COMMENTS AND NEW EXAMPLES FOR THE NATURAL PRODUCT PATENT-ELIGIBILITY GUIDANCE

Paul Cole[1]

New *Prometheus/Myriad* guidance appeared on the USPTO website on 4 March under the title *2014 Procedure For Subject Matter Eligibility Analysis Of Claims Reciting Or Involving Laws Of NaturelNatural Principles, Natural Phenomena, And/Or Natural Products*[2]. The purpose of this paper is to provide comments following the forum held at the USPTO on 9 May 2014. At the forum it was indicated that although the guidance would not be withdrawn in its entirety, it was subject to modification. At the same time additional examples were requested. These comments recommend an alternative overall approach and also provide additional examples.

THE APPROACH TO INTERPRETATION

The task of a court in interpreting §101 is explained in the following passage from *Diamond v Chakrabarty*[3]:

> "Our task, rather, is the narrow one of determining what Congress meant by the words it used in the statute; once that is done, our powers are exhausted. Congress is free to amend § 101 so as to exclude from patent protection organisms produced by genetic engineering. Cf. 42 U.S.C. § 2181(a), exempting from patent protection inventions "useful solely in the utilization of special nuclear material or atomic energy in an atomic weapon." Or it may choose to craft a statute specifically designed for such living things. But, until Congress takes such action, this Court must construe the language of § 101 as it is."

The task of the USPTO in interpreting the *Mayo* and *Myriad* decisions is similarly narrow. It is limited to making of a correct determination from those decisions of the rule(s) of law applied by the Court and then making a corresponding adjustment to examination practice (if needed). Either under-stating such rules and making too

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[1] Visting professor of IP Law, Bournemouth University; European Patent Attorney; Partner, Lucas & Co, 135 Westhall Road, Warlingham, Surrey CR6 9HJ, United Kingdom; e-mail pcole@lucas-uk.com.

[2] http://www.uspto.gov/patents/law/exam/myriad-mayo_guidance.pdf

[3] 447 U.S. 303 (1980)

limited adjustments or gold-plating such rules and making unduly far-reaching adjustments strays outside the metes and bounds of that task.

It is submitted that the second paragraph of the Memorandum over-states the need for a new procedure concerning application of the law relating to natural products. The view as to what amounts to a significant difference from what exists in nature is unduly demanding, and it is not apparent that any meaningful change in the law and practice relating to chemicals derived from natural sources, proteins or peptides and other substances found in nature is required. For all these materials the correct legal test, as explained below continues to be the long-established test of novelty (including novelty of form, concentration or purity) and new utility carried forward from many long-established decisions and approved in *Chakrabarty*. As regards nucleic acids, as discussed below, it is strongly arguable that as a minimum position isolation as a molecular species obtained *in vitro* rather than predicted *in silico* and definition by a molecular formula (nucleotide sequence listing) and credible new utility should suffice for patent-eligibility.

MYRIAD – AN OBVIOUS AND PATENT-FRIENDLY INTERPRETATION

Is *Myriad* truly authority for the proposition that naturally occurring nucleic acid sequences and a host of other naturally occurring materials are no longer patent-eligible? Was it really the intention of the Supreme Court to strip away by a side wind protection for future small molecule innovations of the stature of adrenalin (US 730,176; *Parke-Davis v Mulford*, 189 F. 95, 103 (1911)), digitalis (US 1898199), vitamin B12 (US 2563794; *Merck v. Olin Mathieson*, 253 F.3d 156 (4th Circ. 1958)), vinblastine (US 3097137), doxorubicin (US 3590028) and rapamycin (US 3929992 and 3993749)? According to natural product eligibility guidance issued by the USPTO on 4 March 2014 the answer is "yes" and for a naturally occurring composition of matter the only difference that counts is a marked difference in structure, for example that between a eukaryotic gene and its corresponding cDNA. That guidance has resulted in a storm of protest both from industry and within the profession.

To paraphrase the recent opinion in *Nautilus v Biosig*, a rule of law derivable from an opinion should be precise enough to afford clear notice of what is intended, otherwise there would be a zone of uncertainty: in this instance for inventors, the Office and the public. For that reason, and also because Justice Thomas majored in English literature, the words in which the opinion of the court is summarized

should be presumed to have been chosen with precision and close semantic attention is merited.

The opinion expresses its ruling in two key paragraphs. In his opening paragraph Justice Thomas says:

> "For the reasons that follow, we hold that a naturally occurring DNA segment is a product of nature and not patent eligible **merely because** it has been isolated …"

and he concludes:

> "We **merely** hold that genes and the information they encode are not patent eligible under §101 **simply because** they have been isolated from the surrounding genetic material."

The relevant sense of **mere, a**ccording to the Mirriam-Webster online dictionary, is "nothing more than", as in "a mere mortal", "a mere hint of spice" or "the mere idea of your traveling alone to Europe". The word **simply** in its relevant sense is synonymous with **merely**, also signifying "nothing more than" as in "eats simply to keep alive". The primary meaning of **because** is "for the reason that" as in "rested because he was tired". The words of limitation in the ruling are unmistakable, as also is the link between eligibility and supporting reasons.

Accordingly it is submitted that the rule of law in *Myriad* excludes eligibility for a genetic sequence where the only reason available to support patentability is isolation from the natural environment. It does not provide authority for excluding eligibility for a naturally occurring sequence where there are additional reasons supporting eligibility e.g. new utility. Indeed if the proposition is generalized, it amounts to no more than that a difference unaccompanied by anything more such as new function or new utility does not suffice for patentability. That proposition has been part of US law for two centuries, although it is is normally now stated in the context of §103 rather than §101. It also forms part of European law in the context of problem/solution analysis where technical problem is routinely reconstructed from particular technical success *vis-à-vis* the closest prior art.

