COMMENTS ON THE 2014 INTERIM GUIDANCE ON PATENT SUBJECT-MATTER ELIGIBILITY AND ON THE ACCOMPANYING NATURE-BASED PRODUCT EXAMPLES

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Introduction

Earlier *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*. New Interim Guidance was published in the Federal Register on 16 December 2014 and new Nature-Based Products Examples appeared on the USPTO website.

The writer submitted comments on 15 June 2014 in relation to the March 2014 Guidance, and many of those comments remain applicable to the new Interim Guidance and to the Nature-Based Product Examples. In particular, the comments on *Myriad* under the heading *AN OBVIOUS AND PATENT-FRIENDLY INTERPRETATION* are of continuing relevance. The writer and Dr Timothy Roberts also submitted on 31 July 2014 further comments directed to compliance with the provisions of the TRIPS Agreement, and many of those comments remain applicable.

These comments build on this earlier work and make hopefully helpful comments on of the new Guidance and Examples. It is noted with thanks that much (but by no means all) of the earlier comments have received attention and it is reassuring to see that gunpowder is no longer regarded as a natural product.

The writer has participated at conferences in the US where the implications of the recent Supreme Court decisions has been extensively discussed, and has had the opportunity of participating both at the conference sessions and in one-to-one discussions with US colleagues. As a result a number of general impressions have been formed which it is submitted are relevant.

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For very good reasons the Supreme Court and its Justices are held in the utmost respect in the US, as are the opinions of the Court. For that reason there is a danger of misinterpreting the Court's opinions to give them a more far-reaching significance than was intended. Sometimes the Court hands down opinions of the utmost legal significance which fundamentally change society. Sometimes it hands down opinions of considerable wisdom, as for example in my opinion the adoption of a foreseeability standard in *Festo*. However it does not follow that all the Court's decisions will be of that character.

The danger of over-broad interpretation is illustrated by the revival of interest in the *Funk Brothers* decision which was handed down under pre-1952 law and is one of the most problematic opinions to interpret that the writer has ever seen. It is not even clearly and unambiguously apparent whether the opinion is based on eligibility or obviousness and interpretation in that respect has changed over the years. In reality there are strong arguments for concluding that the decision was correct on its facts but laid down no generally applicable rule of law. It is also illustrated by the reaction to the *Myriad* decision which was expressed in cautious and specific terms, but which has been subject to over-broad interpretation producing consequences which arguably the Court never intended. Insufficient weight is often given to the repeated warnings that "all inventions at some level embody, use, reflect, rest upon, or apply laws of nature, natural phenomena, or abstract ideas," and "too broad an interpretation of this exclusionary principle could eviscerate patent law."

Unfortunately much legal analysis which has been applied to recent Supreme Court decisions is merely what would be expected of an astute columnist on the New York Times with a degree in economics, but is less than would be expected from practising lawyers. The headline news from *Myriad* is that wild-type DNA sequences are not patent-eligible but cDNA is patent-eligible. However, no legal analysis is needed to reach that conclusion and even our NYT contributor might be motivated to wonder whether there is more depth to the opinion. It does not take a law degree to appreciate that if cDNA is not a product of nature then its eligibility says nothing relevant about the rules of eligibility for natural products. The *ratio decidendi* has to be determined by identifying the material facts found by the Court in relation to wild-type cDNA, identifying the conclusion reached on those facts and inferring from these the relevant rule of law[2]. The key fact

[2] See e.g. Arthur L. Goodhart, Determining the ratio decidendi of a case, **40** Yale L. J. 161 1930-1931. Professor Goodhart was an American-born British academic jurist and lawyer, Professor of Jurisprudence at the University of Oxford 1931-1951, Master of University College, Oxford 1951-1963 and editor of Law Quarterly Review for several decades.

