



May 7, 2014

**Comments of Cubist Pharmaceuticals, Inc. in Response to the USPTO’s Guidance for Determining Subject Matter Eligibility of Claims Reciting or Involving Laws of Nature, Natural Phenomena & Natural Products**

**I. INTRODUCTION**

Cubist Pharmaceuticals, Inc. thanks the U.S. Patent and Trademark Office (“USPTO”) for this opportunity to comment on the USPTO’s Guidance for the examination of patent claims concerning laws of nature, natural phenomena, and natural products.<sup>1</sup>

Cubist is a biopharmaceutical company based in Lexington, Massachusetts. Cubist is focused on the research, development, and commercialization of pharmaceutical products that address unmet medical needs in the acute care environment. Our products and product candidates are used, or are being developed to be used, in hospitals and other acute care settings, including home infusion and hospital outpatient clinics.

In 1997, Cubist in-licensed daptomycin, a first-in-class cyclic lipopeptide antibiotic drug candidate. Daptomycin, a small molecule fermentation product, has since been approved as the purified pharmaceutical composition CUBICIN<sup>®</sup>, for the treatment of complicated skin and skin structure infections and *Staphylococcus aureus* bloodstream infections (bacteremia), including right-sided infective endocarditis caused by methicillin-resistant *Staphylococcus aureus*. As of the end of 2013, CUBICIN<sup>®</sup> had been used to treat an estimated two million patients in the United States. Cubist also markets DIFICID<sup>®</sup> (fidaxomicin), another purified fermentation-derived antibiotic composition, and the first antibacterial drug indicated for *Clostridium difficile*-associated diarrhea (CDAD) to be approved in over 25 years in the US. Cubist’s search for new antibiotics is ongoing. For example, Cubist’s clinical product pipeline includes a novel antipseudomonal cephalosporin used with a  $\beta$ -lactamase inhibitor for treating certain serious infections caused by Gram-negative organisms.

Cubist appreciates the USPTO’s efforts to improve the quality of examination and provide guidance regarding patentable subject matter. These comments identify specific

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<sup>1</sup> Memorandum from Andrew H. Hirschfeld, Deputy Comm’r for Patent Examination Policy, 2014 Procedure for Subject Matter Eligibility Analysis of Claims Reciting or Involving Laws of Nature/Natural Principles, Natural Phenomena, and/or Natural Products (Mar. 4, 2014), *available at* [http://www.uspto.gov/patents/law/exam/myriad-mayo\\_guidance.pdf](http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf) (the “Guidance”).

areas in which Cubist believes the Guidance could be tailored to be more consistent with relevant case law and avoid unduly burdening the biopharmaceutical industry, particularly with regard to development of drug products derived from naturally-occurring small molecules.

## **II. INVENTIONS RELATING TO NATURAL PRODUCTS ARE CENTRAL TO THE BIOPHARMACEUTICAL INDUSTRY**

Inventive compositions derived from naturally-occurring small molecules have long been a mainstay of the biopharmaceutical industry,<sup>2</sup> with innovation in this area promoted at least in part by the ability to pursue patents. Pharmaceutical compositions derived from natural products make up a significant percentage of new drugs, and they are disproportionately used to treat high-need diseases, like infections and cancer, that already present challenging economic and scientific hurdles for drug development.<sup>3</sup> Natural product-related drug development is likely to grow in importance in the coming years, as recent advances in related fields have made it possible to access large reserves of natural products that were previously unavailable. Therefore, it is important not to restrict the scope of patentable subject matter with respect to innovations relating to or derived from natural products any more than § 101 and the relevant case law require.

### **A. History of Natural Products in the Biopharmaceutical Industry**

Since the discovery of penicillin and other antibiotics in the early 20<sup>th</sup> century, compositions derived from naturally-occurring small molecules—and patents relating to them—have played a central role. The USPTO issued patents on many early antibiotics derived from natural sources, including streptomycin.<sup>4</sup> These patents, as well as others relating to innovative compositions containing naturally-occurring compounds and their purification, have played a key role in launching the biopharmaceutical industry and helped to “revolutionize[]” medicinal science and clinical practice.<sup>5</sup> Indeed, in response to American penicillin purification patents filed during World War II, a member of the British House of Commons lamented that the British government, “instead of taking over control of this British discovery, had handed over the manufacture almost entirely to the

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<sup>2</sup> See, e.g., Gerard Wright, *Synthetic Biology Revives Antibiotics*, 509 *Nature* S13, S13 (2014).

