligibility under 35 U.S.C. § 101 in view of the Supreme Court Triad and other courts' precedents. The IGE supersedes an earlier set of USPTO guidelines issued on March 4, 2014[8] (''March 2014 Procedure''), which had been published after the Supreme Court's decisions in *Mayo* and *Myriad*.[9] The IGE is now to be used by the USPTO to examine all patent applications filed *before or after* Dec. 16, 2014. Following the Supreme Court's analysis in *Alice*, and supported by the same two-step test used by the Federal Circuit in *BRCA1- and BRCA2 Litigation*, the IGE sets forth a two-part analysis for determining whether a claim is patent eligible or not. The two-step framework is meant to analyze if the claim is directed to a judicial exception of 35 U.S.C. § 101, namely if it embodies nothing more than a law of nature, a natural phenomenon or an abstract idea (and thus is patent ineligible), or if there is ''something more'' to the claim (and thus is patent eligible).

The central question of the case law and the IGE then is, ''How much more'' than just a recitation of a product claimed as such, or claimed with a functional limitation (e.g., ''useful for amplification''), or with a purification one (''purified,'' or ''in isolated form''), is necessary for a natural product to be eligible? Following court precedent, the focus of the IGE is that the patent eligibility of a claim directed to a nature-based product depends on whether or not the claimed product possesses ''markedly different'' characteristics from its natural counterpart. Compared to the March 2014 Procedure, the IGE outlines a significantly modified test for the concept of ''markedly different characteristic'': It takes into consideration not just changes in *structural* properties between a claimed nature-based product and its natural counterpart, but includes *functional* changes in properties as well. The USPTO has also developed and published exemplary claims illustrating the analysis of what is ''markedly different'' as set forth in the IGE. And, the Office has published training materials explaining its analysis of claims under the ''markedly different characteristics'' test.[10]

It is remarkable how rapidly the Supreme Court Triad has affected the legal terrain, whether at the USPTO or at the Federal Circuit. The Triad and its interpretations have cast serious uncertainty on the patent eligibility of purified natural products, such as antibiotics. In this article, we hope to provide some legal clarity to the discoverers of natural products who invent purification methods, and then try and claim the products in purified form.

We propose that a functionally meaningful degree of purity of a nature-based product, reflected by including carefully defined specific activity limitations in a claim, should be a sufficient ''markedly different characteristic'' that will support patent eligibility. After setting forth our proposal, we will briefly test it against the case law and against the two-part analysis for judicial exceptions set forth in the IGE. And, since not all concerns with specific activity-based claims are about eligibility, we conclude by reviewing the case law on proper enablement of such claims, and its relation to preemption.

Claiming Natural Products by Specific Activity

A purified natural product that otherwise remains unchanged structurally, claimed with a minimum specific activity or a range of specific activities and which, as a consequence, is suitable for a new use, should be considered to have ''markedly different characteristics'' compared to its natural counterpart. For a claim directed to a purified natural antibiotic, the recitation of cautiously drafted specific activity limitations—a proxy for the degree of potency in its pharmacological utility—should make it eligible for patent.

The specific activity of a biologically active compound is a measure of its activity per unit of weight, such as per milligram.[11] The measure of activity needs to be defined by a well-described assay. The more activity per milligram, the purer the compound and the higher its specific activity.

Let's start with an example. Assume that researchers discover that an ingredient present in the leaves of a tree that grows in the Amazon is active against bacterial infections, and they purify it.[12] They call it amazonyn. Suppose amazonyn in the tree leaves has a low specific activity of 1×10^{-3} to 1×10^{-2} units/mg determined by a biological assay indicative of its antibiotic activity. The naturally existing amazonyn has little real-world therapeutic utility, as a patient would need to eat 10 kg of tree leaves a day to get 10 mg of amazonyn. After purification, the specific activity of the purified amazonyn is 1×10^{2} to 1×10^{5} units/mg using the same assay. As a result of this purification of over 4 to 7 orders of magnitude, the purified amazonyn is now effective for treating bacterial infections when administered at 10 mg/day to infected patients. A claim directed to the purified amazonyn can be drafted as follows:

> Purified amazonyn having a specific activity of between 1×10^{2} and 1×10^{5} units/mg.[13]

[7] Interim Guidance on Patent Subject Matter Eligibility, 79 Fed. Reg. 74,619 (Dec. 16, 2014), available at http://www.uspto.gov/patent/laws-and-regulations/examination-policy/2014-interim-guidance-subject-matter-eligibility-0.

[8] ''Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena, and/or Natural Products,'' available at http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf.