found by Justice Thomas was that Myriad's principal contribution was uncovering the precise location and genetic sequence of the BRCA1 and BRCA2 genes within chromosomes 17 and 13. His holding was that the single contribution of separating these genes from their surrounding genetic material and nothing more did not amount to an act of invention. We are fortunate that Justice Thomas summarised his holding twice, both at the beginning and at the end of his opinion and his repeated use of the words "merely because", "merely hold" and "simply because" emphasizes the limited and cautious nature of his decision and his openness to evidence of a further contribution e.g. in terms of new utility. As readers of the opinion can see the facts before the Court did not support the existence of such a further contribution in relation to these particular sequences. Also, as mentioned below, the holding is based on its particular fact patters and does not amount to a categorical exclusion of all naturally occurring DNA in all potentially relevant fact patterns. Other cases may on detailed legal analysis also have narrower holdings than a headline approach might suggest.

Thirdly, and as discussed below, the level of knowledge of the TRIPS agreement and its significance amongst US practitioners is low. That fact is not peculiar to US practitioners but is shared at least by European colleagues who also rarely have occasion to consult the provisions of international agreements rather than regional or national law. However, when the existence or otherwise of categorical exclusions comes to be considered the provisions of TRIPS acquire great significance.

The TRIPS Agreement

A major deficiency of the Guidance is that it makes no mention of the TRIPs Agreement and takes no account of its provisions. A search of the published Guidance using the keyword TRIPS proved negative as also did a search using the keyword TRADE.

The TRIPS Agreement is now of central importance to IP law both nationally and internationally as is apparent from the following extract from the relevant Wikipedia entry:

> TRIPS was negotiated at the end of the Uruguay Round of the General Agreement on Tariffs and Trade (GATT) in 1994. **Its inclusion was the culmination of a program of intense lobbying by the United States**, supported by the European Union, Japan and other developed nations. Campaigns of unilateral economic encouragement under the Generalized System of Preferences and coercion under Section 301 of the Trade Act played

> an important role in defeating competing policy positions that were favored by developing countries, most notably Korea and Brazil, but also including Thailand, India and Caribbean Basin states. In turn, the United States strategy of linking trade policy to intellectual property standards can be traced back to the entrepreneurship of senior management at Pfizer in the early 1980s, who mobilized corporations in the United States and made maximizing intellectual property privileges the number one priority of trade policy in the United States (Braithwaite and Drahos, 2000, Chapter 7).
>
> After the Uruguay round, the GATT became the basis for the establishment of the World Trade Organization. Because ratification of TRIPS is a **compulsory requirement** of World Trade Organization membership, any country seeking to obtain easy access to the numerous international markets opened by the World Trade Organization must enact the strict intellectual property laws mandated by TRIPS. For this reason, **TRIPS is the most important multilateral instrument for the globalization of intellectual property laws**. States like Russia and China [3] that were very unlikely to join the Berne Convention have found the prospect of WTO membership a powerful enticement. (emphasis added).

The US acceded to the WTO on 1 January 1995. There must therefore be a strong presumption against any amendment to US intellectual property law, including patent law, that provides a categorical exclusion not existing in US law as of 1 January 1995. That proposition is supported by the well-known substantive canon of interpretation in *Murray v. The Charming Betsy*, 6 U.S. (2 Cranch) 64 (1804) which arguably has much increased persuasive power where the US Government itself was the moving spirit behind the treaty:

> "It has also been observed that an act of Congress ought never to be construed to violate the law of nations if any other possible construction remains..."

Consistent with the above presumption, in *Bilski v Kappos* the Supreme Court considered *inter alia* a categorical exclusion of business method patents under §101 but held that: "A categorical rule denying patent protection for "inventions in areas not contemplated by Congress . . . would frustrate the purposes of the patent law." *Chakrabarty*, 447 U. S.", at 315 and that:

> "Section 101 similarly precludes the broad contention that the term "process" categorically excludes business methods. The term "method," which is within §100(b)'s definition of "process," at least as a textual matter and before consulting other limitations in the Patent Act and this Court's precedents, may include at least some methods of doing business. See, e.g., Webster's New International Dictionary 1548 (2d ed. 1954) (defining "method" as"[a]n orderly procedure or process . . . regular way or manner of doing anything; hence, a set form of procedure adopted in investigation or instruction"). The Court is unaware of any argument that the "'ordinary, contemporary, common meaning,'" *Diehr, supra*, at 182, of "method" excludes business methods. Nor is it clear how far a prohibition on business method patents would reach, and whether it would exclude technologies for conducting a business more efficiently.@

