Lessons Learned From *Prometheus, Myriad* and *Classen* On Drafting Patent-Eligible Biomarker-Related Claims

Steve Lendaris

Baker Botts LLP

NJIPLA's 25th Annual
Pharmaceutical / Chemical Patent Practice Update
December 7, 2011

BAKER BOTTS LLP

It's All About Claim Drafting

- **"Inevitably, the subject matter exclusions of eligibility doctrines depend on the way that claims are drafted. Thus, careful claim drafting or new claim forms can often avoid eligibility restrictions. Eligibility then becomes a game where lawyers learn ingenious ways to recast technology in terms that satisfy eligibility concerns."**

- Chief Judge Rader
(from his "additional views" in *Classen*)

BAKER BOTTS LLP

Overview

- **What we have learned from *Myriad, Prometheus* and *Classen* about claiming:**
  - Biomarkers, as compositions of matter
  - Biomarker - related methods
- **Questions that remain unanswered**
  - Lab Corp-type diagnostic method claims
- **Avoiding Joint Infringement Pitfalls**
- **Getting it Right: Suggestions for drafting claims that pass §101 muster**

BAKER BOTTS LLP

Myriad: Impact on Biomarker Claims

- **Composition of Matter Claims at Issue in U.S. Patent No. 5,747,282**
  - 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.
  - 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.
- **Key Word = "ISOLATED"**

BAKER BOTTS LLP

Test Applied By Federal Circuit In *Myriad*

- **"Specifically, The Supreme Court has drawn a line between compositions that, even if combined or altered in a manner not found in nature, have similar characteristics as in nature, and compositions that human intervention has given 'markedly different', or 'distinctive', characteristics"**
- **On the non-eligible side of the line:**
  - *American Fruit Growers v. Brogdex Co.,* 283 U.S. 1(1931) (borax-coated oranges)
  - *Funk Bros. Seed Co. v. Kalo Inoculant Co.,* 333 U.S. 127(1948) (non-inhibitory mixtures of N_2-fixing bacteria)
- **On the eligible side of the line:**
  - *Diamond v. Chakrabarty*, 447 U.S. 303 (genetically-engineered, oil-eating bacteria)

BAKER BOTTS LLP

Test Applied By Federal Circuit In *Myriad (cont.)*

- **Court (per Judge Lourie) adopts "markedly different" or "distinctive" characteristics test**
- **"Enlargement of the range of utility" is also a relevant test for distinctiveness (Moore, Bryson)**
- **Non-naturally occurring/man-made is not enough**
  - *But, see,* USPTO Guidelines, 66 Fed. Reg. 1092 (2001) ("An isolated . . . DNA molecule [having a naturally occurring sequence] . . . is eligible for a patent . . . because that DNA molecule does not occur in that isolated form in nature.")

BAKER BOTTS LLP

Do the Claimed Isolated DNAs Pass the Test?

- **All agree cDNA passes the test**
- **Claims 1, 2, 5**
  - Lourie: Distinctive chemical identity by virtue of being a sub-portion of larger naturally-occurring DNA molecule ("cleavage", "synthesis"); ISOLATED ≠ PURIFIED
  - Moore: Concurs, but size matters; easier to find smaller isolated DNAs distinct, based on utility
  - Bryson: Dissents; not markedly different because information content is the same

BAKER BOTTS LLP

What Will The Supreme Court Think?

- **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.**
- **5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.**

DO THESE CLAIMS READ ON AN ISOLATED CHROMOSOME?