<sup>3</sup> *Id.* (noting that “[m]any antibiotics, for example, have their origins in bacteria or fungi”).

<sup>4</sup> U.S. Patent No. 2,449,866 (issued Sept. 21, 1948).

<sup>5</sup> See, e.g., Selman A. Waksman, Nobel Prize Lecture (Dec. 12, 1952), *available at* [http://www.nobelprize.org/nobel\\_prizes/medicine/laureates/1952/waksman-lecture.pdf](http://www.nobelprize.org/nobel_prizes/medicine/laureates/1952/waksman-lecture.pdf).

**Comments of Cubist Pharmaceuticals, Inc.**  
**May 7, 2014**

United States.”<sup>6</sup> This was in direct response to the rapid growth of the antibiotics industry in the US, which those penicillin-related patents largely enabled.<sup>7</sup>

The age of natural product-related drug discovery continued past the mid-20<sup>th</sup> century. Natural products have been, and continue to be, an invaluable source of novel drug compositions for the treatment of many diseases.<sup>8</sup> Of the 1073 small molecules approved as drugs between 1981 and 2010, 59 (6%) are compositions containing natural products.<sup>9</sup> Another 299 (28%) are derived from natural products, 177 (16%) are synthetic structures that are derived directly from natural products, and 146 (14%) are synthetic structures that are modeled on a natural product.<sup>10</sup> Only 36% of all approved drugs as purely synthetic structures derived without reliance on natural products.<sup>11</sup>

**B. Drugs Derived from Natural Products Are Disproportionately Used to Treat High-Need Diseases**

Drug compositions derived from naturally-occurring small molecules are also disproportionately used to treat diseases for which few other options exist. The largest proportions of such drugs approved between 1981 and 2010 are anti-infectives (12 anti-infective drugs, representing 20% of drug compositions containing natural products approved during this time period).<sup>12</sup> These drugs address a particularly acute medical need. Governments around the world have highlighted the problem of antibiotic resistance and sounded the alarm for new antibiotic development.<sup>13</sup> Despite the great need for such drugs, however, the economics faced by pharmaceutical companies seeking

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<sup>6</sup> See Robert Bud, *Penicillin and the New Elizabethans*, 31 *Brit. J. for Hist. Sci.* 305, 315 (1998); see also Ronald Bentley, *Different Roads to Discovery; Protonosil (Hence Sulfa Drugs) and Penicillin (Hence  $\beta$ -lactams)*, 36 *J. Industrial Microbiology & Biotechnology* 775, 783 (2009).

<sup>7</sup> Bud, *supra* note 6, at 314-15.

<sup>8</sup> See, e.g., Gordon M. Cragg, Paul G. Grothaus & David J. Newman, *New Horizons for Old Drugs and Drug Leads*, 77 *J. Natural Products* 703, 704 (2014).

<sup>9</sup> David J. Newman & Gordon M. Cragg, *Natural Products as Sources of New Drugs over the 30 Years from 1981 to 2010*, 75 *J. Natural Products* 311, 313 (2012).

<sup>10</sup> *Id.*; see also Gordon M. Cragg & David J. Newman, *Natural Products: A Continuing Source of Novel Drug Leads*, 1830 *Biochimica et Biophysica Acta* 3670, 3679 (2013).

<sup>11</sup> Newman & Cragg, *supra* note 9, at 312; Cragg & Newman, *supra* note 10, at 3679.

<sup>12</sup> Newman & Cragg, *supra* note 9, at 312, 314-15.

<sup>13</sup> See, e.g., Rear Adm. Boris D. Lushniak, Acting Surgeon Gen., *Preserving Antibiotics Key to Protecting Patients*, CDC SAFE HEALTHCARE BLOG, (Mar. 6, 2014 10:41 AM), <http://blogs.cdc.gov/safehealthcare/2014/03/06/preserving-antibiotics-key-to-protecting-patients/>; Dame Sally C. Davis, Chief Medical Officer, UK Dep't of Health, Annual Report of the Chief Medical Officer, available at <https://www.gov.uk/government/publications/chief-medical-officer-annual-report-volume-2>; cf. Alexander Fleming, Nobel Prize Lecture (Dec. 11, 1945) (raising concern about penicillin resistance as early as 1945).