If that submission is accepted, and given that a plural reason test is immediately identifiable by and obvious to arts-trained readers outside our profession, an explanation is needed why it is not yet widely accepted as the rule of law handed down in *Myriad*. Part of the

explanation may be confusion between the factual finding and the underlying legal rule, the immediate reaction especially of scientifically trained readers being that the dividing line is between eligible cDNA and non-eligible genomic DNA. Those were the different outcomes that could be perceived in *Myriad* without more detailed legal analysis. Reinforcing that confusion is an expectation that Supreme Court rulings will be far-reaching and not limited and, in the case of our profession, a mindset focusing on differences rather than reasons. However, as soon as cDNA is identified as other than a product of nature it loses all relevance to the §101 enquiry: the test for eligibility for something that is a product of nature cannot be equated either with the test for eligibility of something that is other than a product of nature or with the test whether or not a composition of matter falls within the definition of a product of nature.

It remains to ascertain whether the plural reason test is consistent with other key opinions on product of nature eligibility.

Hartranft v. *Wiegmann*, 121 U.S. 609, 615 (1887) is the oldest of the opinions cited in *Myriad* and was a Supreme Court case concerning liability to import duty rather than patents. It nevertheless contains illustrative findings that support the plural reason test:

- The application of labor to an article either by hand or by machine does not necessarily make that article a manufactured article within the meaning of the tariff laws. Blocks of marble cut to convenient size for transport are not regarded as manufactured.

- Cleaning or decontaminating a product also does not necessarily produce a new manufacture. Washing and scouring wool does not make the resulting wool a manufacture of wool. Cleaning and ginning cotton does not make the resulting cotton a manufacture of cotton. In the present case ornamental shells that have been cleaned to remove the epidermis and then polished on an emery wheel to expose the pearly interior remain shells and have not been manufactured into a new and different article having a distinctive name, character, or use from that of a shell.

- Packaging does not necessarily create a new manufacture. Hay pressed into bales ready for market is not a manufactured article, though labor has been involved in cutting and drying the grass and baling the hay.

- Even a change in physical form does not necessarily create a new manufacture. Round copper plates turned up and raised at the edges

from four to five inches by the application of labor to fit them for subsequent use in the manufacture of copper vessels, but which are still bought by the pound as copper for use in making copper vessels, were held not to be manufactured copper.

- However, India-rubber shoes, made in Brazil by simply allowing the sap of the India-rubber tree to harden upon a mold, were manufactured articles because they were capable of use in that shape as shoes, and had been put into a new form capable of use and designed to be used in such new form.

Analysis of the *Hartranft* findings shows that an article does not become a manufacture simply on change of form or on isolation from impurities but that, consistently with the present submissions, such a change suffices if accompanied by the additional reason of new utility.

The plural reason test finds a paradigm example in US Patent 141072 issued to Louis Pasteur in 1873. The problem with which Pasteur was concerned was changes in the condition of brewers' yeast, worts and beer and limitations on these keeping beyond a certain time. He concluded that these problems arose from microorganisms that contaminated the yeast, devised a procedure that would eliminate these contaminants and claimed:

> "Yeast, free from organic germs of disease, as an article of manufacture."

The decontaminated yeast does not occur in nature and is markedly different from naturally occurring yeast which has harmful contaminant organisms. The composition has the new name, germ-free yeast. It has new characteristics because it does not contain other potentially harmful organisms. It has new utility because it can be used in brewing to create batches of beer with a reduced risk that a batch will be unusable, and the brewed beer has a better taste and longer shelf life. It therefore satisfies the *Hartranft* test approved in *Chakrabarty* and subsequently in *Myriad*, and it was implicitly held patent-eligible in *Chakrabarty* (see footnote 9).

Although it is not strictly speaking a natural product case, another example of the plural reason test may be found in *Kuehmsted v Farbenfabriken of Elberfeld Co 179 F. 701, 1910, 7th Circuit* where acetylsalicylic acid (aspirin) had previously been known but only in an impure form. The Court affirmed patentability for pure aspirin as follows:

> "Hoffmann has produced a medicine indisputably beneficial to mankind – something new in a useful art, such as our patent policy was intended to promote. Kraut and his contemporaries, on the other hand, had produced only, at best, a chemical compound in an impure state. And it makes no difference, so far as patentability is concerned, that the medicine thus produced is lifted out of a mass that contained, chemically, the compound; for, though the difference between Hoffmann and Kraut be one of purification only – strictly marking the line, however, where the one is therapeutically available and the others were therapeutically unavailable – patentability would follow. In the one case the mass is made to yield something to the useful arts; in the other case what is yielded is chiefly interesting as a fact in chemical learning."

A further instance where isolation of a natural product to give a new form with new properties was held to give rise to patentable subject-matter involves the 1900 success of Dr Jokichi Takamine in isolating and purifying adrenalin in fine crystalline form from the adrenal glands of sheep and oxen, for which as explained above he was granted a US Patent. The new product was said to be storage-stable when dry and when injected into an animal to bring about a rise in blood pressure. A number of product claims were granted of which the following is representative:

> "A substance possessing the herein described physiological characteristics and reactions of the suprarenal glands, having approximately the formula $C_{10}H_{15}NO_3$ and having an alkaline reaction."

Patentability of adrenalin was affirmed by Judge Learned Hand in *Parke-Davis & Co. v. H.K. Mulford Co* 189 F. 95, 103 (C.C.S.D.N.Y. 1911) in a ruling that is wholly consistent with the plural reason test:

> "[E]ven if [Adrenalin] 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."

The otherwise puzzling opinion of Justice Douglas in *Funk Brothers* satisfies the plural reason test, although the facts before the court

differed in some respects from those in *Kuehmsted* and *Parke-Davis*. The claim considered in that case read as follows:

> "An inoculant for leguminous plants comprising a plurality of selected mutually noninhibitive strains of different species of bacteria of the genus *Rhizobium*, said strains being unaffected by each other in respect to their ability to fix nitrogen in the leguminous plant for which they are specific."

