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CLAIMING BIOTECH/PHARMA INVENTIONS IN VIEW OF THE *PROMETHEUS* AND *MYRIAD* DECISIONS

Decisions in USA and Australia

USA – *Prometheus Labs. v. Mayo, 132 S. Ct. 1289 (2012)*

Assoc'n for Mol. Path. v. Myriad Genetics, Inc. 569 U.S. 689 (2013)

Australia - *D'Arcy v Myriad Genetics Inc.*, FCAFC 115 (5 September 2014)

Prometheus Brief History

Claim 1 of the patent reads:

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

(a) administering ***a drug providing 6-thioguanine*** to a subject having said immune-mediated gastrointestinal disorder; and

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

wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and

wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Prometheus – Supreme Court, cont'd

- HELD: It is not patentable subject matter under § 101 to claim a law of nature, natural phenomena, and abstract idea only.
- An *application* of a law of nature, phenomena or abstract idea *may* be patentable.
- However, not enough to simply state the law of nature in the patent claims while adding a well-known or conventional step.

Prometheus – Supreme Court, cont'd

Generally: simply adding **well-understood, routine, conventional** actions of administering the drug and checking its blood concentration in the most general of terms, however, does not confer eligible patent subject matter as the claims themselves are effectively directed to a law of nature.

Myriad Brief History - USA

Myriad's claims at issue involved three types of claims: isolated genes, a screening method for potential drug candidates, and a diagnostic method aimed at "comparing" or "analyzing" DNA sequences.

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1. (cDNA sequence)

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MYRIAD – SUPREME COURT

Holding: “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.”

Limit to Holding: “cDNA does not present the same obstacles to patentability as naturally occurring, isolated DNA segments.”

USPTO GUIDELINES – March 4, 2014

- *"Myriad* also clarified that not every change to a product will result in a marked difference, and that the mere recitation of particular words (e.g., "isolated") in the claims does not automatically confer eligibility."
- While *Myriad* was limited to nucleic acids, USPTO now states that all claims reciting or involving natural products should be examined for a marked difference under *Chakrabarty's* admonition against patents on naturally occurring things.

Four Sections in USPTO Guidance

- Part I – overall process for analyzing subject matter eligibility under 35 U.S.C. § 101;
- Part II – how to determine whether the claim as a whole recites eligible subject matter (something significantly different than a judicial exception);
- Part III – multiple examples; and
- Part IV – new form paragraph to be used when rejecting claims in accordance with this guidance.

Three Questions for Analysis

- Question 1: Is the claimed invention directed to one of the four statutory patent-eligible subject matter categories: process, machine, manufacture, or composition of matter?
- Question 2: Does the claim recite or involve the judicial exceptions?
- Question 3: Does the claim as a whole recite something *significantly different* than the judicial exception(s)?

Key issue: does claim recite something “significantly different” than judicial exceptions, *e.g.* law of nature or natural product.

- Consider factors that weigh toward eligibility.
- Consider factors that weigh against eligibility.
- Balance factors.

“Significantly Different” Addresses Supreme Court’s Two Pathways to Eligibility

- New Guidance brings together the outcomes of both *Myriad* and *Mayo* in its expression of the “significantly different” standard for eligibility.
- “Significantly different” standard addresses the Supreme Court’s two articulated pathways to eligibility for claims reciting judicial exceptions such as natural products:
  1. ***Marked difference*** from what exists in nature; or
  2. Addition of ***significantly more*** to the judicial exception.

Summary of Factors

Factors that weigh <u>toward</u> eligibility (significantly different)

a) Product claim recites something that initially appears to be a natural product, but after analysis is determined to be non-naturally occurring and markedly different in structure from naturally occurring products.

Claim recites elements/steps in addition to the judicial exception(s) that:

b) Impose meaningful limits on the claim scope.
c) Relate to the judicial exception(s) in a significant way, e.g., they are more than insignificant extra- solution activity.
d) Do more than describe the judicial exception(s) with general instructions to apply/use it.
e) Include a particular machine or particular transformation, which implements or integrates the judicial exception(s).
f) Add a feature that is more than well-understood, purely conventional or routine.

Factors that weigh <u>against</u> eligibility (not significantly different)

g) Product claim recites something that appears to be a natural product that is not markedly different in structure from naturally occurring products.

Claim recites elements/steps in addition to the judicial exception(s) that:

h) Are recited at a high level of generality.
i) Must be used/taken by others to apply the judicial exception(s).
j) Are well-understood, purely conventional or routine.
k) Are insignificant extra-solution activity, e.g., are merely appended to the judicial exception(s).
l) Amount to nothing more than a mere field of use.