**Comments of Cubist Pharmaceuticals, Inc.**  
**May 7, 2014**

to develop them are challenging.<sup>14</sup> After granting 19 new drug applications related to antibiotics in the first half of the 1980s, the FDA has approved only four since 2005.<sup>15</sup> Commentators have noted that, even with the patent system providing protection for antibiotic compositions of naturally-occurring small molecules, “we need a new financial way forward to incentivize the discovery, development and registration of new antibiotics.”<sup>16</sup> Unnecessarily restricting patentable subject matter as it relates to compositions of naturally-occurring small molecules, a major source of new antibiotics, would hinder such efforts.

**C. Undue Restrictions on Patentable Subject Matter Would Hinder Drug Development**

Over the coming years, the number of drug compositions derived from naturally-occurring small molecules is likely to increase. The development of combinatorial chemistry through the 1990s and 2000s led many pharmaceutical companies to move away from natural products, but that trend is reversing as synthetic small molecule pipelines are drying up.<sup>17</sup> New tools are also emerging to allow scientists to access and study natural products.<sup>18</sup> Scientists have estimated that less than 1% of all microorganisms that have been seen under a microscope have been cultivated.<sup>19</sup> Improved culture procedures are making it possible to grow microorganisms that were previously unavailable, and to study the molecules that they produce.<sup>20</sup> Advances in oceanography and environmental science also are making it possible to collect samples from previously inaccessible areas.<sup>21</sup> Furthermore, recent findings suggest that organisms produce a host of novel products when grown together instead of separately, providing new products for researchers to study.<sup>22</sup> Molecular biologists have also discovered silent genes that code for products hidden in bacterial and fungal genomes,

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<sup>14</sup> See Mark S. Butler, Mark A. Blaskovich & Matthew A. Cooper, *Antibiotics in the Clinical Pipeline in 2013*, 66 J. Antibiotics 571, 572 (2013) (“The net present value for an antibiotic to treat acute infections does not compare to the values ascribed to most other therapeutic areas.”).

<sup>15</sup> Karyn Hede, *An Infectious Arms Race*, 509 Nature S2, S3 (2014).

<sup>16</sup> Butler, *supra* note 14, at 572; see also Richard P. Wenzel, *The Antibiotic Pipeline—Challenges, Costs, and Values*, 351 New Eng. J. Med. 523, 525 (2004).

<sup>17</sup> Dwight D. Baker et al., *The Value of Natural Products to Future Pharmaceutical Discovery*, 24 Natural Product Rep. 1225, 1227 (2007); Guy T. Carter, *Natural Products and Pharma 2011: Strategic Changes Spur New Opportunities*, 28 Natural Product Rep. 1783, 1783 (2011); see also Isabel Najera et al., *Focused Research in Different Approaches to Antibiotic Resistance: Roche’s Re-entry into Antibiotics*, 509 Nature (Sponsor Feature) 1 (May 1, 2014).

<sup>18</sup> Wright, *supra* note 2, at S13.

<sup>19</sup> Cragg & Newman, *supra* note 8, at 3681.

<sup>20</sup> *Id.*

<sup>21</sup> *Id.* at 3682; Katherine Gammon, *Leaving No Stone Unturned*, 509 Nature 510, 511 (2014).

<sup>22</sup> Cragg & Newman, *supra* note 10, at 3683.

and they are working to find ways to express and isolate these previously unknown drug candidates.<sup>23</sup>

Researchers must now build upon these discoveries to develop new therapeutic compositions and methods of making and using them. Significant inventive efforts will be required to realize the potential of such naturally-occurring molecules for providing new pharmaceutical treatments. These advances have the potential to produce important new drugs, but only if the economy and the patent system provide appropriate incentives for natural products-related research. Cubist, for example, has invested over \$1 billion to bring important life-saving antibiotics to the market, including CUBICIN® and DIFICID®. Unlike diagnostic methods, which were at issue in several of the recent patentable subject matter cases, antibiotics require extensive clinical trials, with substantially more time and resources invested to bring a product to market. If the USPTO now goes beyond the Supreme Court's requirements in refusing to grant patents on inventions derived from or relating to natural products, Cubist and other companies like it will not be able to protect their research and development investments. Therefore, the Guidance should not extend recent Supreme Court decisions to unduly restrict patentable subject matter with respect to natural products-related inventions.