[9] The IGE also supplements the ''Preliminary Examination Instructions'' published on June 25, 2014, shortly after the Supreme Court handed down *Alice*.

[10] *See* IGE, 79 Fed. Reg. 74,625-74,626; Nature-based Product Claim Examples, available at http://www.uspto.gov/patents/law/exam/mdc_examples_nature-based_products.pdf.

[11] Proxies for specific activity can also be used, such as, for enzymes, turnover number per milligram, or per unit of spectral absorbance.

[12] Inspiration for this hypothetical comes from Justice Samuel Alito, who first raised a very similar one at oral hearing in *Myriad*.

[13] Note that this claim is carefully drafted to avoid including in the range of specific activity the values of the product in its natural state.

  LSLR ISSN 1935-7257

Although natural amazonyn has some antibiotic activity, it is not pharmacologically useful due to its low specific activity. A great amount of the product—10 kg of tree leaves—has to be administered per day. Purification greatly enriches amazonyn and increases its pharmacological activity, making possible its reproducible therapeutic use. This difference in specific activity between the purified amazonyn and the product existing in nature, which is directly related to pharmacological utility, should rise to the level of a ''marked difference.'' Additionally, a carefully crafted claim including a minimum specific activity or a range of activities will not tie up or preempt all future uses of the natural amazonyn, which will still be available for study and use.

We will demonstrate that such a claim should be patent-eligible under the IGE and the case law, starting with the Supreme Court decision in *Myriad*. Our view is based on two central conclusions that reasonably may be reached from *Myriad*. First, we believe that the Supreme Court intended its holding to be narrowly drawn to isolated genes claimed by sequence. Second, the Court did not critique or expressly overrule lower court precedents dealing with claims to purified natural products.

The *Myriad* Holding and Opinion

The *Myriad* holding is narrow. The oral hearing itself set the stage. At the hearing there were some illuminating exchanges between the Justices and counsel for petitioners AMP (Christopher A. Hansen), which give us some insight into the concerns of the Court. They support a view that purified natural products claimed by specific activity are distinguishable from isolated DNA sequences:

> JUSTICE GINSBURG: Mr. Hansen, Respondents say that isolating or extracting natural products, that has long been considered patentable. Examples were aspirin and whooping cough vaccine. How is this different from natural products? . . . .
>
> ***
>
> JUSTICE ALITO: . . . Suppose there is a substance, a chemical, a molecule in the leaf—the leaves of a plant that grows in the Amazon, and it's discovered that this has tremendous medicinal purposes. Let's say it treats breast cancer. A new discovery, a new way is found, previously unknown, to extract that. You make a drug out of that. Your answer is[,] that cannot be patented; it's not eligible for patenting, because the chemical composition of the drug is the same as the chemical that exists in the leaves of the plant.
>
> ***
>
> JUSTICE ALITO: . . . . It's not just the case of taking the leaf off the tree and chewing it. Let's say if you do that, you'd have to eat a whole forest to get the value of this. But it's extracted and reduced to a concentrated form. That's not patent eligible?
>
> MR. HANSEN: No, that may well be eligible, because you have now taken what was in nature and you've transformed it in two ways. First of all, you've made it substantially more concentrated than it was in nature; and second, you've given it a function. If it doesn't work in the diluted form but does work in a concentrated form, you've given it a new function. And by both changing its nature and by giving it a new function, you may well have a patent.[14]

Obviously, questions and answers at an oral hearing are not the law of the land. However, even the Petitioners agreed that concentrating the Amazonic drug and generating a new function are two transformations that would make it eligible. And, upon reading the opinion in *Myriad*, one cannot but be struck by how carefully the Court left untouched the issues it raised at hearing. The Court did not mention purified natural products, not even in *dicta*.

The fact that the purified natural product cases from lower courts (such as *Parke-Davis*, see below) were discussed in the Federal Circuit's decision and were briefed to the Supreme Court,[15] but were not mentioned in *Myriad*, further indicates the conscious narrowness of the Court's holding. Let us look at a few of these lower court decisions.