As explained in the previous Roberts and Cole submission, Article 27.1 of TRIPs entitled "Patentable Subject Matter" provides a complete code for patent-eligibility which WTO member countries including the US are required to respect. It reads:

> "1. Subject to the provisions of paragraphs 2 and 3, patents shall be available for any inventions, whether products or processes, in **all fields of technology**, provided that they are new, involve an inventive step and are capable of **industrial application**. Subject to paragraph 4 of Article 65, paragraph 8 of Article 70 and paragraph 3 of this Article, patents shall be available and patent rights enjoyable without discrimination as to the place of invention, the field of technology and whether products are imported or locally produced." (emphasis added).

By Note 5 the terms "inventive step" and "capable of industrial application" may be deemed by a Member to be synonymous with the terms "non-obvious" and "useful" respectively.

Exclusions are covered by Articles 27.2 and 27.3:

> "2. Members may exclude from patentability inventions, the prevention within their territory of the commercial exploitation of which is necessary to protect ordre public or morality, including to protect human, animal or plant life or health or to avoid serious prejudice to the environment, provided that such exclusion is not made merely because the exploitation is prohibited by their law.

> 3. Members may also exclude from patentability:
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> (a) diagnostic, therapeutic and surgical methods for the treatment of humans or animals;
>
> (b) plants and animals **other than micro-organisms**, and essentially biological processes for the production of plants or animals other than non-biological and microbiological processes. (emphasis added).

No other exclusions are provided for in the TRIPS Agreement.

Categorical exclusion of microorganisms found in the wild – relevance of US domestic law and also the TRIPS Agreement

It is noted that Example 6 of the Nature-Based Product examples is based on the fact pattern in *Funk Bros. Seed Co. v. Kalo Inoculant Co.*, 333 U.S. 127 (1948) and that claim 1 of the example is identical to the claim objected to by the Supreme Court. The eligibility finding for claim 2 is a positive development, both as regards the possibility that the claimed bacteria might be mixed together in nature but only possibly as a rare and unusual phenomenon and as regards the recognised importance of a different characteristic.

The analysis of claims 1 and 4 in Example 9 could be expressed in terms of *Myriad*, the claimed pacemaker cells expressing marker P qualifying as isolated products but having no new utility, the holding in *Myriad* being that mere isolation does not suffice.

It is reassuring to find that notwithstanding a dictum in *In re Roslin Institute (Edinburgh)*, 750 F.3d 1333, 1338-39 (Fed. Cir. 2014) concerning the patentability of any existing organism or any plant found in the wild, reliance on that dictum has not featured either in the Interim Guidance or in the Nature Based Product Examples. For the reasons explained below, it is submitted that the dictum incorrectly expresses US domestic law, if followed could place US law in conflict with TRIPS, and is therfore not to be relied on.

In its *Roslin* opinion the Federal Circuit held, based in its interpretation of *Chakrabarty* and *Funk*, that naturally occurring organisms are not patentable. Accordingly the Federal Circuit held that any existing organism or any plant found in the wild is not patentable.

It is doubtful that such a far-reaching rule of law can be derived from *Funk*. The Circuit Court of Appeals held that the invention was more than the discovery of a law of nature since the inventor had made a new

and different composition of non-inhibitive strains which contributed utility and economy to the manufacture and distribution of commercial inoculants. The status of the claimed inoculant as a composition of matter was not disturbed by Justice Douglas in his majority opinion on appeal and was not material to his decision. Instead he held that the aggregation of a plurality of the specified bacterial species to form an inoculant fell short of invention because once nature's secret of the non-inhibitive quality of certain strains had been discovered, the state of the art made the production of a mixed inoculant a simple step, falling within the skill of the calling rather than revealing the flash of creative genius, the test in *Cuno Engineering Corp. v. Automatic Devices Corp.*, 314 U. S. 84. His decisive conclusion was that the flash of creative genius needed to satisfy the *Cuno* test could not be equated with the discovery of non-inhibition "unless we borrowed invention from the discovery of the natural principle itself." Nothing in that opinion supports a categorical exclusion of naturally occurring microorganisms, especially in the different and often technically and commercially important factual situation where such microorganisms have been newly isolated and found to have valuable properties e.g. because they produce new and valuable antibiotics or anti-cancer drugs.