It had been known to make inoculants containing more than one strain of the different bacterial species, but these were mutually inhibitive. The only novel feature in the inoculant as claimed was that it succeeded whereas previous inoculants had not, the bacteria having gone through some process of selection that was left wholly undefined, as were the bacteria themselves. The word "selected" covered both purposive selection and arbitrary selection and therefore contributed nothing meaningful to the subject matter claimed. The situation was therefore the reverse of that in *Myriad* with new utility defined but not any supporting difference. It is not surprising in the circumstances that Justice Douglas refused to borrow invention from the discovery of the natural principle itself, but nothing more. The concurring opinion of Justice Frankfurter concluded that the particular strains by which compatibility was achieved should have been adequately identified, but this had not happened either in the claims or in the supporting description and the claimed strains were identifiable only by their compatibility. References in subsequent opinions to the bacteria in *Funk* being unaltered should be understood against this factual background: the bacteria in the inoculants supplied to farmers had indeed been altered by isolation, selection and cultivation but none of these features had been specified in any way in the subject-matter claimed.

The bacterium in *Chakrabarty* which was oil-digesting by virtue of additional plasmids creating new metabolic pathways was, strictly speaking, not a product of nature but was held to be a product of human ingenuity having a distinctive name, character and use as in *Hartranft*. However, the reasoning here was again consistent with the plural reason test.

The opinion in *Myriad* is (unsurprisingly) consistent with the plural reason test if the factual situation before the Court is correctly analyzed. In his dissent in the Federal Circuit, Judge Bryson relied on *Chakrabarty* and held that as between what is claimed and what is found in nature the focus should be firstly on the similarity in structure and secondly on the similarity in utility. His analysis, which like that of

Justice Thomas was from the standpoint of a geneticist rather than a chemist, emphasized the absence of any new utility for the isolated wild-type BRCA1 gene:

> "The structural differences between the claimed "isolated" genes and the corresponding portion of the native genes are irrelevant to the claim limitations, to the functioning of the genes, and to their utility in their isolated form. The use to which the genetic material can be put, i.e., determining its sequence in a clinical setting, is not a new use; it is only a consequence of possession. In order to sequence an isolated gene, each gene must function in the same manner in the laboratory as it does in the human body. Indeed, that identity of function in the isolated gene is the key to its value. The naturally occurring genetic material thus has not been altered in a way that would matter under the standard set forth in *Chakrabarty*. For that reason, the isolation of the naturally occurring genetic material does not make the claims to the isolated BRCA genes patent-eligible."

Justice Thomas agreed that *Chakrabarty* was central to the enquiry, and that qualifying subject-matter had to be a product of human ingenuity having a distinctive name, character and use. In relation to the wild-state gene Myriad had not created anything. As previously explained he ruled that genes and the information that they encode are not patent-eligible under §101 **simply** because they had been isolated from the surrounding genetic material. In relation to genomic BRCA1 all that could be said in favor of eligibility was that it had been claimed as an isolated sequence, and that was not enough.

Isolation or purification of a naturally occurring substance leading to a non-natural composition of matter with desirable new properties has provided basis for patent grant for over a century in the US and continues to provide such basis in the UK, before the EPO and before the patent offices of substantially every country in the industrialised world. What is remarkable about the *Parke-Davis* opinion is how seldom it has been challenged in the century since it was handed down notwithstanding the multiplicity of patents for naturally-occurring products of great utility and commercial value that have been granted during that time, and how widely the same logic has been adopted in other countries. It is submitted that this long standing line of authority and established practice, implicitly approved in *Chakrabarty* can only be overruled by clear language, and that such language is not found in *Myriad* or in any earlier opinion on the eligibility of products of nature.

Patent eligibility based on purification or isolation and new utility would minimise the problem expressed by Justice Ginsburg during oral argument in *Myriad* that the US was at risk of being placed in a singular position compared to other industrialised nations. Under the European Biotechnology Directive[4] biological material which is isolated from its natural environment or produced by means of a technical process may be the subject of an invention even if it previously occurred in nature. However, it is an essential condition for grant of a patent for a genetic sequence is that industrial applicability should be disclosed in the application as filed. It has been held that under a.57 EPC it is necessary to disclose in definite technical terms the purpose of an invention and how it can be used in industry to solve a given technical problem[5], this being the actual benefit or advantage of the invention. In *Human Genome Sciences*[6] the principles adopted by the EPO Appeal Boards were reviewed by the Supreme Court (UK) which held that a patent must disclose "a practical application" and "some profitable use" for the claimed substance, and that a merely speculative statement of use would not suffice. Merely identifying the structure of a protein, without attributing to it a clear role, or suggesting any practical use for it was not enough. The words "merely" and "simply" in *Myriad* leave room for development of US law along analogous lines to those under the EPC and point away from a bright line rule prohibiting patent-eligibility of all naturally occurring sequences.

It is difficult to identify any new rule of law from *Mayo*. In summarising its conclusions the Court recognised that monetary incentives that lead to creation, invention and discovery must be balanced against raising the price of using the patented ideas once created, requiring potential users to conduct costly and time-consuming

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[4] *DIRECTIVE 98/44/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL* of 6 July 1998 on the legal protection of biotechnological inventions, [1998] OJL 175/1. In Case C-428/08 *Monsanto* the ECJ pointed out that Article 1(1) of the Directive requires member states to protect biotechnological inventions under their national patent laws and to make adjustments in accordance with the provisions of the Directive. Accordingly the harmonization effected by Article 9 of the Directive (which refers to scope) should be regarded as exhaustive and precludes national legislation from producing a different effect. It will be apparent that the same argument is equally applicable to Articles 3 and 5 and is consistent with the ruling in the *Kingdom of the Netherlands* case C-377/98. The EPO incorporated the provisions of Articles 3 and 5 of the Directive into the Implementing Regulations to the EPC without modification as EPC 2000 rules 27 and 29. These rules now provide legislative authority for the patent-eligibility of claims covering naturally occurring gene under the EPC, and that the resulting patents can be brought into effect in all EPC contracting states, see e.g. T 272/95 *Relaxin/HOWARD FLOREY INSTITUTE*.