How to Analyze “Significantly Different”

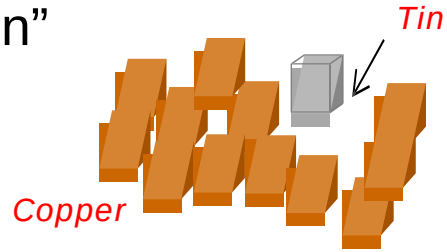
A significant difference can be shown in multiple ways, such as:

(1) the claim includes elements or steps in addition to the judicial exception that practically apply the judicial exception in a significant way, e.g., by adding significantly more to the judicial exception; and/or

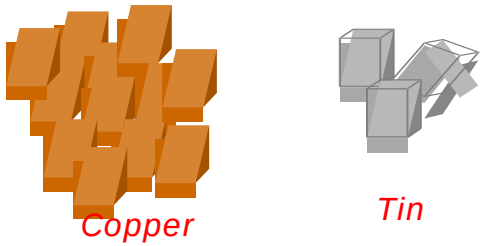
(2) the claim includes features or steps that demonstrate that the claimed subject matter is markedly different from what exists in nature (and thus not a judicial exception).

Examples: No Marked Difference – Not Patent Eligible

Claimed “Composition Comprising 90% copper and 10% tin”



Naturally occurring copper and tin



1. Fails to satisfy non-naturally occurring requirement because copper and tin exist in nature.

2. No structural difference because the mere mixture or aggregation of naturally occurring metals together as a **different** “composition” does not change the metals from what exists in nature.

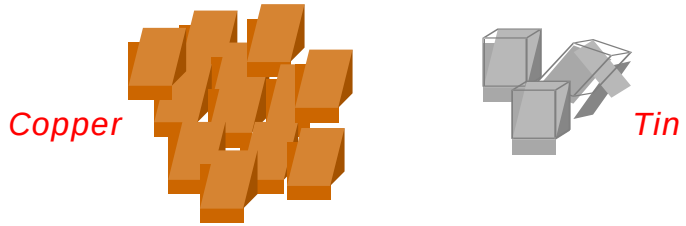
- No marked difference – Factor g) is satisfied = not patent eligible subject matter

Examples: Marked Difference – Patent Eligible (Factor a) is Satisfied)

Claimed “alloy comprising 90% copper and 10% tin”

Alloy (bronze)

Naturally occurring copper and tin



1. Non-naturally occurring because the alloy of copper and tin does not occur in nature, but instead was created by human manipulation. This particular alloy is a type of bronze.

2. Markedly different in structure

- structural difference (the alloy is a solid solution of tin in copper, which has a different crystalline arrangement of atoms than in the natural metals);
- structural difference results in change to properties of alloy (the alloy has a different color, tensile strength, hardness, and melting point than either natural metal).

Examples: Judicial Exception + Additional Elements/Steps

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.

Examples: Judicial Exception + Additional Elements/Steps (continued)

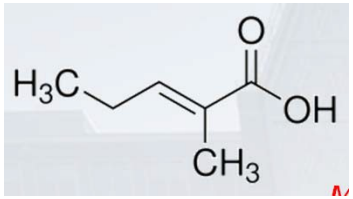
- Questions 1 & 2: YES
- Directed to a manufacture
- Recited Judicial Exception (calcium chloride, gunpowder – a mixture of saltpeter, sulfur and charcoal)
- Question 3: YES
- Recites something significantly different than the natural products themselves: sparking composition, cardboard body, ignition fuse = specific practical application of invention

Examples: Judicial Exception + Additional Elements/Steps (continued)

- Factors favoring patent eligibility:
- Factor a) = NO, calcium chloride and gunpowder are not markedly different from what exists in nature.
- Factor b) = YES, 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
- Factor c) = YES, the claimed elements relate to the calcium chloride and gunpowder in a significant way, e.g., elements form a structure into which the calcium chloride and gunpowder are physically integrated
- Factor d) = YES, claimed elements do more than describe the natural products with general instructions to use them.

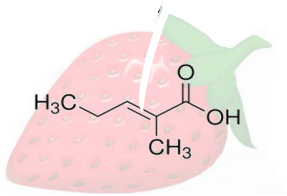
Example: No Marked Difference Factor g) is Satisfied

Claimed purified 2-methyl-2-pentenoic acid



Mild fresh strawberry flavor and aroma

Naturally occurring 2-methyl-2-pentenoic acid



Mild fresh strawberry flavor and aroma

Claimed acid is not markedly different

1.Fails to satisfy non-naturally occurring requirement, because the acid occurs naturally in strawberries.