Lower Court Decisions

In the oft-cited case of *Parke-Davis & Co. v. H. K. Mulford Co.*,[16] the natural product in U.S. Patent No. 730,176 was adrenalin. It was claimed ''. . . in a stable and concentrated form, and practically free from inert and associated gland-tissue.'' The claim was challenged on the basis that this was not a new ''composition of matter'' in that it differed from the prior art substance only in degree of purity. In an opinion by Judge Learned Hand, the court upheld the claim as patentable. Judge Hand implied that a purified product is patent eligible if it is ''a new thing commercially and therapeutically'':

> But, even if it were merely an extracted product without change, there is no rule that such products are not patentable. [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.[17]

In *Merck & Co. v. Olin Mathieson Chem. Corp.*,[18] the Court of Appeals for the Fourth Circuit upheld the validity of a patent claiming purified vitamin B12, a naturally occurring vitamin that treats pernicious anemia. The claims of U.S. Patent No. 2,703,302 were treated as products *per se*, regardless of the process of manufacture (by fermentation from fungi). Claim 1 is representative:

> A vitamin B12-active composition comprising recovered elaboration products of the fermentation of a vitamin B12-activity-producing strain of Fungi selected from the class consisting of *Schizomycetes, Torula,* and *Eremothecium*, the L.L.D. activity of said composition being at least 440 L.L.D. units per milligram and less than 11 million L.L.D. units per milligram.

---

[14] Transcript of Oral Argument at 3, 6, and 8, *Association for Molecular Pathology v. Myriad Genetics, Inc.,* 133 S. Ct. 2107 (2013).

[15] *E.g.,* Brief for the American Intellectual Law Association as *Amicus Curiae* in Support of Neither Party, p. 9.

[16] *Parke-Davis & Co. v. H.K. Mulford Co.,* 189 F. 95 (Cir. Ct. SD NY 1911).

[17] *Id.* at 103.

[18] *Merck & Co. v. Olin Mathieson Chem. Corp.,* 253 F.2d 156 (4th Cir. 1958).

Note that the B12 composition is claimed with an L.L.D. range value of 440 to 11 million units per milligram, i.e., its specific activity.[19] The district court had concluded that the claim was invalid for claiming a product of nature. The Fourth Circuit reversed and held that the claimed invention is a new composition that never existed before and has a utility that natural fermentates do not have:

> From the natural fermentates, which, for this purpose, were wholly useless and were not known to contain the desired activity in even the slightest degree, products of great therapeutic and commercial worth have been developed. The new products are not the same as the old, but new and useful compositions entitled to the protection of the patent.[20]

In *In re Bergstrom* (1970),[21] the Court of Customs and Patent Appeals held that claimed purified prostaglandin compounds are ''new'' compositions under 35 U.S.C. § 101. Relevant claim 23 of the Bergstrom application recites:

> 7-[3-hydroxy-2(3-hydroxy-1-octenyl)-5-oxocyclopentyl]-5-heptenoic acid, said acid being sufficiently pure to give a substantially ideal curve on partition chromatography . . .

The USPTO examiner had rejected the claim under Section 101 because the ''claimed compounds are naturally occurring'' and therefore are not ''new'' within the meaning of the statute. The Board affirmed, but the C.C.P.A. reversed both, stating (emphasis on preemption concepts is added):

> . . . what appellants claim—pure PGE2 and pure PGE3—is not 'naturally occurring.' Those compounds . . . do not exist in nature in pure form, and appellants have neither merely discovered, *nor claimed sufficiently broadly to encompass, what has previously existed in fact in nature's storehouse*, albeit unknown, or what has previously been known to exist.[22]

In sum, in *Parke-Davis*, *Merck* and *Bergstrom* the courts held that purified adrenaline, vitamin B12 and prostaglandins are eligible subject matter. The language from *Parke-Davis* and from *Merck* was clearly echoed in the *Myriad* exchange at oral hearing about cancer-treating compounds from the Amazon. And, while the *Merck* and *Bergstrom* language sounds in novelty, it is clear that, in reversing the lower court's or Board's decisions (which had been based on the fact that vitamin B12 or prostaglandin could not be patented because they are products of nature), the appellate courts held squarely on the claims' eligibility. In reaching these conclusions, the courts recognized that these purified products are not naturally occurring; rather, they are new products, ''commercially and therapeutically.'' The C.C.P.A. was reassured that the prostaglandin claims weren't so broad as to preempt all uses of the products as they ''existed in . . . nature's storehouse,'' and also concluded that the purified products have medicinal and commercial utilities that do not exist in the impure products. In other words, compared to the natural products, the purified products in these three cases have ''markedly different characteristics.''[23]

Myriad did not mention (never mind overrule) *Parke-Davis, Merck or Bergstrom*. Consistent with the Justices' concerns at oral hearing, the Court's holding in *Myriad* is narrow. The Court ''merely hold[s] that genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material,'' and even qualified its holding by noting what was ''not implicated'' by the decision.[24] We are justified then in concluding that, in the Supreme Court's view, purified natural products (*e.g.*, purified adrenalin or vitamin B12) could, *if properly claimed*, be distinguishable from isolated genes claimed by sequence.