BAKER BOTTS LLP

Method Claims and §101: The Emerging Standards

- **Claims involve a correlation**
  - genetic sequence/disease *(Myriad)*
  - drug metabolite/efficacy or toxicity *(Prometheus)*
  - vaccination schedule/chronic disease *(Classen)*
- **Mental Steps Only : NO GOOD**
- **Preemption of Correlation : NO GOOD**
- **Application of Correlation : GOOD**
- **Transformative Steps**
  - If central to the method : GOOD
  - If mere data gathering : NO GOOD
    or extra-solution activity

BAKER BOTTS LLP

Method Claims in *Myriad*: Too Mental

- **1. A method for detecting a[n] . . . alteration in a BRCA1 gene, . . . which comprises *analyzing* a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or *analyzing* a sequence of BRCA1 cDNA made from mRNA . . .**

*** * ***

- **1. A method for screening a tumor sample . . . for a[n] alteration in a BRCA1 gene in said tumor which comprises . . . *comparing* a first sequence . . . from said tumor sample with a second sequence . . . from said nontumor sample, wherein a difference in the sequence . . . indicates a somatic alteration . . .**

BAKER BOTTS LLP

Method Claims in *Classen*: Mixed Bag

- **1. A method of immunizing a mammalian subject which comprises:**
  - (I) screening a plurality of immunization schedules [for the one with least risk of chronic disorders]
  - (II) immunizing said subject [according to the low risk schedule]

TRANSFORMATIVE

* * *

- **1. A method of determining whether an immunization schedule affects the incidence or severity of [a chronic disorder] . . . which comprises**
  - [immunizing a control and test group]
  - [comparing the incidence/severity of disease]

MENTAL

BAKER BOTTS LLP

Method Claims in *Prometheus*: Transformative

- **1. A method of optimizing therapeutic efficacy for treatment of an immune-mediated gastrointestinal disorder, comprising:**
  - (a) *administering* a [pro-drug] to a subject having said . . . disorder; and
  - (b) *determining* the level of [active metabolite] said subject . . .

  wherein [one] level of [metabolite] . . . *indicates a need to increase* the amount of said [pro-drug] . . . and

  wherein [another] level of [metabolite] . . . *indicates a need to decrease* the amount of said [pro-drug] drug

  * * *

- **46. A method of optimizing therapeutic efficacy and reducing toxicity associated with treatment of an immune-mediated gastrointestinal disorder, comprising:**
  - (a) *determining* the level of [metabolite] in a subject administered a [pro-drug] . . . said subject having said immune-mediated gastrointestinal disorder,

  wherein [one] level of [metabolite] . . . *indicates a need to increase* the amount of said [pro-drug] . . . and

  wherein [another] level of [metabolite] . . . *indicates a need to decrease* the amount of said [pro-drug] subsequently administered to said subject.

BAKER BOTTS LLP

The Unanswered Question: Is The Lab Corp-Type Claim Patent-Eligible?

- **Claim language:**
  - A method for detecting a deficiency of cobalamin or folate in warm-blooded animals comprising the steps of:

    assaying a body fluid for an elevated level of total homocysteine; and

    correlating an elevated level of total homocysteine in said body fluid with a deficiency of cobalamin or folate.
- **Purely diagnostic; not part of a method of treatment, as in *Prometheus***
- **Biomarker was a well known amino acid**

BAKER BOTTS LLP

Joint Infringement

- **Direct infringement requires a single party to perform every step of a claimed method**

- **There can only be joint infringement when:**
  - there's an agency relationship between the parties who perform the method steps or
  - when one party is contractually obligated to the other to perform the steps

BAKER BOTTS LLP

Joint Infringement (cont.)

- **Cases for en banc review**
  - *Akamai Techs. Inc. v. Limelight Networks, Inc., Appeal Nos. 2009-1372, -1380, -1416, 1417*
  - *McKesson Techs. Inc. v. Epic Sys-Corp., Appeal No. 2010-1291*
- **Questions**

  (1) If separate entities . . . perform separate steps . . . under what circumstances, if any, would either entity . . . be liable for [induced or contributory infringement]

  (2) Does the nature of the relationship between [entities], -- e.g., . . . doctor/patient--affect the question of direct or indirect infringement liability?

BAKER BOTTS LLP

Strategies For Re-Drafting Claims

BAKER BOTTS LLP

Drafting Composition-of-Matter Claims

- **What type of subject matter is being pursued in biomarker composition-of-matter claims?**
  - Nucleic acids:
    - Nucleic acid sequences that correlate with a predisposition for a disease.
    - Nucleic acid sequences that correlate with a likelihood that a particular therapy for a disease will be beneficial.
    - Examples include the BRCA1 and BRCA2 nucleic acid sequences at issue in *Myriad*.