[5] T 0898/05 *Hematopoietic receptor/ZYMOGENETICS*.

[6] [2011] UKSC 51; see also T 0018/09 *Neutrokine/HUMAN GENOME SCIENCES*

searches of existing patents and pending patent applications, and requiring the negotiation of complex licensing arrangements, and that:

> "At the same time, patent law's general rules must govern inventive activity in many different fields of human endeavor, with the result that the practical effects of rules that reflect a general effort to balance these considerations may differ from one field to another.
> In consequence, we must hesitate before departing from established general legal rules lest a new protective rule that seems to suit the needs of one field produce unforeseen results in another. And we must recognize the role of Congress in crafting more finely tailored rules where necessary. Cf. 35 U. S. C. §§161–164 (special rules for plant patents)."

It will be apparent that the abundance of cautious language in Justice Breyer's opinion points away from any dramatic and wide-ranging change in legal principle. In that respect there is similarity in the approaches in *Mayo* and in *Myriad*.

GUIDANCE – DETAILED COMMENTS

I. Overall Process for Subject Matter Eligibility Under 35 U.S.C. 101

In question 2 of the flowchart the judicial exceptions are misstated. They should be stated as set out in *Myriad* and earlier opinions of the Supreme Court, i.e.

"laws of nature, natural phenomena, and abstract ideas"

It is dangerous and potentially misleading to paraphrase language from the Supreme Court of this importance.

The following language is suggested between questions 2 and 3:

Natural products merely isolated and not exhibiting new characteristics or utility may fall within the judicial exception.

As discussed above the rule that can be derived from the *Funk*, *Chakrabarty* or *Myriad* opinions is that natural products do not become patentable by merely by isolation or other simple change, but may be eligible if the change results in new characteristics and utility. A slighltly

more specific test derived from *Hartranft v Weigmann*, applied in *Chakrabarty* and approved in *Myriad* is whether the claimed manufacture or composition of matter has a distinctive name, character and use. Analysis of the numerous examples in *Hartranft* shows that a change in form accompanied by a new function or utility provides the dividing line.

2. Question 2: Does the claim recite or involve one or more judicial exceptions?

Amendment is needed to further clarify that if a claim appears to recite or involve a judicial exception then exclusion is not automatic.

For example, materials derived from, natural sources do not inevitably fall within the prohibition, and whether or not they do so depends on the form in which they are claimed.

Using an example from *Hartranft*, rubber is a naturally-occurring material but when molded into a shoe it becomes patent-eligible because of its new shape and utility. It is not a legitimate objection that the shoe remains ineligible because the material of which it is made remains natural rubber. A diamond is a naturally occurring product, it is not patent-eligible simply because it has been extracted from the ground, but it may become eligible by shaping to form a pattern of facets that refract and internally reflect light in a new and ingenious way that imparts greater brilliance to the stone. It is not then a legitimate ground of objection that the stone is still diamond. Yeast is a natural product but when freed from germs of disease as taught by Louis Pasteur becomes patent-eligible because of its new purified form and its expanded utility. It is not a legitimate ground of objection that the purified yeast remains natural yeast. Streptomycin is a natural product, but when concentrated into the pure material becomes patent-eligible because it becomes for every practical purpose a new thing commercially and therapeutically. It is not a legitimate ground of objection that the purified streptomycin remains a natural product.

In each case, as explained in the existing text, the analysis must proceed to Question 3, in order to determine whether the protein or mineral is claimed in a manner that is significantly different than naturally material. This is the case regardless of whether particular words (e.g., "isolated", "recombinant", or "synthetic") are recited in the claim.

II. How to analyze "Significantly Different"

Questions (a) and (g) are unduly restrictive because the only type of difference that is acknowledged is a **structural** difference. The proposition is repeated in the paragraph following question (l) and in Examples A and E.

Structural difference is neither a **necessary** nor a **sufficient** condition for eligibility. If it were a **necessary** condition, then purified natural products of pharmaceutical use, conceded as being eligible in oral argument in *Myriad*, would become non-eligible. A fundamental legal change of this kind, affecting the pharmaceutical industry which is one of the most significant classes of user of the patent system, requires explicit language. It should not be imposed by mere assumption of what is implicit in a decision affecting sequences isolated for genetic testing, which is a field of endeavor distant from small molecule natural products or even from isolated plasmids and other sequences useful in genetic engineering e.g. to make products of industrial importance. It is submitted that it was not the intention of the Supreme Court to invalidate protection for natural product inventions such as adrenaline and other compounds set out above. If structural difference were a **sufficient** condition then the copper plates of the *Hartranft* example would be eligible because of their raised edges, whereas they were not classified as manufactured articles because insufficient new utility had been demonstrated, the plates being sold by weight and the change in physical form contributing nothing to their value.

As previously explained, the dividing line is therefore a difference leading to new utility. Such differences need not be based on structure but could arise from any human activity leading to new utility including selection, isolation, multiplication, concentration and purification. Questions (a) and (g) therefore require expansion to cover the full range of relevant human activities that could be relevant to eligibility.

REWORKED AND ADDITIONAL GUIDANCE EXAMPLES

A. Composition and method claims each reciting a natural product

[NOTE: See US 3929992 and 3993749; for litigation concerning derivatives see the Federal Circuit opinion in *Wyeth v*

***Abbott* (2013) This replaces the Amazonic acid example B in the existing guidance, and covers substantially the same points but with a more realistic background and claim set].**

Background: The naturally-occurring organism *Streptomyces hygroscopicus* NRRL 5491 was isolated from a sample of soil from Easter Island. It can be cultivated by natural fermentation and produces a triene antibiotic called rapamycin. The antibiotic can be harvested by extraction of the fermentation medium with a water-immiscible solvent such as methylene chloride which can be evaporated to give crude rapamycin as an oily residue. Two stages of preparative column chromatography and precipitation followed by recrystallization give a purified product which was initially of interest for its antifungal properties. A dimethylphosphate derivative of rapamycin has anti-cancer activity.