The *Roslin* categorical exclusiuon also cannot be derived from *Chakrabarty*, where the question before the Court was whether a live man-made microorganism was a manufacture or composition of matter under §101. The Court's holding, following *Hartranft v. Wiegmann*, 121 U. S. 609, 121 U. S. 615 (1887) was that the claimed microorganism was not a hitherto unknown natural phenomenon, but was a non-naturally occurring manufacture or composition of matter - a product of human ingenuity "having a distinctive name, character and use." There is nothing in *Chakrabary* to cast doubt on the proposition that a biologically pure culture of a newly isolated microorganism having a distinctive character and use would be equally deserving of protection, the microorganism existing in nature but not in the form of a biologically pure culture and identification of its utility being a further contribution of the inventors. That proposition is implicit in the factual finding in *Chakrabarty* that the USPTO had prior to 1970 issued patents for bacteria and in the footnote reference to Louis Pasteur's 1973 patent on "yeast, free from organic germs of disease, as an article of manufacture."

In addition to the issues under US domestic law, the *Roslin* opinion arguably puts the US in contravention of TRIPS by categorically excluding naturally occurring microorganisms from patentability. Article 27(3)(c) of TRIPS expressly permits the exclusion from patentability of plants whether cultivated or found in the wild but correspondingly forbids the exclusion of microorganisms. They are widely and internationally treated as patentable

and fall under heading C12N 1/00 of the Cooperative Patent Classification. The EPO has granted patents for naturally occurring microorganisms from its inception and continues to do so.

> Granted EP-B-0029976 (Nakajima, Unitika) is concerned with the provision of a thermophilic bacterium having an easily settlable cell and an easily breakable cell wall and which claims "A biologically pure culture of *Bacillus stearothermophilus* (IFO No. 14O93) the cell of which is longer than about 10 microns and which permits easy release of an intracellular component.
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> EP-B-1436380 (Wynne, Reading University) is concerned with a probiotic strain of Lactobacillus isolated from the human gut and in addition to exhibiting characteristics typical of Lactobacilli in general having the further surprising properties that it can suppress the growth of Candida species to a degree never previously achieved through use of a probiotic and that it is unaffected by tetracycline and related antibiotics. Since Candida in any region of the body is considered to be a causative factor in irritable bowel syndrome (IBS), the novel strain is useful in treating or preventing that disorder. The granted main claim is directed to: "A lactobacillus strain as deposited under accession number NCIMB 41114"; claim 1 of the corresponding US patent 7152708 is directed to "a biologically pure culture" of the same strain.
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> Granted patent EP-B-2154238 claims a strain of *Lactobacillus pentosus* for use in the preparation of a fermented food or drink.
>
> Granted EP-B-2785826 (Zielinska) was concerned with the technical problem of isolating from ensiled corn grains a new strain of the *Lactobacillus buchneri* species that, without genetic modifications, would efficiently synthesize 1,2-propanediol and metabolize it to propionic acid, both compounds improving the durability and aerobic stability of starch-rich fodder. The granted main claim was directed to: "A new bacterial strain of *Lactobacillus buchneri A* deposited in the Collection of Industrial Microorganisms in the Institute of Agricultural and Food Biotechnology in Warsaw, under the number KKP 2047."

The newly expressed categorical exclusion set out in *Roslin* therefore amounts to a fundamental change in US domestic law from what was understood at the time when TRIPS was entered into, and if followed would put US grant practice and substantive law fundamentally at variance with practice and substantive law before the EPO and in other major

industrialised countries. Any more extended reliance on *Roslin* would therefore be a matter for concern.