Subsequent decisions from the Federal Circuit do not undermine our conclusion. In *Roslin*, a claim to a clonally made sheep was admitted by the applicants to reflect an animal that was ''identical'' to the naturally occurring one. While a source of pride for the inventors who had achieved such a feat, this fact doomed the claim's eligibility, as not having any ''markedly different characteristic.''[25] While the primer claims in *BRCA1- and BRCA2- . . . Litigation* were drawn to nature-based products, *i.e.*, pairs of DNA fragments, the primers were not claimed by specific activity. These two cases did not test the eligibility of natural products in purified form claimed in such manner. They do not stand in the way of claiming natural products by specific activity. Neither does the USPTO and its IGE of December 2014.

The IGE and the USPTO's Illustrative Examples

Perhaps inspired by Justice Alito's Amazonian example at oral hearing, an illustrative example in the

[19] The L.L.D. value represents the activity of vitamin B12 in an assay that stimulates the growth of the bacterium *Lactobacilis lactis Dorner*. The higher the L.L.D. value, the purer the vitamin B12. The L.L.D. value recited in the claim indicates that the compound is sufficiently pure to be therapeutically useful, but is less than that of pure vitamin B12. *Merck,* 253 F.2d at 160.

[20] *Id.* at 164.

[21] *Application of Sune Bergstrom and Jan Sjovall,* 427 F.2d 1394 (C.C.P.A. 1970)

[22] *Id*. at 1401.

[23] *See also, In re Merz*, 97 F.2d 599, 601 (C.C.P.A 1938), where the C.C.P.A. acknowledged that a purified product may be eligible for patent protection if it differs in kind, *e.g*., has a new use, compared with that of the impure product.

[24] *Myriad*, at 2119. First, said the Court, ''no method claim was before the Court.'' If Myriad had created ''an innovative method of manipulating genes,'' that method could be patent eligible. *Id*. Second, Myriad ''does not involve patents on new applications of knowledge about the BRCA1 and BRCA2 genes.'' *Id*. at 2120. And many of the unchallenged claims are new applications of knowledge of the BRCA genes (*e.g*., claims directed to a cloning vector, an expression system, or a host cell comprising the gene, or a method for producing the BRCA polypeptides) and could be patent eligible. *Id*. Third, according to the Court, DNAs with altered nucleotide sequence ''present a different inquiry'' and could be patent eligible. *Id*. For example, DNAs having mutated nucleotide sequence (*e.g*., insertions, deletions, substitutions) are not products of nature due to the mutations, and could be patent eligible. Admittedly, the Court did not mention purified natural products as ''not implicated,'' leaving us with some residual ambiguity on the matter.

[25] In fact, the *Roslin* claim is similar to an attempt to claim as ''synthetic'' a molecule made in the laboratory by organic synthesis, so that it is identical to the natural counterpart. ''Synthetic'' has two infirmities. *First*, it is a process limitation, which (like the process limitations in *Roslin's* claim) provides no patentable weight to the product, and will not help in overcoming a challenge for lack of novelty. *Second*, without more, the word ''synthetic'' adds nothing that is ''markedly different'' to the product, a legal requirement that is necessary to place it at legal distance from the natural counterpart.

  LSLR ISSN 1935-7257

March 2014 Procedure hypothesized a claim to ''Purified amazonic acid.''[26] At the time the USPTO took the position that ''because there is no structural difference between the purified acid in the claim and the acid in the leaves,'' the claimed product is not markedly different from naturally occurring amazonic acid. The USPTO concluded that such claim would not qualify as eligible subject matter.[27]

In a remarkable turnaround—and after extensive critical public comments—the IGE of December 2014 no longer states that a claimed product needs to be *structurally* different from the product in nature to be eligible.[28] It is now sufficient to demonstrate marked differences in properties or function.[29] This view provides a clear opening to draft claims based on specific activity. We propose that—with great care—claiming a product by specific activity holds the key to success at the USPTO.

The Two-Step, Two-Sub Parts Eligibility Analysis

According to the IGE, before examining a claim, Examiners should establish the broadest reasonable interpretation of the claim and analyze the claim as a whole when evaluating patent eligibility and other patentability requirements (35 U.S.C. §§ 102, 103, 112, statutory and obviousness-type double patenting).[30] Subject matter eligibility of a claim is analyzed in two steps. First, the Examiner should determine whether the claim is directed to a category recognized in Section 101—a process, machine, manufacture or composition of matter; the claim may qualify as eligible subject matter only when it is drawn to one of the four categories (Step 1).[31] If the answer to Step 1 is yes, the Examiner should proceed with a two-sub part analysis (Steps 2A and 2B) derived from *Alice*, to determine whether or not the claim falls within a judicial exception and hence its subject matter may not be eligible.[32] In the first sub-part (Step 2A), the Examiner should determine whether the claim is directed to a judicial exception: a law of nature, a natural phenomenon or an abstract idea. If the answer is no, the analysis stops and the claim is directed to eligible subject matter.[33] If the answer to the analysis of Step 2A is yes, additional analysis is required to determine whether the claim recites additional elements that amount to significantly more than the judicial exception (Step 2B).[34]