Claim 1: Purified rapamycin, an antibiotic which

(a) is a colourless, crystalline compound with a melting point of 183 - 185°C, after recrystallization from ether;
(b) is soluble in ether, chloroform, acetone, methanol and dimethylformamide, very sparingly soluble in hexane and petroleum ether and substantially insoluble in water;
(c) shows a uniform spot on thin layer plates of silica gel;
(d) has a characteristic elemental analysis of about C, 66.84%, H, 8.84%; N, 1.37%,
(e) exhibits the following characteristic absorption maxima in its ultraviolet absorption spectrum (95% ethanol): [details]
(f) has a characteristic infrared absorption spectrum shown in accompanying FIG.
(g) has a characteristic nuclear magnetic resonance spectrum as shown in accompanying FIG. 2;
(h) has a minimum inhibitory concentration of 0.02 to 0.1 μg/ml against *Candida albicans*; and
(i) exhibits a LD50 (i.p., mice) of 597.3 mg/kg and a LD50 (p.o., mice) of >2,500 mg/kg.

Claim 2: A pharmaceutical composition which comprises a fungicidally effective dose of the antibiotic rapamycin as defined in claim 1 together with a pharmaceututically effective carrier or diluent.

Claim 3: A method of inhibiting the growth of pathogenic fungi in a mammal which comprises administering to said mammal an antifungally effective amount of the antibiotic rapamycin as defined in claim 1.

Claim 4: Rapamycin dimethylphosphate.

Analysis of claim 1: The answers to questions 1 and 2 are both "yes" because the claim is to a composition of matter and because the claim recites a judicial exception, i.e. rapamycin is a naturally occurring chemical produced by *Streptomyces hygroscopicus* NRRL 5491 growing in soil.

Factors that weigh towards significantly different:

- (a) Although rapamycin initially appears to be a natural product it is non-naturally occurring because it does not exist in nature as a pure material but only in association with soil containing the specified bacterial strain. It satisfies the *Hartranft* test approved in both *Chakrabarty* and *Myriad* since it has a distinctive name, distinctive characteristics since it is markedly different in concentration and physical form from the naturally occurring substance being a colorless crystalline solid with a sharp melting point and significant new utility as an anti-fungal agent.

- Factors (b) through (f) are not relevant since the claim does not include any elements in addition to the specified product.

Factors that weigh against patentability:

- (g) is not satisfied since the claim is to a product markedly different in purity and characteristics from the natural product.
- Factors (h) through (l) are not relevant because the claim does not include any elements in addition to the claimed produce, i.e. there is nothing in the claim other than the claimed product.

In sum when the relevant factors are analyzed they weigh towards significantly different. Accordingly claim 1 qualifies as eligible subject-matter.

Analysis of claim 2:

- Factor (b) is satisfied in addition to factor (a) since the claim recites elements in addition to the judicial exception, namely a pharmaceutically acceptable carrier and an antifungally effective amount of the antibiotic rapamycin.
- Factor (c) is satisfied because the elements in addition to the judicial exception relate to the judicial exception in a significant way, defining an application of rapamycin for its hitherto unknown anti-fungal activity.

- Factor (d) is satisfied since formulations have for many decades been accepted as additional steps that relate to the judicial exception in a significant way and are more than a general instruction to apply an exception.
- Factors (e), (f) and (g) are not relevant.
- Factors (h) and (i) are not satisfied since practical applications outside the pharmaceutical field remain free for use.
- Factor (j) is not covered since the use of rapamycin as an anti-fungal was not well-understood, purely conventional or routine in the pharmaceutical field.
- Factors (k) and (l) are not relevant.

In sum when the relevant factors are analyzed they weigh towards significantly different. Accordingly claim 2 qualifies as eligible subject-matter independent of claim 1.

Analysis of claim 3: The answers to Questions 1-2 in the above analysis are both "yes", because the claim is to a process, and because the claim recites a judicial exception, i.e. rapamycin is a naturally occurring chemical as explained above. The answer to Question 3 is "yes", because the claim as a whole recites something significantly different than the natural product, e.g. the claim includes elements in addition to the judicial exception that add significantly more to the judicial exception.

With respect to factors weighing <u>toward</u> eligibility:

- Factor a) is not relevant, because the claim is a process claim, not a product claim.
- Factor b) is satisfied. The step of administering rapamycin to a mammal to inhibit the growth of pathogenic fungi meaningfully limits the scope of the claim to a particular application of rapamycin. Because the specific treatment limitation narrows the scope of the claim, others are not substantially foreclosed from using rapamycin in other ways, e.g., to treat other infections or other types of disease.
- Factor c) is satisfied. The administering step is significantly related to the judicial exception, because it is a step in which rapamycin is manipulated in a particular and significant way.
- Factor d) is satisfied. The administering step requires administration of rapamycin to a mammal with a specific type of disease, and thus is more than a general instruction to use rapamycin.
- Factor e) is not satisfied. There is no machine or transformation recited in the claim.

- Factor f) is satisfied. Rapamycin had no previously known use, medical or otherwise.

With respect to factors weighing against eligibility:

- Factor g) is not applicable because the claim is not a product claim.
- Factor h) is not satisfied, because the administering step is not recited at a high level of generality, but instead recites rapamycin to be administered to a mammal to treat a specific type disease state.
- Factor i) is not satisfied. Rapamycin can be applied in other ways, e.g., to treat other types of disease.
- Factor j) is not satisfied. It was not well-known to use either the microorganism or rapamycin to treat infectious disease.
- Factor k) is not satisfied. The administering step is not merely appended to the judicial exception, but instead is significantly related to purified rapamycin and its properties.
- Factor l) is not satisfied. Administering rapamycin for the treatment of fungal infection is more than a mere field of use, because it limits the claim scope to a particular application of rapamycin.