### **III. THE GUIDANCE IS UNDULY RESTRICTIVE OF PATENTABLE SUBJECT MATTER WITH RESPECT TO INVENTIVE COMPOSITIONS AND METHODS DERIVED FROM NATURAL PRODUCTS**

The Guidance indicates that all inventions bearing any relation to natural products will be subject to heightened scrutiny with respect to patentable subject matter. This approach captures compositions containing small molecule natural products, proteins, and vaccines, as well as the DNA segments that were expressly addressed by the Supreme Court in the *Myriad* case. The Guidance adopts a “significantly different” test for evaluating whether natural product-related inventions are directed to patentable subject matter, as illustrated by examples in the Guidance. Cubist respectfully believes that this “significantly different” test is not required by the Supreme Court's patentable subject matter decisions, extends further than necessary in restricting patentable subject matter, and, unless revised, risks depriving true innovations of the patent protection that the statute properly accords them.

#### **A. The Supreme Court's Patentable Subject Matter Decisions Are Narrow**

The Supreme Court cases cited as justification for the broad approach taken in the Guidance do not directly address inventive compositions derived from naturally-occurring small molecules, and each of these decisions contains language expressly narrowing the scope of its holding.

The *Myriad* opinion addressed two specific questions: (1) “whether a naturally occurring segment of deoxyribonucleic acid (DNA) is patent eligible under 35 U.S.C. § 101 by

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<sup>23</sup> Newman & Cragg, *supra* note 9, at 331-32.

**Comments of Cubist Pharmaceuticals, Inc.**  
**May 7, 2014**

virtue of its isolation from the rest of the human genome,” and (2) whether “synthetically created DNA known as complementary DNA (cDNA), which contains the same protein-coding information found in a segment of natural DNA but omits portions within the DNA segment that do not code for proteins” was patent-eligible.<sup>24</sup> The Supreme Court expressed its holding in narrow terms as well, concluding only “that a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated, but that cDNA is patent eligible because it is not naturally occurring.”<sup>25</sup> The Court further pointed out that there were no method claims, no “patents on new applications of knowledge,” and no claims to “DNA in which the order of the naturally occurring nucleotides has been altered” before it.<sup>26</sup> The Court “*merely* h[e]ld that genes and the information they encode are not patent eligible under § 101 simply because they have been isolated from the surrounding genetic material.”<sup>27</sup> As the Court noted, “Myriad’s claims are simply not expressed in terms of chemical composition, nor do they rely in any way on the chemical changes that result from the isolation of a particular section of DNA. Instead, the claims understandably focus on the genetic *information* encoded in the [DNA segment].”<sup>28</sup>

*Myriad*’s holding does not determine whether classes of inventions not addressed in the opinion, such as inventive compositions derived from naturally-occurring small molecules, are patentable subject matter. For example, the holding relating to isolation of genetic information is not determinative of claims based on extraction, purification, concentration, or synthetic techniques that result in a new composition that is different from what is found in nature.

Indeed, oral argument reinforced that purified or concentrated compositions of small molecule natural products were not before the Court, and suggested that the Court had some concerns about extending holdings relating to non-patentable subject matter to such inventions. Justice Ginsburg engaged in the following exchange with counsel for the Association for Molecular Pathology (“AMP”) at the beginning of oral arguments:

JUSTICE GINSBURG: Mr. Hansen, Respondents say that isolating or extracting natural products, that has long been considered patentable, and give -- examples were aspirin and whooping cough vaccine. How is this different from -- those start with natural -- natural products.

MR. HANSEN: Well, in -- in essence, Your Honor, everything starts with a natural product. And this Court has said repeatedly that just extracting a natural product is insufficient. For example, this Court has used the example

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<sup>24</sup> *Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107, 2111 (2013).

<sup>25</sup> *Id.*

<sup>26</sup> *Id.* at 2120 (emphasis removed).

<sup>27</sup> *Id.* (emphasis added).

<sup>28</sup> *Id.* at 2118 (emphasis added).

**Comments of Cubist Pharmaceuticals, Inc.**  
**May 7, 2014**

of gold. You can't patent gold because it's a natural product.