Our claim to ''purified amazonyn having a specific activity of between 1 x 10^2 and 1 x 10^5 units/mg'' is ''directed to'' a nature-based product, since it recites or describes a product (amazonyn) that is derived from natural sources (the leaves of a tree). Purified amazonyn is thus a composition of matter or a manufacture, and the answer to Step 1 of the IGE is yes. Therefore, patent eligibility of our claim depends on the analysis of Step 2, the two-subpart analysis.

[26] March 2014 Procedure, Example III. B. Claim 1.
[27] *Id*.
[28] IGE, 79 Fed. Reg. 74,623.
[29] *Id*.
[30] IGE, 79 Fed. Reg. 74,621.
[31] *Id*. at 74,622.
[32] *Id*.
[33] *Id*.
[34] *Id.*

The Markedly Different Characteristics Analysis

Only if our purified amazonyn has *markedly different characteristics* from its naturally occurring counterpart is it not judicially precluded from eligibility. Further analysis of our claim under Step 2 is thus required.[35]

The IGE provides illustrative examples of the types of characteristics that can be used for determining whether there is a ''marked difference.'' They include ''[b]iological or pharmaceutical functions or activities; [c]hemical and physical properties; phenotype, including functional and structural characteristics; and structure and form whether chemical, genetic or physical.''[36] According to the IGE, ''[m]arkedly different characteristics can be expressed as the product's structure, function, and/or other properties, and will be evaluated based on what is recited in the claim on a case-by-case basis.''[37] Let us test our claim by these standards and by the examples provided by the USPTO.

The 10 examples provided by the USPTO cover a broad range of nature-based products, including food, nucleic acids, living organisms and, most importantly for us, purified molecular products (*e.g*., purified proteins or small molecules).[38] The examples demonstrate the USPTO's broad thinking on the markedly different characteristics analysis. A few principles can be derived from these examples.

Chemical or Physical Structural Differences

If there is a structural difference, either physical or chemical, between a claimed nature-based product and its natural counterpart, there is a ''markedly different characteristic.'' It is not necessary to inquire if there is any functional change resulting from the structural change. For instance, in the USPTO's amazonic acid example (Example 3), the IGE describes two chemical derivatives of amazonic acid (5-methyl amazonic acid and deoxyamazonic acid).[39] Both of these are considered *per se* to have markedly different characteristics due to their structural differences.[40] Similarly, a change in physical structure is considered a markedly different characteristic. In Example 4, the purified antibiotic is in the form of tetrahedral crystals while the naturally occurring antibiotic is in the form of hexagonal-pyramidal crystals.[41] A purified antibiotic having such a different crystal form compared to its natural counterpart is con-

[35] Our claim, while reciting a nature-based product, is not of the type that would be considered patent eligible without going through the ''markedly different characteristics'' analysis. Our claim is not a process claim (*e.g*., a method of treating bacterial infections by administering amazonyn) which would be eligible without subjecting it to the IGE analysis. A claim to ''treating bacterial infections'' (as opposed to simply ''providing amazonyn'') is directed to a practical application of our nature-based product and would qualify as eligible subject matter. IGE, 79 Fed. Reg. 74,623.
[36] IGE, 79 Fed. Reg. 74,623.
[37] *Id*.
[38] Nature-based Product Exemplary Claim, available at http://www.uspto.gov/patents/law/exam/mdc_examples_nature-based_products.pdf.
[39] The relevant claims of Example 3 recite ''[p]urified 5-methyl amazonic acid'' (claim 2) and ''[d]eoxyamazonic acid''(claim 3).
[40] *Id*.
[41] The relevant claims of Example 4 recite ''[p]urified Antibiotic L'' (claim 2) and ''[t]he Antibiotic L of claim 1, which is in a tetrahedral crystal form'' (claim 3).

sidered to have met the markedly different characteristics analysis.

Since there are no chemical or physical structural differences between our amazonyn antibiotic as claimed and that in the tree leaves, this portion of the analysis cannot be the basis for eligibility. The result must depend on an analysis of the next—functional—portion of the IGE.