In sum, when the relevant factors are analyzed, they weigh toward significantly different. Accordingly, claim 3 qualifies as eligible subject matter.

Analysis of Claim 4: The answers to Questions 1-2 in the above analysis are both "yes", because the claim is to a composition of matter, and because the claim recites (or may recite) a judicial exception, i.e., rapamycin is a naturally occurring chemical as explained above. The answer to Question 3 is "yes", because the claim as a whole recites something significantly different than the natural product, e.g., the claim includes features that demonstrate that the recited product is markedly different from what exists in nature.

With respect to factors weighing toward eligibility:

- Factor a) is satisfied. Rapamycin dimethylphosphate is structurally different than naturally occurring rapamycin (because of the addition of the dimethylphosphate group), and this structural difference has resulted in a functional difference, providing anti-cancer properties. While a functional difference is not necessary in order to find a marked difference, the presence of a functional difference resulting from the structural difference makes a stronger case that the structural difference is a marked difference. Therefore,

rapamycin dimethylphosphate acid is markedly different than naturally occurring rapamycin.

- Factors b) through f) are not relevant, because the claim does not include any elements in addition to the acid.

With respect to factors weighing against eligibility:

- Factor g) is not satisfied. The claim is a product claim reciting a substance that is markedly different from what exists in nature.
- Factors h) through l) are not relevant, because the claim does not include any elements in addition to the substance.

In sum, when the relevant factors are analyzed, they weigh toward significantly different. Accordingly, claim 4 qualifies as eligible subject matter.

B1 Composition/Manufacture Claim Reciting a single Natural Product

[New example: fact pattern based on US Patent 4506014]

Background: Giuseppe Brotzu isolated a library of bacteria from a sewage outfall off the Sardinian coast a fungus called *Cephalosporium acremonium* which when cultured provided crude filtrates having antibacterial activity. Those filtrates were subsequently found to contain cephalosporin antibiotics. Amongst the naturally occurring fungi that he isolated was a strain called *Acremonium chrysogenum* ATCC 14553.

Producing fungal strains with increased productivity for cephalosporin was an unsolved problem. Although genetic engineering using plasmids had become known, success could only be achieved when a plasmid was available which was not immediately eliminated from the host cell which was to be genetically improved, as happens in microorganisms that are unrelated. No such plasmid had been found either in *Acremonium* or in other closely related strains of fungi. The invention was based on the unexpected discovery of a plasmid in the 14533 strain which had been given the name pAC 1. It was particularly suitable for forming a hybrid vector by cleaving at restriction sites andfor inserting a gene for promoting the synthesis of β-lactam antibiotics.

CLAIM: A plasmid, pAC 1, isolated from Acremonium chrysogenum ATCC 14553 and having a contour length of about 6.7 microns and a molecular size of about 20.9 kilobases,

which plasmid is divided into six fragments having the sizes 5.10, 4.75, 4.30, 3.50, 2.15 and 1.05 kilobases by the restriction endonuclease Bgl II,

is divided into five fragments having the sizes 8.1, 4.7, 4.4, 2.6 and 1.3 kilobases by the restriction endonuclease Eco R I, and

is divided into nine fragments having the sizes 5.61, 4.30, 3.50, 2.72, 1.35, 1.25, 0.82, 0.74, and 0.61 kilobases by the restriction endonuclease Hpa I.

Analysis of the claim: The answer to Question 1 is "yes", because the claim is to a plasmid, which is a composition of matter. The answer to Question 2 is "yes", because the claim recites a plasmid that is naturally occurring, and thus the claim as a whole may be reciting nothing more than a natural product. After inquiring into the nature of the claimed invention by reviewing the specification and the record of the application, and by considering and weighing the relevant factors, the answer to Question 3 is determined to be "yes", because the claim as a whole recites something that is significantly different than what exists in nature.

With respect to factors weighing <u>toward</u> eligibility:

- Factor (a) is satisfied because the isolated plasmid does not occur in nature and is markedly different from the naturally occurring material which is mixture of bacterial strains. The hand of man is involved firstly in isolating and culturing the 14533 strain, secondly in detecting the existence of a plasmid in that strain and thirdly in the procedures needed to isolate the plasmid from the cellular material with which it is normally associated.

In contrast to the BRCA1 sequence considered in *Myriad* the plasmid was isolated *in vitro* and not simply reconstructed *in silico* and is capable of chemical manipulation using restriction enzymes. Its novelty and utility falls to be judged by a biochemist from the standpoint of practical manipulation to produce hybrid vectors and not simply by a geneticist from the standpoint of its informational content.

The plasmid has the new name pAC1. It has new characteristics because in pure form it can be manipulated at defined sites by restriction enzymes, whereas that is not possible with the plasmid as it occurs in nature. It has new utility because it can be used in genetic engineering to form hybrid vectors that can be reintroduced into *Acremonium* species to promote antibiotic synthesis. It therefore satisfies the *Hartranft* test approved in *Chakrabarty* and subsequently approved in *Myriad*. The use to which the plasmid can be put is a new use and not the mere consequence of its possession (see the dissent of Judge Bryson in *Chakrabarty*, subsequently approved by Justice Thomas). Selection

and isolation has therefore created a new product whose utility goes beyond simple isolation from the surrounding cellular material.

- Factors b) through f) are not relevant, because the claim does not include any elements in addition to the natural product.

With respect to factors weighing against eligibility:

- Factor (g) is not satisfied because the claimed plasmid is in markedly different physical form from what exists in nature by virtue of its separation from other cell contents, and its new utility is more than an incidental or trivial utility.
- Factors (h) through (l) are not relevant, because the claim does not include any elements in addition to the isolated plasmid.

In sum, when the relevant factors are analyzed, they weigh towards a significant difference. Accordingly, and in contrast to *Myriad*, the claim qualifies as eligible subject matter. There is nothing in *Chakrabarty* which impugns the patent-eligibility of a plasmid when isolated from the cell contents with which it is normally associated, and in that case a stable energy-generating plasmid which provided a hydrocarbon degradative pathway would have been patent-eligible if novel.