The examples that you cite all involve further manipulation of a product of nature, so that the product of nature is no longer what it was in nature; it's become something different, and in many instances has taken on a new function.<sup>29</sup>

Justice Alito later returned to the topic, posing a hypothetical similar to the amazonic acid example (Example B) in the Guidance:

JUSTICE ALITO: Can I take you back to -- to Justice Ginsburg's question, because I'm -- I don't -- I'm not sure you got at what troubles me about that.

Suppose there is a substance, a -- a chemical, a molecule in the -- 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 -- it treats breast cancer.

A new discovery, a new way -- a way is found, previously unknown, to extract that. You make a drug out of that. Your answer is that cannot be patent -- patented; it's not eligible for patenting, because the chemical composition of the -- of the drug is the same as the chemical that exists in the leaves of the plant.

MR. HANSEN: If there is no alteration, if we simply pick the leaf off of the tree and swallow it and it has some additional value, then I think it is not patentable. You might be able to get a method patent on it, you might be able to get a use patent on it, but you can't get a composition patent.

But as --

JUSTICE ALITO: But you're making -- you keep making the hypotheticals easier than they're intended to be. 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 -- the value of this. But it's extracted and -- and reduced to a concentrated form. That's not patent -- that's not eligible?***

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<sup>29</sup> Transcript of Oral Argument at 3:24-4:15, *Ass'n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (No. 12-398).

**Comments of Cubist Pharmaceuticals, Inc.**  
**May 7, 2014**

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 the -- by both changing its nature and by giving it a new function, you may well have patent --<sup>30</sup>

*Prometheus*<sup>31</sup> and *Funk Brothers*<sup>32</sup> took a similar approach to *Myriad*, in that the Court expressly limited the scope of its holdings. The question presented in *Prometheus* was “whether the claimed processes have transformed these unpatentable natural laws [describing the relationships between the concentration in the blood of certain thiopurine metabolites and the likelihood that the drug dosage will be ineffective or induce harmful side-effects] into patent-eligible applications of those laws.”<sup>33</sup> It then “conclude[d] that the patent claims at issue *here* effectively claim the underlying laws of nature themselves . . . [and] are consequently invalid.”<sup>34</sup> Justice Frankfurter, concurring in *Funk Brothers*, referenced the need to “avoid a formulation which, while it would in fact justify [the patent at issue], would lay the basis for denying patentability to a large area within existing patent legislation.”<sup>35</sup> The final two opinions cited in the Guidance, *J.E.M.* and *Chakrabarty*, both declined to limit the scope of § 101 and affirm the principle that “the language of § 101 is extremely broad.”<sup>36</sup> Thus, the Guidance should allow for patentability of inventions and discoveries according to the full scope of § 101 (*i.e.*, “[w]hoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof”), except as specifically required by the Court’s limited exceptions.

In light of these cases, it appears that the Guidance should be more narrowly tailored in implementing the USPTO’s conclusion that “the Supreme Court has made it clear that

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<sup>30</sup> *Id.* at 6:24-8:12.

<sup>31</sup> *Mayo Collaborative Servs. v. Prometheus Labs., Inc.*, 132 S. Ct. 1289 (2012).

<sup>32</sup> *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948).

<sup>33</sup> *Prometheus*, 132 S. Ct. at 1294.

<sup>34</sup> *Id.* at 1305.

<sup>35</sup> *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 135 (1948) (Frankfurter, J., concurring).

<sup>36</sup> *J.E.M. Ag Supply, Inc. v. Pioneer Hi-Bred Int’l, Inc.*, 534 U.S. 124, 130 (2001); *id.* at 131 (“[W]e are mindful that this Court has already spoken clearly concerning the broad scope and applicability of § 101.”); *Diamond v. Chakrabarty*, 447 U.S. 303, 308 (1980) (“Congress plainly contemplated that the patent laws would be given wide scope.”).



**Comments of Cubist Pharmaceuticals, Inc.**  
**May 7, 2014**

‘naturally occurring things’ is a broad term.”<sup>37</sup> The Supreme Court has addressed limited, specific issues in each of the opinions cited in the Guidance, and has made clear that it is § 101 that is broad, not the exceptions to it. These cases do not appear to provide sufficient basis for applying heightened scrutiny to every claim with a limitation bearing any relation to a natural product and requiring that inventions relating to or derived from natural products must meet a new “significantly different” test with respect to patentable subject matter.