New Properties, Functions or Activities

The IGE states that ''a product that is purified or isolated . . . will be eligible when there is a resultant change in characteristics sufficient to show a marked difference from the product's naturally occurring counterpart.'' It also indicates that marked differences can be shown in ''biological or pharmacological functions or activities.''[42] While the IGE appears to indicate that, under proper circumstances, purity alone can support patent eligibility, the USPTO examples do not illustrate under what circumstances a purified natural product can be claimed based on its degree of purity alone and how such claims can be drafted.

Three USPTO examples are drawn to claims reciting purified natural products: purified amazonic acid (Example 3, claim 1), purified antibiotic L (Example 4, claim 2), and isolated nucleic acid (Example 7, claim 1). The lack of eligibility of the isolated nucleic acid in claim 1 of Example 7 is based on the holding of *Myriad*. For the remaining two claims, the USPTO concludes that the purified antibiotic L of Example 4, claim 2, but not the purified amazonic acid of Example 3, claim 1, is patent-eligible subject matter. Based on the fact pattern, only the former but not the latter, has markedly different characteristics from its natural counterpart. According to Example 4, the purified antibiotic L differs structurally from the antibiotic L existing in nature as it either has a different crystalline form (if purified from natural source) or has a different glycosylation pattern (if purified from a recombinant source). In contrast, there is no different ''characteristics (structural, functional, or otherwise)'' between the plainly claimed ''purified amazonic acid'' and the naturally occurring amazonic acid.

Unfortunately, neither the IGE nor the 10 examples go further, and positively illustrate how a claim directed simply to ''purified amazonic acid'' could be made patent eligible based solely on higher purity. It is clear that the word ''purified'' alone will not impart eligibility to a natural product. However, if the claim is to ''purified amazonyn with a specific activity between X and Y,'' the specific activity does provide the needed ''markedly different characteristic.'' This may have to be coupled with a demonstration that the specific activity limitation provides a new property or function to the claimed product (for example, a significant and reproducible pharmacological use) that does not exist for the natural counterpart. The product claimed by specific activity has become a new thing, commercially and therapeutically.

Two problems still to be addressed with such claims are, *first*, how to properly enable them and, *second*, how to balance the issues of scope and eligibility, i.e., the problem of preemption. We turn to these next.

[42] IGE, 79 Fed. Reg. at 74,623.

Properly Enabling Claims With Specific Activity Limitations

Claims to purified natural products including specific activity limitations are quite ubiquitous in the case law. By reviewing the precedents we can learn some fundamental lessons on how to properly claim natural products so that they do not run afoul of other sections of the patent statute such as, critically, 35 U.S.C. § 112, 1st paragraph.

It is tempting for an inventor who first purifies a natural product to try and claim the product as ''. . . having a purity greater than . . .'' Depending on the facts, such a claim runs the risk of being held invalid for lack of enablement. The classic example is *In re Fisher*,[43] where the invention was to a purified form of the natural product adrenocorticotrophic hormone, claimed as follows (specific activity emphasized):

> An adrenocorticotrophic hormone preparation containing *at least 1 International Unit of ACTH per milligram* and containing no more than 0.08 units of vasopressin and no more than 0.05 units of oxytocin per International Unit of ACTH, ...

The court observed that the claim had a lower but not an upper limit. Since this was unpredictable technology (involving ''physiological activity''), the specific activity of the theoretically 100 percent pure ACTH was not known and could not be known *a priori*.[44] Since the specification failed to enable how to provide ACTH preparations much above 2.3 IU/mg, the claim was held invalid for lack of enablement under 35 U.S.C. § 112, 1st paragraph.[45]

The issue of open-ended specific activities also came up in *Scripps Clinic v. Genentech*,[46] in the context of unenforceability. One of the claims was to purified natural product Factor VIII with a minimum specific activity (emphasis added):

> Claim 28. A human VIII:C preparation having *a specific activity greater than 2240 units/mg*.

Claim 28 is as open-ended as the claim in *Fisher*. In fact, the claim was challenged for unenforceability based on statements made by the Scripps inventors in attempting to distinguish *Fisher*.[47] Genentech alleged that the inventors had misled the USPTO in saying that they had ''levels closely approaching the theoretical limit.'' The Federal Circuit reversed and remanded the summary judgment of unenforceability.[48] In the process, the Court had this to say about open-ended claims:

> Open-ended claims are not inherently improper; as for all claims, their appropriateness depends on the particular facts of the invention, the disclosure, and the prior art. They may be supported if there is an inherent, albeit not precisely known, upper limit and the specification enables one of skill in the art to approach that limit.[49]

Erythropoietin (''EPO''), another natural product, was claimed by an open-ended specific activity in *Am-*

[43] *In re Fisher*, 427 F.2d 833 (C.C.P.A. 1970).
[44] *Id*. at 839.
[45] *Id*.
[46] *Scripps Clinic & Research Foundation v. Genentech, Inc.*, 927 F.2d 1565 (Fed. Cir. 1991).
[47] *Id*. at 1572.
[48] *Id*. at 1573.
[49] *Id*. at 1572.