B2 Composition/Manufacture Claim Reciting a single Natural Product

Background: US Patent 141072 issued to Louis Pasteur in 1873. The problem with which he was concerned was changes in the condition of brewers' yeast, worts and beer and limitations on these keeping beyond a certain time. He concluded that these problems arose from microorganisms that contaminated the yeast, devised a procedure that would eliminate these contaminants.

Claim: Yeast, free from organic germs of disease, as an article of manufacture.

Analysis of the claim: The answer to Question 1 is "yes", because the claim is to yeast, which is a composition of matter. The answer to Question 2 is "yes", because the claim recites yeast that is naturally occurring, and thus the claim as a whole may be reciting nothing more than a natural product. After inquiring into the nature of the claimed invention by reviewing the specification, and by considering and weighing the relevant factors, the answer to Question 3 is determined to be "yes", because the claim as a whole recites something that is significantly different than what exists in nature.

With respect to factors weighing toward eligibility:

- Factor (a) is satisfied because the decontaminated yeast does not occur in nature and is markedly different from the naturally occurring material which has harmful contaminant organisms. The composition has the new name, germ-free yeast. It has new characteristics because it does not contain other potentially harmful organisms. It has new utility because it can be used in brewing to create batches of beer with a reduced risk that a batch will be unusable, and the brewed beer has a better taste and longer shelf life. It therefore satisfies the *Hartranft* test approved in *Chakrabarty* and subsequently approved in *Myriad.* It was approved by the Supreme Court in *Chakrabarty* (see footnote 9), and that approval was not the subject of adverse comment in either *Mayo* or *Myriad.*
- Factors b) through f) are not relevant, because the claim does not include any elements in addition to the natural product.

With respect to factors weighing against eligibility:

- Factor (g) is not satisfied because the claimed decontaminated yeast has been purified compared to what exists in nature, and its new utility is more than an incidental or trivial utility.
- Factors (h) through (l) are not relevant, because the claim does not include any elements in addition to the yeast.

In sum, when the relevant factors are analyzed, they weigh towards a significant difference. Accordingly, and in contrast to *Myriad*, the claim qualifies as eligible subject matter.

C Manufacture Claim Reciting Natural Products [Revised]

Claim: A fountain-style firework comprising:
(a) a sparking composition,
(b) calcium chloride,
(c) gunpowder,
(d) a cardboard body having a first compartment containing the sparking composition and the calcium chloride and a second compartment containing the gunpowder, and
(e) a plastic ignition fuse having one end extending into the second compartment and the other end extending out of the cardboard body.

Analysis: The answers to Questions 1-2 in the above analysis are both "yes", because the claim is to a manufacture, and because the claim recites judicial exceptions: calcium chloride, which is a naturally occurring mineral; and gunpowder, which is a mixture of naturally occurring saltpeter, sulfur and charcoal (although the occurrence of charcoal in nature is marginal,, charcoal predominantly being made by heating wood in kilns in the absence of air). The answer to Question 3 is also "yes", because the claim as a whole recites something significantly different than the natural products by themselves, i.e., the claim includes elements in addition to calcium chloride and gunpowder (the sparking composition, cardboard body and ignition fuse) that amount to a specific practical application of the natural products.

With respect to the factors weighing toward eligibility:

- Factor (a) is satisfied, because gunpowder as recited in the claim is markedly different from what exists in nature. Sufur and saltpeter occur naturally but charcoal is, as previously explained, made by the slow pyrolysis of wood in kilns in the absence of oxygen. The hand of man further intervenes (i) in selecting the proportions in which the ingredients are mixed, (ii) in finely dividing each ingredient, and (iii) in intimately mixing the ingredients e.g. in amounts of 75% saltpeter, 15% charcoal and 10% sulfur, these amounts not being random but determined by the stoichiometry of the intended reaction. The ingredients have to be finely ground e.g. in a ball mill. Juxtaposed sacks of sulphur, saltpeter and charcoal have no explosive properties: it is the grinding and mixing steps mentioned above that give rise to a material that deflagrates at sub-sonic speeds and provides the well-known explosive and propellant. Even assuming that the materials are all natural products, the physical change and mixing step in making gunpowder satisfy the *Hartranft* test (cited in Myriad). In gunpowder the ingredients are changed in physical form and mixed, which having regard to the new utility in that form satisfies the requirements of new name, new explosive characteristics and new utility.
- Factor b) is satisfied because the claimed elements in addition to the calcium chloride and gunpowder narrow the scope of the claim so that others are not foreclosed from using the natural products in other ways, e.g., others can still use calcium chloride in products such as concrete, foods, fire extinguishers, etc., and can still use gunpowder in other products such as rifle cartridges.
- Factor c) is satisfied because the claimed elements relate to the calcium chloride and gunpowder in a significant way, e.g., the combination of the claimed elements forms a structure into which the calcium chloride and gunpowder are physically integrated. In

other words, the claim is drawn to a combination of physically interrelated elements including the natural products.

With respect to the factors weighing against eligibility:

- Factor (g) is not satisfied, because the claimed calcium chloride and gunpowder are not markedly different from what exists in nature.
- Factor (h) is not satisfied, because the claimed elements are not recited at a high level of generality, but instead are recited with specificity such that all substantial applications of the natural products are not covered, e.g. others can still use calcium chloride in products such as concrete, foods, fire extinguishers, etc., and can still use gunpowder in other products such as rifle cartridges.
- Factor (i) is not satisfied, because the claimed elementsare not required to use calcium chloride or gunpowder, e.g., others can still use calcium chloride and gunpowder in other ways without the claimed elements such as the cardboard body and the ignition fuse.
- Factor (j) is satisfied, because the elements in addition to the natural products are well-understood, purely conventional, and routine in the firework art.
- Factors (k) and (l) are not satisfied, because the claimed elements are a significant part of the claim (factor k), e.g., the combination of the claimed elements forms a structure into which the calcium chloride and gunpowder are physically integrated, and are substantial limitations that integrate the calcium chloride and gunpowder into a specific application as opposed to being mere fields of use (factor (l)).