Categorical exclusion of isolated naturally occurring nucleotide sequences

In their earlier submission the writer and Dr Roberts explained that a categorical exclusion of nucleotide sequences, including such sequences providing new utility in their isolated form goes beyond the holding in *Myriad* and brings US domestic law into conflict with TRIPS. The relevant passage reads:

> 10. The scope of Article 27 is demonstrated by EU Directive 98/44/EC on the legal protection of biotechnological inventions. This was drafted *inter alia* to be compliant with the TRIPs Agreement to which it makes no less than five specific references. Article 1 of the Directive requires that member states shall protect biotechnological inventions under national patent law and is without prejudice to the implicitly over-riding obligations under the TRIPs Agreement. Article 3.3 provides that 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*. Article 5.2 provides that an element isolated from the human body or otherwise produced by means of a technical process, *including the sequence or partial sequence of a gene*, may constitute a patentable invention, *even if the structure of that element is identical to that of a natural element*. That is subject to the provisions of Article 5.3 that the industrial application of a sequence or a partial sequence of a gene (i.e. its utility) must be disclosed in the patent application. We submit that the Directive accurately reflects the requirements of the TRIPS agreement, and that national law providing any lesser eligibility falls short of compliance with that Agreement.
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> 11. It follows that the ruling of Justice Thomas in *Myriad* is consistent with the TRIPs Agreement *only* on the narrow interpretation identified by Professor Cole, i.e. that mere isolation of a DNA sequence unaccompanied by new, improved or extended utility does not give rise to eligibility. Any broader interpretation of the ruling e.g. to exclude natural products selected or isolated by the hand of man and possessing new or improved utility would be inconsistent with the express provisions of the Agreement. It will be recollected that Justice Ginsburg during oral argument in *Myriad* was concerned that the US was at risk of adopting a rule quite different from that of other industrialised nations and would be placing itself in an isolated

position. Only the suggested interpretation would avoid those concerns, and it is submitted that the Court had these considerations in mind when it handed down its limited and cautious opinion in *Myriad*.

To reinforce this point, and as evidence of what ought to be allowable, the following information is provided about grant practice in Europe.

European patents with claims to genes and proteins encoded by specified nucleotide sequences continue to be granted by the EPO, and the following examples are believed representative:

EP-B-2155219 (United States of America as represented by the Secretary of Agriculture) for an isolated or recombinant DNA molecule encoding a polypeptide of listed amino acid sequence that is responsible for the AltSB locus for aluminum tolerance in *Sorghum bicolor* and granted on 19 February 2014.

EP -B- 2311468 (Perseus Proteomics) for a gene and protein useful in the treatment of bone cancer granted on 15 January 2014.

EP-B-2129781 (Novozymes) for an isolated polypeptide having phytase activity and an isolated nucleotide sequence that encodes it, granted 22 January 2014.

EP-B-2028278 (Whitehead Institute for Biomedical Research) for isolated double stranded RNA of from 21 to 23 nucleotides in length in the form of two separate RNA strands, perfectly complementary to an mRNA and mediating RNA interference by directing cleavage of the mRNA to which it is perfectly complementary, granted 19 March 2014.

EP-B-2021362 (Innoventus) for an isolated and purified structural gene encoding a fluorescent protein, granted 8 January 2014.

EP-B-1668029 (International Livestock Research Institute, Kenya) for sequences useful e.g. as probes for tick-borne diseases in cattle and other animals and for the production of vaccines granted 25 December 2013.

Implementation of the Biotechnology Directive in German national law followed extended debate, but that debate only proved significant for human genes. For genetic sequences from other organisms the practice of

the German Patent Office is to allow patents with claims covering isolated DNA without specific mention of utility in the claim itself and the following examples are believed representative:

> DE-B-19983297 (Flament, D. et al; US 6511838 corresponds) granted 4 July 2013 covering naturally occurring gene sequences from a marine bacterium coding for a β-agarase.
>
> DE-B-10149715 (Schwab, H. et al.) granted 18 April 2013 covering polynucleotides from the bacterium *Rhodococcus ruber* and encoding an esterase; also covering short sequences.
>
> DE-B-102004386 (Chen, Y. et al.; US 7482157 corresponds) granted in June 2010 having as its object the provision of genes related to the production of monacolin K (a naturally occurring statin also known as lovastatin) from the mold *Monascus*. The claims cover an isolated DNA molecule comprising a polynucleotide relating to mkA and encoding a polypeptide having an activity selected from β-ketoacyl synthase, acetyl-transferase, dehydratase, methyltransferase and ketoreductase.