2.No structural difference because removal or "purification" of the acid from strawberries did not change its structure.

Discussion of Purification

In nature the acid is part of a strawberry, and as claimed it is separated from the other components of the strawberry. So why isn't the purified acid eligible?

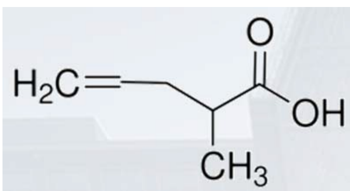
– Cannot base eligibility determination on the mere recitation of the word "purified" in the claim.

– To be eligible, the product as claimed must reflect a marked difference from what exists in nature. This is a case-by-case determination.

– In this case, although the purified acid is separated from the other components of the strawberry, the acid itself is unchanged. In other cases, the specific purification process may lead to changes that amount to a marked difference.

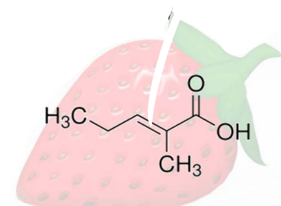
Example: Marked Difference Factor a) is Satisfied

Claimed
2-methyl-2-pentenoic acid



"Cooked" strawberry jam-like flavor and aroma

Naturally occurring
2-methyl-2-pentenoic acid



Mild fresh strawberry flavor and aroma

Claimed acid is markedly different

1. Non-naturally occurring because acid does not occur in nature, but instead was created by human manipulation.

2. Markedly different in structure. The claimed acid is structurally different (the double bond of the claimed acid is at the 4th carbon as compared to the naturally occurring double bond at the 2nd carbon). It is reasonable to conclude that this structural difference is a marked difference, because the structural change results in a change to the properties of the acid (flavor and aroma are "cooked" strawberry jam-like as compared to naturally occurring "fresh" strawberry flavor & aroma).

Most recent USPTO Comments – June Cohan, Sept. 26, 2014

1. Revised Guidance, expected shortly, would not be confined to DNA.

2. Likely to change analysis from claims that “involve” or “recite” a judicial exception, to clams that are “directed” to a judicial excption.

3. Likely to eliminated “significantly different” standard.

4. Likely to eliminate the twelve-factor test as being too complicated.

5. May use examples from the public comments.

Resources

USPTO Myriad – Mayo Guidance Web Page

http://www.uspto.gov/patents/announce/myriad-mayo.jsp

Australia

Appealed Claim 1:

‘An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19’.

Case Comparisons

Prometheus	*Myriad* USA	Myriad Australia
1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising: (a) administering *a drug providing 6-thioguanine* to a subject having said immune-mediated gastrointestinal disorder; and (b) determining the level of 6-thioguanine in said subject having said immune-mediated gastrointestinal disorder, wherein the level of 6-thioguanine less than about 230 pmol per 8 x 10^8 red blood cells indicates a need to increase the amount of said drug subsequently administered to said subject and wherein the level of 6-thioguanine greater than about 400 pmol per 8 x 10^8 red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.	1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2. 2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1. (cDNA sequence)	Appealed Claim 1: An isolated nucleic acid coding for a mutant or polymorphic BRCA1 polypeptide, said nucleic acid containing in comparison to the BRCA1 polypeptide encoding sequence set forth in SEQ.ID No:1 one or more mutations or polymorphisms selected from the mutations set forth in Tables 12, 12A and 14 and the polymorphisms set forth in Tables 18 and 19.