  LSLR ISSN 1935-7257

gen v. Chugai.[50] Claim 1 was as follows (emphasis added):

> Homogeneous erythropoietin characterized by a molecular weight of about 34,000 daltons on SDS PAGE, movement as a single peak on reverse phase high performance liquid chromatography and *a specific activity of at least about 160,000 IU per absorbance unit at 280 nanometers*.

This claim was invalidated for lack of enablement, albeit not because it was open-ended, as in *Fisher* or *Scripps*. The reason was simpler: there was no evidence that Chugai had ever prepared EPO with a specific activity of at least 160,000 IU/AU. Chugai had obtained EPO of about 80,000 IU/AU.[51] They showed that it was about 50 percent pure, and so they calculated the maximum theoretical limit to be about twice as much. The court concluded that Chugai did not have a workable method to make the claimed product.[52]

Finally, in *Genentech v. Wellcome*,[53] the natural product was human tissue plasminogen activator, t-PA. Claim 1 was as follows (emphasis added):

> Human plasminogen activator, having thrombolytic properties, immunologically distinct from urokinase and *having a specific activity of about 500,000 IU/mg.* using the WHO [World Health Organization] First International Reference Preparation of t-PA (tissue plasminogen activator) as assay standard . . .

The main problem here was that, while the claim was not open-ended and contained an assay *standard*, it was not clear from the specification what assay *method* was actually used to reach the number of ''about 500,000 IU/mg.''[54] The numerical measurement of specific activity of t-PA can vary by more than a factor of three depending on the specific assay method used.[55] The court held that ''assay'' meant the ''bovine fibrin plate assay,'' which the court chose so that the accused activity could be properly compared to the prior art and to the claim.[56] Under that assay, the values of specific activity of the accused product were between 200,000 IU/mg and 300,000 IU/mg, quite below the claimed 500,000 IU/mg.[57] There was no literal infringement.[58]

While these cases did not address eligibility issues but were based primarily on enablement and claim construction, they demonstrate that the courts have carefully scrutinized claims with specific activity limitations. We believe that the claims in these cases, by including specific activity limitations, would pass the eligibility standards of the Supreme Court Triad and the USPTO's IGE. The materials there are not just claimed as ''purified'' or ''isolated,'' but are markedly different than the natural counterparts. Because of the magnitudes of their claimed specific activity, they have significant pharmacological or biological activities that the natural products do not have.

Notwithstanding eligibility, the cases show that great care needs to be exercised under 35 U.S.C. § 112, first paragraph, the enablement requirement, when drafting product claims with specific activity limitations. For example,

- If the theoretical degree of maximum purity is not known (as in *Fisher*), a claim cannot be open-ended;[59]
- An applicant risks a finding of inequitable procurement if, without corroboration, she alleges that the specific activity in an open-ended claim is ''near the theoretical maximum'' (as in *Scripps v. Genentech*[60]);
- If a specific activity is claimed by lower limit or by range, there must be described an enabling method of achieving it (not like in *Amgen v. Chugai*[61]); and
- Care must be taken to provide clear descriptions of what assay is to be used in the definition of ''specific activity'' (as in *Genentech v. Wellcome*.[62])

The Balance Between Claim Scope and Eligibility

The IGE recognizes that if there is sufficient difference between the claimed nature-based product and its natural counterpart to ensure that the claim is not improperly tying up the future use of the naturally occurring product, the difference rises to the level of a marked difference and supports patent eligibility of the claim.[63] The USPTO derived this rule based on the Supreme Court's analysis in *Myriad*. While acknowledging that the claimed isolated genes[64] differ in chemical structure from their natural counterparts, the Supreme Court held that the isolated gene claims are not patent eligible, as they were concerned primarily with the information contained in the genetic sequence, which is the same as that existing in nature.[65] Such sequence-based claims would preempt any work on the genes themselves and thus are not eligible. By contrast, the Court reached the opposite conclusion for a cDNA claim[66] despite the fact that the information content of a cDNA sequence is the same as that of the corresponding, naturally occurring mRNA sequence. The Court likely concluded that the cDNA claim is patent eligible, for it is of a narrower scope and does not preempt. Unlike the isolated gene claims that block the use of any and all DNA sequences encoding the BRCA1 protein, the cDNA claim was drawn to a sub-universe of all DNA molecules. The IGE echoes these court holdings:

> Under the holding of *Myriad*, this isolated but otherwise unchanged DNA [claim 1 to the isolated gene] is not eligible because it is not different enough from what exists in na-

[50] *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200 (Fed. Cir. 1991).
[51] *Id*. at 1216.
[52] *Id*. at 1217.
[53] *Genentech v. The Wellcome Foundation Ltd.*, 29 F.3d 1555 (Fed. Cir. 1994).
[54] *Id*. at 1562.
[55] *Id*.
[56] *Id*.
[57] *Id*. at 1566-1567.
[58] *Id*.
[59] *In re Fisher*, 427 F.2d at 839-840.
[60] *Scripps v. Genentech, Inc.*, 927 F.2d at 1572.
[61] *Amgen v. Chugai*, 927 F.2d at 1216-1217.
[62] *Genentech v. Wellcome*, 29 F.3d at 1562.
[63] IGE, 79 Fed. Reg. at 74,625-74,626.
[64] For example, claim 1 of the '282 patent is drawn to isolated genomic genes and reads as follows, ''An isolated DNA coding for a BRCA1 polypeptide . . . having the amino acid sequence set forth in SEQ ID NO:2.''
[65] *Id*. at 2116-2119.
[66] Claim 2 of the '282 patent is directed to a cDNA sequence and recites ''[t]he isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1.''

ture to avoid improperly tying up the future use and study of the naturally occurring BRCA1 gene.

***

[The] differences in structural characteristics between the claimed DNA [claim 2 to the cDNA gene] and the natural gene are significant, *e.g.*, they are enough to ensure that the claim is not improperly tying up the future use of the BRCA1 gene. Thus, they rise to the level of a marked difference, and the claimed DNA is not a 'product of nature' exception.[67]

Indeed, in its Triad, the Supreme Court has described the underlying concern that drives the judicial exceptions ''as one of pre-emption,'' and urged that patent law not inhibit further discovery by improperly tying up the future use of natural building blocks.[68] Interestingly, the IGE suggests that if the claim is drafted in a manner that does not preempt use of the natural product it will be considered eligible, regardless of whether the claimed product exhibits new functions or properties.

The theme of preemption appears in multiple cases dealing with Section 101. The theme links the concept of claim eligibility with that of claim scope. The conclusion seems to be that at some level of breadth one crosses over from eligibility to non-eligibility; i.e., one is then including in the claim the phenomenon of nature, and such inclusion makes the claim as a whole ineligible. The broader the claim, the more likely that it preempts a fundamental block of nature. The narrower the claim, the more likely that it is eligible. Enablement of broad claim scope under Section 112 is not the same as its eligibility. While it is possible to fully enable a broad claim, its breadth might still be so wide as to render it invalid under Section 101 for preemption. The converse is also true: even though a narrowly drafted claim might avoid pre-emption challenges, the claim still needs to be properly enabled.

Applying this to our amazonyn claim, if the specific activity limitations encompass the natural product's purity all the way from that in the leaves of the tree (e.g., 10^{-3} units/mg) to that in the material having 100 percent purity (e.g., 10^{5} units/mg), then the claim will be invalid as ineligible for improper preemption. Even if fully enabled, such a claim (purified amazonyn having a specific activity of 1×10^{-3} units/mg to 1×10^{5} units/mg) will be unobtainable at the USPTO and could readily be invalidated in the courts.

Conclusion

The IGE of December 2014 is a substantial clarification (and, we suggest, an improvement) over the March 2014 Procedure. The IGE goes beyond chemical or structural changes, and embraces several types of different ''characteristics,'' including biological or pharmacological functions or activities. This represents a welcome change to the biotechnology or pharmaceutical industries, where nature-based products represent an important source for innovation.

We propose that, even if structurally unchanged, purified natural products such as antibiotics should be claimed by specific activity. The scope of such claims needs to strike a balance between eligibility and enablement. However, by including specific activity in the claim, such products become suitable for new biological or pharmaceutical uses, or, if the specific activity is of proper scope, the claims will not be so broad as to preempt use of the product as found in nature. In either of such situations the purified products have ''markedly different characteristics'' compared to their natural counterparts and should be eligible for patent. The discovery, purification, patenting and commercialization of natural antibiotics will not be severely hindered if claims to the purified products are properly drafted.

---

[67] IGE, 79 Fed. Reg. at 74,626.

[68] *Alice*, 134 S. Ct. at 2358; *Myriad*, 133 S. Ct. at 2116; *Mayo*, 132 S. Ct. at 1302.

   ISSN 1935-7257