When the relevant factors toward and against eligibility are balanced, the factors weigh toward a significant difference. Accordingly, the claim qualifies as eligible subject matter. The same would be true for gunpowder itself which has different characteristics and a new utility compared to its ingredients.

D. Composition Claim Reciting Multiple Natural Products

Background: *Rhizobia* are naturally occurring bacteria that infect leguminous plants such as clover, alfalfa, beans and soy. After the bacteria become established in a plant host, they are able to fix nitrogen gas from the atmosphere into a different chemical form that is more reactive and usable by the plant host. Each species of bacteria will only infect certain types of plants, for example *R. meliloti* will only infect alfalfa and sweet clover, and *R. phaseoli* will only infect garden beans. It was assumed in the prior art that all *Rhizobium* species were mutually inhibitive, because prior art combinations of different bacterial species

produced an inhibitory effect on each other when mixed together, with the result that their efficiency was reduced. Applicant has discovered that there are particular strains of each Rhizobium species that do not exert a mutually inhibitive effect on each other, and that these mutually non-inhibitive strains can be isolated and used in mixed cultures.

Claim 1. An inoculant for leguminous plants comprising a plurality of selected mutually non-inhibitive strains of different species of bacteria of the genus Rhizobium, said strains being unaffected by each other in respect to their ability to fix nitrogen in the leguminous plant for which they are specific.

Claim 2. An inoculant for leguminous plants, comprising:

a plurality of pure bacterial cultures of different species of the genus Rhizobium selected by testing in admixture on plants grown aseptically on a nitrogen-free substrate for non-interference in respect of their ability to fix nitrogen in the leguminous plants for which each of them is specific;

said cultures being in admixture with each other and with a moist powder base containing a substantially negligible concentration of bacterial nutrients whereby growth of the bacteria therein is inhibited.

Claim 3. The inoculant of claim 2, wherein the pure bacterial cultures comprise two or more strains selected from the group consisting of

Rhizobium meliloti ATCC 12345 Strain 234,
Rhizobium trifolii ATCC 23456 Strain 256,
Rhizobium leguminosarum ATCC 24567 Strain 268,
Rhizobium phaseoli ATCC 25678 Strain 270,
Rhizobium lupine ATCC 25678 Strain 282 and
Rhizobium japonicum ATCC 26789 Strain 294.

Claim 1 Analysis:

The answer to question 1 is "yes" because the claim is to a composition of matter. The answer to question two is also "yes" because the claim covers a combination of strains of organisms that exist in nature. The answer to question 3 is "no" because the combination of strains is markedly different in properties and utility from that existing in nature.

Factors weighing <u>toward</u> eligibility (significantly different):

- Factor (a) is satisfied. The claim is a product claim reciting a combination of bacterial strains that is novel, does not exist in nature, is markedly different by virtue of the non-interfering properties and has consequential new utility.

- (b) through (f) are not relevant, because the claim does not include any elements in addition to the natural products, i.e., there is nothing in the claim other than the bacteria and the law of nature.

Factors weighing against eligibility:

- Factor (g) is not applicable because the product has novel properties and utility;
- (h) The selection step is defined at a high level of generality, but not all practical applications of the underlying law of nature are covered. For example a machine could be provided enabling different bacterial strains to be applied in a single step but using individual inocculants.
- (i) through (l) are not relevant for the same reasons as b) through f).

In sum, when the relevant factors are analyzed, they weigh towards significantly different. Accordingly, claim 1 qualifies as eligible subject matter.

As explained above, the above conclusion may be compared with the outcome in in *Funk Brothers Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127, 131 (1948). However, the majority opinion in that case mixes issues of eligibility with issues of lack of invention (citing the earlier *Cuno* opinion concerning inventive step) and it is submitted was significantly influenced by the undue breadth of the claim, lack of supporting technical features and the lack of specificity as to the strains selected (see the concurring opinion of Justice Frankfurter which raises issues that would now be considered under § 112). Recently, the Supreme Court looked back to this claim as an example of ineligible subject matter, stating that "the composition was not patent eligible because the patent holder did not alter the bacteria in any way." *Myriad*, 133 S. Ct. at 2117. However, that observation can be understood in terms of the absence in the Bond claim to any detailed selection procedure, any separation of the bacteria from their natural environment, cultivation of the selected bacteria, use of pure strains of the cultured bacteria to produce the desired inoculant or even mixing of the selected strains of bacteria.

Claim 2 analysis:

- Factor (b) - the claim contains elements in addition to the naturally occurring organisms that impose meaningful limits on claim scope: a selection procedure, mixing of the selected strains and the use of a moist powder base as carrier. Others are not foreclosed from employing a different test procedure (e.g. not requiring asepsis), applying the bacteria in individual inoculants simultaneously or

sequentially rather than in admixture or using a liquid base rather than a powder base.

In sum the case of eligibility is stronger than for claim 1, but § 112 issues remain.

Claim 3 analysis:

- Selection of particular strains is now specified in detail, reducing the force of the argument that the hand of man exercised through the activity of selection should be ignored.

E. Composition vs. Method Claims, Each Reciting Two Natural Products

Reconsideration of claim 1 is required having regard to the observations set out above. The primers are identified by oligonucleotide sequence, they are isolated molecules having physical existence, their novelty is considered from a chemical rather than a genetic standpoint because they are intended to participate in a PCR reaction, and they have new utility. Commonly they are not derived from natural sources but are made by oligonucleotide synthesis. It would be an oddity if a prohibition relating to products of nature were extended to molecules made by stepwise chemical synthesis and HPLC to ensure purity, whether or not those synthetic molecules are identical to regions within naturally-occurring sequences. In terms of length and selection they are markedly different from anything occurring in nature.

15 June 2014