Discussion Questions

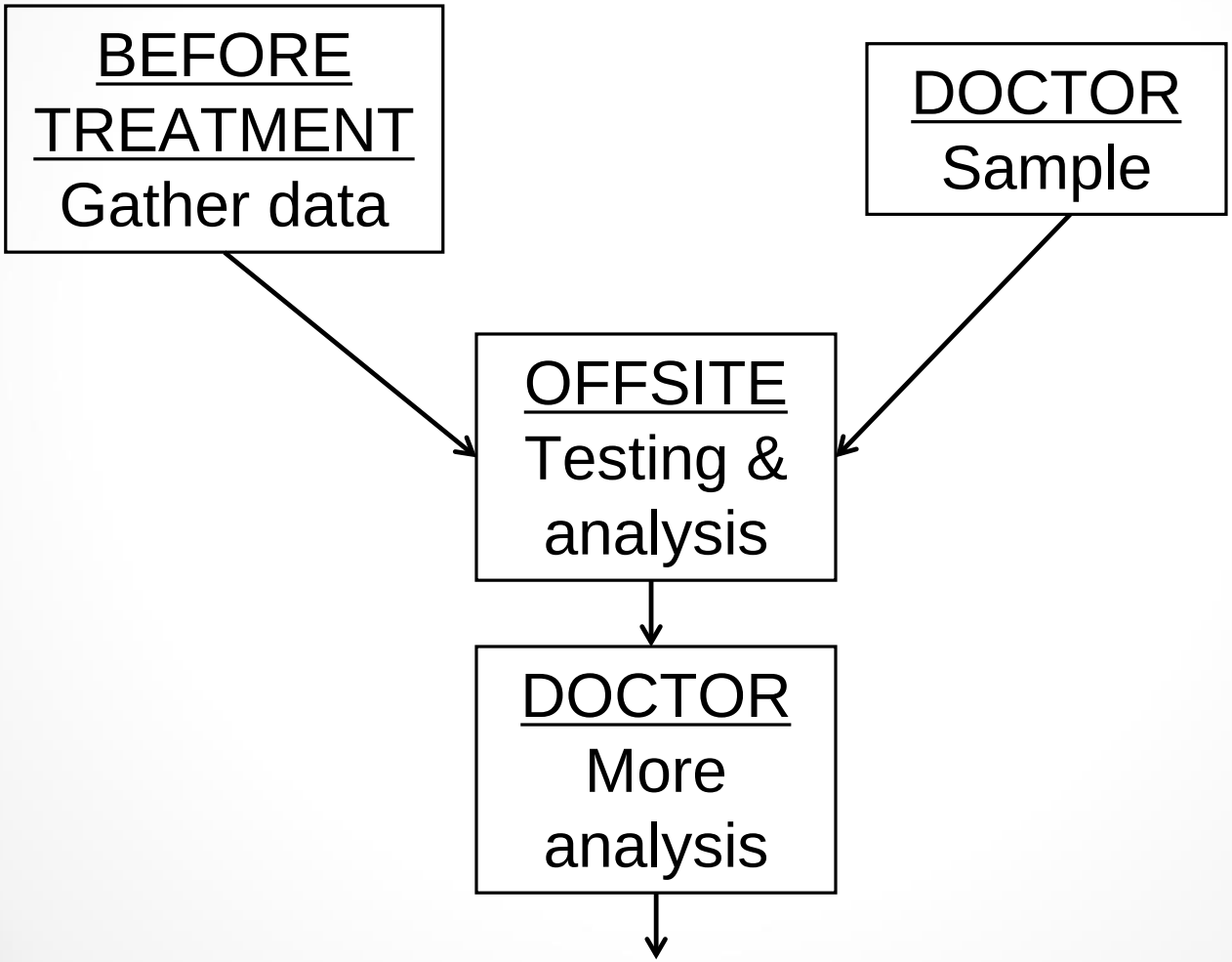
1. Diagnostic/personalized medicine invention.