Since at least the 1940s, the USPTO has been granting patents on inventions relating to naturally-occurring small molecules, for example, the antibiotics streptomycin,<sup>38</sup> actinomycin,<sup>39</sup> neomycin,<sup>40</sup> and candidin.<sup>41</sup> These patents have covered, *inter alia*, inventive processes for producing the molecules and compositions of the molecules. Courts have also recognized that compositions containing naturally-occurring small molecules (similar to the amazonic acid in the Guidance’s Example B) may be patentable subject matter. As discussed above, the Supreme Court’s holding in *Myriad* with respect to isolated DNA is limited, and not determinative of all such situations.

For example, in the *Parke-Davis* adrenaline patent case, Judge Learned Hand concluded 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.<sup>42</sup>

In another case involving a purified composition of vitamin B<sub>12</sub>, the Fourth Circuit (relying upon the reasoning in *Parke-Davis*) concluded that “[t]he fact . . . that a new and useful product is the result of processes of extraction, concentration and purification of natural materials does not defeat its patentability.”<sup>43</sup>

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<sup>37</sup> June Cohen et al., Office of Patent Legal Admin., U.S. Patent & Trademark Office, Presentation to the Biotechnology/Chemical/Pharmaceutical Customer Partnership at 20 (Apr. 16, 2014), *available at* [http://www.uspto.gov/patents/announce/myriad-mayo\\_bcp\\_20140416.pdf](http://www.uspto.gov/patents/announce/myriad-mayo_bcp_20140416.pdf) (the “Apr. 16, 2014 Guidance Presentation”).

<sup>38</sup> U.S. Patent No. 2,449,866 (issued Sept. 21, 1948).

<sup>39</sup> U.S. Patent No. 2,378,876 (issued June 19, 1945).

<sup>40</sup> U.S. Patent No. 2,799,620 (issued July 16, 1957).

<sup>41</sup> U.S. Patent No. 2,992,162 (issued July 11, 1961).

<sup>42</sup> *Parke-Davis & Co. v. H.K. Mulford Co.*, 189 F. 95, 103-04 (C.C.S.D.N.Y. 1911) (Hand, J.) (emphasis added) (sustaining product claims of a patent to purified adrenalin).

<sup>43</sup> *Merck & Co. v. Olin Mathieson Chem. Corp.*, 253 F.2d 156, 163-64 (4th Cir. 1958) (finding claim to purified vitamin B<sub>12</sub> to be within the scope of patentable subject matter because “the natural fermentates are quite useless, while the patented compositions are of great medicinal and commercial value”).

**Comments of Cubist Pharmaceuticals, Inc.**  
**May 7, 2014**

The Court of Customs and Patent Appeals followed this trend. In *Application of Bergy*, the C.C.P.A., citing *Parke-Davis* and *Merck*, concluded that “[t]he law has long and unhesitatingly granted patent protection to new, useful, and unobvious chemical compounds and compositions, in which category are to be found such important products of microbiological process as vitamin B-12 and adrenalin and countless other pharmaceuticals.”<sup>44</sup> The Federal Circuit observed in its *Myriad* opinion in 2012, in dicta, that this principle remains true.<sup>45</sup> The Supreme Court’s ruling in *Myriad* did not purport to overturn these precedents, and continuing to recognize patentability of inventive compositions derived from naturally-occurring small molecules is not inconsistent with *Myriad*. Accordingly, the Guidance should not apply the new “significantly different” test (e.g., with respect to amazonic acid in Example B) to restrict patentable subject matter in this area beyond what has been expressly required by the Supreme Court.

**B. The “Significantly Different” Test as Applied in the Guidance Is Overly Restrictive of Patentable Subject Matter Relating to Natural Products**

The “significantly different” test applied by the Guidance does not appear in the cases cited in the Guidance (i.e., *Myriad*, *Prometheus*, *Funk Brothers*, *J.E.M.*, or *Chakrabarty*). Rather, the USPTO appears to have arrived at this standard by “bring[ing] together the outcomes of both *Myriad* and *Mayo*,” and outlining two main routes in which patentable subject matter can be demonstrated: a claim can either (1) recite a “[m]arked difference from what exists in nature” (relying on *Myriad*’s citations to *Chakrabarty*<sup>46</sup>); or (2) involve the “[a]ddition of significantly more to the judicial exception” (relying on *Prometheus*<sup>47</sup>).<sup>48</sup>