Furthermore, even in relation to isolated human sequences patent-eligibility remains in Germany provided that the sequences have identifiable new utility which is the inventors' own contribution over and above mere isolation and sequence determination and that the new utility is specified in the claim.

In a recent decision in *University of Utah v Ambry Genetics* (15 December 2014) the Federal Circuit rejected as ineligible a claim to a pair of single-stranded DNA primers for use in the polymerase chain reaction resulting in the synthesis of DNA having all or part of the sequence of the BRCA1 gene. It is submitted that the Court inappropriately focused on structural identity to the exclusion of isolation and new utility and therefore extended the *Myriad* reasoning beyond the holding of Justice Thomas. The holding in this case is inconsistent with the obligations of the US under TRIPS because these primers would be plainly patent-eligible in the EPO and in other industrialised countries. Even under German national law a claim to these sequences would be patent-eligible because they have been newly synthesized in isolated form, have new utility because they can serve as primers in PCR, and because their new utility is specified in the claim.

In the Nature-Based Product Examples, the blanket ineligibility of naturally-occurring sequences is exemplified by the ineligibility in Example 6 of the claim to the stable energy-generating plasmid. That plasmid in

isolated form has new utility because it can be transferred to other bacteria to create new and useful bacterial strains, as exemplified by the fact pattern in *Chakrabarty*. Attention is also directed to the *Acremonium* plasmid example in my earlier submission. It cannot have been the intention of Justice Thomas in Myriad to create an exclusion so broad as to cover newly isolated sequence of such manifest utility.

Categorical exclusion of other natural products

It will be recalled that the March 2014 Myriad/Mayo Guidance included an example that discusses the patent eligibility of a purified amazonic acid. The USPTO example then read as follows:

> "The Amazonian cherry tree is a naturally occurring tree that grows wild in the Amazon basin region of Brazil. The leaves of the Amazonian cherry tree contain a chemical that is useful in treating breast cancer. However, to be effective, a patient must eat 30 pounds of the leaves per day for at least four weeks. Many have tried and failed to isolate the cancer-fighting chemical from the leaves. Applicant has successfully purified the cancer-fighting chemical from the leaves and has named it amazonic acid. The purified amazonic acid is structurally identical to the amazonic acid in the leaves, but a patient only needs to eat one teaspoon of the purified acid to get the same effects as 30 pounds of the leaves…"

In the original example the claim to isolated amazonic acid was held to be ineligible notwithstanding that the compound had been purified and had new utility. In Example 3 of the Nature-Based Product examples the scenario has been revised to delete the reference to improved utility and it is explained that there is no indication that purified amazonic acid has any characteristics (structural, functional, or otherwise) that are different from naturally occurring amazonic acid. The example is now counter-factual because any person knowledgeable about drugs and their administration will be well aware of the change in functional characteristic consequent upon the provision of amazonic acid in pure form.

It is still unclear why the USPTO seeks to remove the patent-eligibility of isolated or purified natural products of new medical or other utility, which has been taken as a given in the US for 100 years and is consistent with practice in Europe and other major industrialised countries. The scenario in the new example still makes it clear beyond dispute that it was directly derived from the scenario in oral argument in *Myriad*. The

relevant exchanges with counsel for the petitioners in oral argument in *Myriad* establish that the point was considered to be well-settled:

> "JUSTICE GINSBURG: Mr. Hansen, Respondents say that isolating or extracting natural products, that has long been considered patentable. Examples were aspirin and whooping cough vaccine. How is this different from natural products? …….
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> JUSTICE ALITO: Can I take you back to Justice Ginsburg's question, because I'm not sure you got at what troubles me about that. Suppose there is a substance, a chemical, a molecule in the leaf – the leaves of a plant that grows in the Amazon, and it's discovered that this has tremendous medicinal purposes. Let's say it treats breast cancer. A new discovery, a new way is found, previously unknown, to extract that. You make a drug out of that. Your answer is that cannot be patented; it's not eligible for patenting, because the chemical composition of the drug is the same as the chemical that exists in the leaves of the plant.
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> 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.
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> JUSTICE ALITO: But 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 value of this. But it's extracted and reduced to a concentrated form. That's not patent eligible?
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> MR. HANSEN: No, that may well be eligible, because you have now taken what was in nature and you've transformed it in two ways. First of all, you've made it substantially more concentrated than it was in nature; and second, you've given it a function. If it doesn't work in the diluted form but does work in a concentrated form, you've given it a new function. And by both changing its nature and by giving it a new function, you may well have patent …"

The Association for Molecular Pathology itself expressly disapproved the amazonic acid example in the earlier Guidance in their comments of 30 July 2014 and explained their position as follows:

> "On page 7, USPTO begins its analysis of Claim 1 involving purified amazonic acid, and concludes that Claim 1 does not involve subject matter that is significantly different than natural amazonic acid. We disagree with this conclusion. Instead, we believe that the purified amazonic acid described in Claim 1 is markedly different than the amazonic acid that exists in nature because purification has changed its functional properties in a manner that is substantially different from the functional properties of amazonic acid in its natural, unpurified form. Following purification, concentrated amazonic acid can be administered in a pill form. Concentration is central to the functionality of amazonic acid, as it directly impacts the means of administration of this exogenous drug, and allows the patent applicant to control the manner and precise quantity in which the drug is given. This example is distinguishable from the naturally occurring nucleic acids at issue in *AMP v. Myriad*, because the integral functional property at stake in *Myriad* was the unchanged informational content of the DNA sequence. Moreover, in *Myriad*, the plaintiffs merely sought to access or "read" the information in the DNA. This information is stored within the sequence of base pairs and is not altered by isolating the DNA sequence. Thus, in contrast to Claim 1 involving amazonic acid, isolation had no impact on the function of the DNA for the purposes at issue, and the structural transformations described in *Myriad* were peripheral to the use of the DNA."

Arguably there should be a canon of construction that an opinion should not contradict a factual or legal position that has been conceded e.g. in oral argument and has become common ground between the parties. The patent-eligibility of purified amazonic acid was no longer the subject of a claim or controversy between the parties, there was no reason for the Court to rule on it, and hence there was no basis for interpreting the Court's opinion so as to over-rule the position that the parties had already agreed in argument.

The amazonic acid example is therefore inappropriate and should be replaced by the rapamycin example of my earlier comments or an entirely fictional example modelled closely on the rapamycin example.

Example 4 insofar as it rejects eligibility of claim 1 suffers from the same deficiencies as Example 3. It postulates Antibiotic L, a protein formed as crystalline inclusions within cells of *Streptomyces arizoneus*. The example is atypical because most antibiotics are small molecules. There is recent work on antibiotic proteins in bacteria and viruses, but neither the proteins nor the small molecules occur within the cell in crystalline form. Even if the

postulates are accepted, however, the isolation of Antibiotic L from *Streptomyces* and its provision in purified form gives rise to a manufacture or composition of matter in new form and having new activity for the reasons explained by the Association for Molecular Pathology. My previous comments asked whether it was 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). It is submitted that the answer is negative and that the same reasoning is applicable to the protein antibiotic of Example 4. Furthermore, a categorical exclusion of isolated naturally occurring substances creating new utility would not be consistent with the obligations of the US under TRIPS.

Similar considerations apply to the antibody of claim 1 in Example 8, although the claim should be written to distinguish from the antibody occurring naturally in mice and coyotes.

Reconsideration of the Examples at least in the light of these comments is therefore requested.

Paul Cole
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