2. Based on “naturally occurring” compounds (USPTO Example)

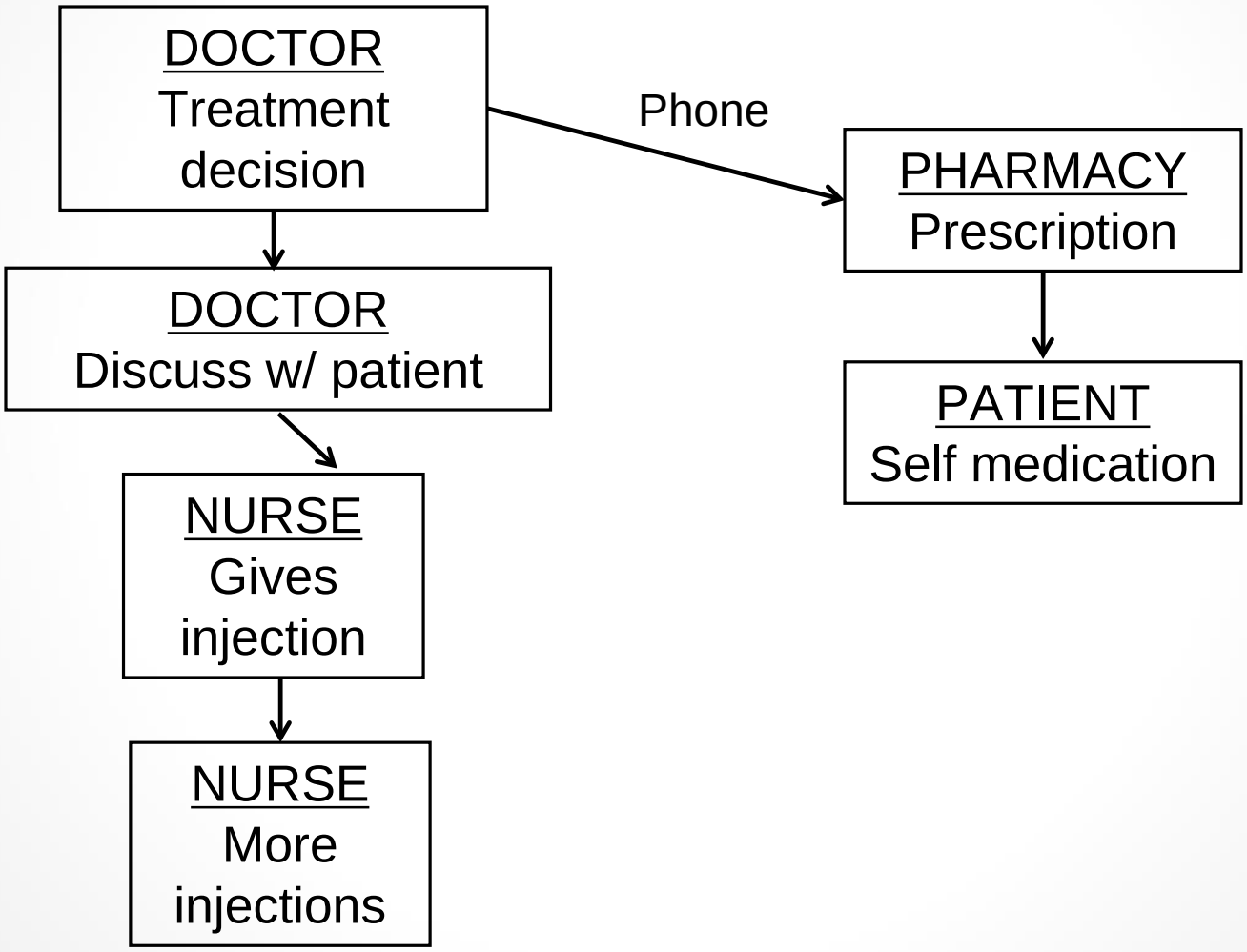
Diagnostic Claims

- Diagnostics – diagnostic claims are often multi-step processes. Initial step sometimes involves collecting sample from patient (doctor) and subsequent steps involve real diagnostic procedure (outsourced).
  - *Mayo*: the diagnosis on metabolite levels depended on how patient's body metabolized drug
- Personalized Medicine – multiple steps (by multiple entities).

Personalized Medicine



Personalized Medicine (cont'd)



How to Claim This Invention?

1. Where is it possible to protect?

2. What kind of claims is acceptable?

1. What infringement issues arise?

Sample Claims from Subject Matter Eligibility Discussion at 2014 BIO International Convention

June 27, 2014

Factual Assumptions

- Antibiotic L is a naturally occurring protein produced by a particular bacterial species. It exhibits antibiotic activity in nature (e.g., it kills other bacterial species in its natural environment).
- SEQ ID NO: 1 is the naturally occurring DNA sequence that encodes Antibiotic L.
- SEQ ID NO: 2 is the naturally occurring amino acid sequence of Antibiotic L.
- Some “fluorescent labels” are naturally occurring.
- Antibodies to Antibiotic L are naturally occurring in wild coyotes, but not in humans or mice.

Small Changes To A Natural Product

1. Isolated nucleic acid comprising a sequence that has at least 90% identity to SEQ ID NO: 1 and contains at least one sequence modification relative to SEQ ID NO: 1.

2. Polypeptide comprising an amino acid sequence that has at least 90% identity to SEQ ID NO: 2 and contains at least one sequence modification relative to SEQ ID NO: 2.

Derivatives of Natural Products

3. A nucleic acid comprising SEQ ID NO: 1 and a fluorescent label attached to the nucleic acid.

4. A chimeric or humanized antibody to Antibiotic L.

5. Purified Antibiotic L.

Products Created By Human Manipulation Of Natural Processes

6. Antibiotic L, which is expressed by recombinant yeast.

7. A human or fully human antibody to Antibiotic L.