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<sup>44</sup> 596 F.2d 952, 975 (C.C.P.A. 1979), *vacated in part sub nom. Diamond v. Chakrabarty*, 444 U.S. 1028, *aff’d sub nom. Diamond v. Chakrabarty*, 447 U.S. 303 (1980) (footnote omitted). Although Judge Lourie suggested that *Bergy* was vacated by the Supreme Court in a footnote in the first *Myriad* Federal Circuit opinion, only the judgment in one of the two consolidated cases addressed by the *Bergy* opinion was vacated. The *Bergy* opinion and judgment in the second of the two consolidated cases (*Chakrabarty*) remains good law that has been affirmed, and later cited, by the Supreme Court. *See Diamond v. Diehr*, 450 U.S. 175, 189 (1981).

<sup>45</sup> *Ass’n for Molecular Pathology v. U.S. Patent & Trademark Office*, 689 F.3d 1303, 1328 (Fed. Cir. 2012), *cert. granted in part*, 133 S. Ct. 694 (2012), *aff’d in part, rev’d in part on other grounds sub nom. Ass’n for Molecular Pathology v. Myriad Genetics, Inc.*, 133 S. Ct. 2107 (2013) (explaining that “purified natural products . . . may or may not qualify for patent under § 101” and noting that *Myriad* “is not a situation, as in *Parke-Davis & Co. v. H.K. Mulford Co.*, in which purification of adrenaline resulted in the *identical* molecule, albeit being ‘for every practical purpose a new thing commercially and therapeutically’”).

<sup>46</sup> Apr. 16, 2014 Guidance Presentation at 37.

<sup>47</sup> *Id.* at 50.

<sup>48</sup> *Id.* at 31; Guidance at 3-4.

1. **The Supreme Court’s Decisions Do Not Support a Requirement That Inventions Be “Markedly Different in Structure” from Naturally-Occurring Products**

The Supreme Court’s holding in *Myriad* does not support the broad reading of “markedly different” that the Guidance applies in its examples. For example, in the claim to the natural product composition in the Guidance’s Example B (“amazonic acid”), the USPTO explains that “Factor a) [the “markedly different in structure” requirement] is not satisfied, because there is no **structural** difference between the purified acid in the claim and the acid in the leaves.”<sup>49</sup> As an initial matter, this ignores that a purified **composition** may well be structurally different from a composition containing various contaminants found in nature. Moreover, the Supreme Court’s “markedly different” analysis has not been limited to structural differences. In concluding that the invention in *Chakrabarty* was patentable subject matter, the Court found that “the patentee has produced a new bacterium with **markedly different characteristics** from any found in nature **and** one having the **potential for significant utility**.”<sup>50</sup> The *Myriad* Court drew on this language from *Chakrabarty*, noting that the invention there “was new ‘with markedly different **characteristics** from any found in nature,’ . . . due to the additional plasmids and **resultant ‘capacity** for degrading oil.’”<sup>51</sup>

Thus, the Supreme Court has considered whether the characteristics of the claimed invention, **taken as a whole**, are different from a product occurring in nature. These differences have included not only structural differences (as the Guidance recognizes), but also functional differences (*e.g.*, a new “resultant capacity”) and technical/economic differences (*e.g.*, a “potential for significant utility”). Other differences might include differences in concentration, differences in associated impurities, or differences resulting from preparation using new synthetic methods. Turning to Example B of the Guidance, being able to administer “one teaspoon of the purified acid”—the claimed invention in Example B—“to get the same effects as 30 pounds of the leaves”<sup>52</sup> is a significant functional and technical/economic difference from the product that existed before (*i.e.*, the claimed composition provides a useful therapeutic drug product, while a composition made up of 30 pounds of leaves containing amazonic acid to be ingested daily does not). As explained above, the concept of a small molecule isolated from the leaves of a plant in the Amazon (very similar to the Guidance’s Example B) came up during the *Myriad* oral argument. The above-quoted exchange suggests some concern by the Court about extending a finding of non-patentable subject matter to this situation, which was not at issue in the case. Thus, the Guidance should not rely on *Myriad* to do so. *Myriad* also

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<sup>49</sup> Guidance at 7 (emphasis added); *see also* Guidance at 6 (“This question can be resolved by first identifying the differences between the recited product and naturally occurring products, and then evaluating whether the identified differences together rise to the level of a **marked** difference in structure.”).

<sup>50</sup> *Chakrabarty*, 447 U.S. at 310 (emphasis added).

<sup>51</sup> *Myriad*, 133 S. Ct. 2017, at 2117 (quoting *Chakrabarty*, 447 U.S. at 310, 305 n.1) (emphasis added).

<sup>52</sup> Guidance at 7.

should not be applied to invoke heightened scrutiny of, for example, method of treatment claims, when the Court expressly noted that it was not addressing method claims,<sup>53</sup> nor claims directed to new applications of knowledge.

## **2. The Proposed “Significant Addition” Requirement Suggests Heightened Scrutiny with Respect to Prior Art**

The “significant addition” pathway proposed in the Guidance may also be overbroad, to the extent that it suggests excessive analysis of the prior art as part of the patentable subject matter determination. The USPTO bases this pathway on *Prometheus*, in which the Supreme Court evaluated patentable subject matter by setting aside the claim limitations allegedly relating to a law of nature and asking whether the “*additional* steps consist of well-understood, routine, conventional activity already engaged in by the scientific community.”<sup>54</sup> As the Federal Circuit has explained, the Supreme Court’s concern in this portion of the *Prometheus* opinion was that a claim may not “pre-empt[] all practical uses of an abstract idea.”<sup>55</sup> Rather, the Supreme Court requires that a claim be “meaningfully limited.”<sup>56</sup> A claim is not directed to a judicial exception when it includes “added limitations which are essential to the invention.”<sup>57</sup> Determining whether the additional steps are well-understood, routine, or conventional serves to ensure that this requirement is met. This inquiry is not intended to import novelty or non-obviousness requirements into the patentable subject matter determination.<sup>58</sup>

The Guidance’s proposed approach of separating out claim limitations not found in nature and evaluating whether those add “significantly more” suggests a potentially heightened scrutiny beyond simply determining whether the additional steps are routine, conventional, or insignificant. The Guidance refers to examining whether a claim involves “well-understood, purely conventional or routine” steps or “insignificant extra-

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<sup>53</sup> *Myriad*, 133 S. Ct. at 2119 (“[T]here are no method claims before this Court.”); *see also Prometheus*, 132 S. Ct. at 1032 (“Unlike, say, a typical patent on a new drug or a new way of using an existing drug, the patent claims do not confine their reach to particular applications of those laws.”).

<sup>54</sup> *Prometheus*, 132 S. Ct. at 1294, 1298 (emphases added).

<sup>55</sup> *Ultramercial, Inc. v. Hulu, LLC*, 722 F.3d 1335, 1346 (Fed. Cir. 2013).

<sup>56</sup> *Id.* at 1347.

<sup>57</sup> *Id.*

<sup>58</sup> *See id.* at 1347-48 (“While these inquiries do require an understanding of what existed in the ken of those skilled in the art during the relevant time frame, principles of patent eligibility must not be conflated with those of validity, however. . . . Because a new combination of old steps is patentable, as is a new process using an old machine or composition, subject matter eligibility must exist even if it was obvious to use the old steps with the new machine or composition. Otherwise the eligibility analysis ignores the text of §§ 101 and 100(b), and reads § 103 out of the Patent Act.”); *see also Diehr*, 450 U.S. at 190 (“The question therefore of whether a particular invention is novel is ‘wholly apart from whether the invention falls into a category of statutory subject matter.’”) (quoting *In re Bergy*, 596 F.2d at 961).

**Comments of Cubist Pharmaceuticals, Inc.**  
**May 7, 2014**

solution activity.”<sup>59</sup> However, examiners should be cautioned that the “significantly more” requirement is limited to review of such routine and conventional knowledge in the prior art, and does not equate to a novelty or non-obviousness analysis, which must be conducted with respect to the claimed subject matter as a whole under §§ 102 and 103. The Guidance should not be applied to conflate the analysis of different elements of patentability, or to suggest that claim limitations bearing any relation to a natural product could be ignored in assessing novelty or inventiveness over the prior art.

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Cubist appreciates the USPTO’s efforts to develop guidance materials implementing recent judicial decisions concerning patentable subject matter and values this opportunity to comment on the Guidance.

Sincerely,



Thomas DesRosier  
Executive Vice President,  
Chief Legal and Administrative Officer  
Cubist Pharmaceuticals, Inc.

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<sup>59</sup> Guidance at 4-5.