BAKER BOTTS LLP

Drafting Composition-of-Matter Claims

- **What type of subject matter is being pursued in biomarker composition-of-matter claims?**
  - Polypeptides:
    - Newly identified polypeptides, modified polypeptides (*e.g.*, glyco-modified polypeptides), or polypeptide fragments that correlate with a predisposition for a disease.
    - Polypeptides, such as those outlined above, that correlate with a likelihood that a particular therapy for a disease will be beneficial.
    - Examples include traditional "isolated polypeptide" claims as well as "diagnostic composition" claims, which comprise the polypeptide and one or more additional components.

BAKER BOTTS LLP

Drafting Composition-of-Matter Claims

- **What is the concern and how is it addressed?**
  - Compositions-of-Matter are expressly identified in Section 101 as patent-eligible.
  - The issue is whether the claimed subject matter falls within the "laws of nature, physical phenomena, and abstract ideas" exceptions.
  - The exception is avoided by establishing "marked differences" or "distinctive characteristics" relative to patent-ineligible subject matter.

Drafting Composition-of-Matter Claims

- **Techniques for establishing marked differences:**
  - **Isolated Compositions**:
    - An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
    - An Isolated polypeptide having the amino acid sequence set forth in SEQ ID No: 1, wherein position 254 is fucosylated.

Specification should outline how the isolated sequences differ from naturally occurring sequences (*e.g.*, how they differ chemically and/or from the perspective of their range of utilities).

BAKER BOTTS LLP

Drafting Composition-of-Matter Claims

- **Techniques for establishing marked differences:**
  - **Diagnostic Compositions**:
    - A diagnostic composition comprising a DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2, and an acceptable carrier.
    - A diagnostic composition comprising a polypeptide having the amino acid sequence set forth in SEQ ID No: 1, wherein position 254 is fucosylated, and an acceptable carrier.

Specification should outline how the diagnostic compositions are employed and how they differ from naturally occurring compositions (*e.g.*, how they differ chemically and/or from the perspective of their range of utilities).

BAKER BOTTS LLP

Drafting Biomarker Method Claims

- **What type of subject matter is being pursued in biomarker - related method claims?**
  - Methods of diagnosis based on the identification of a biomarker.
  - Methods of determining whether a patient will respond to a particular therapeutic.
  - Methods of optimizing therapeutic efficacy by monitoring clearance of a therapeutic.
  - Methods of optimizing a therapeutic regime by monitoring the development of therapeutic resistance mutations.

Drafting Biomarker Method Claims

- **What are the concerns and how are they addressed?**
  - Method claims are considered to fall within the category of "processes", which are identified in Section 101 as patent-eligible.
  - The issue is whether the claimed subject matter falls within the "laws of nature, physical phenomena, and abstract ideas" exceptions.
  - The exception is avoided by establishing that either a particular machine is employed or a transformation occurs ("the Machine or Transformation Test").
  - Note that this is not the exclusive test, however the law has yet to develop with regard to the application of other tests.

BAKER BOTTS LLP

Drafting Biomarker Method Claims

- **What are the concerns and how are they addressed?**
  - Even if a claim is found to comply with Section 101, it may not be enforceable due to a failure to establish direct infringement if it is drafted to require the actions of more than one entity to complete all of the claimed steps.
  - This issue is avoided by drafting claims to capture the activity of a single actor (preferably the diagnostic lab).

Drafting Biomarker Method Claims - Example 1

- **1. A method of diagnosing disease X comprising:**

  a) measuring the expression level of RNA encoding a polypeptide comprising the sequence of SEQ ID No.2 in a tissue test sample; and

  b) comparing said expression level of said RNA from a normal tissue sample; wherein an increased expression level of said RNA in said normal sample is indicative of disease X or a predisposition to disease X.

  - Does it involve a particular machine? No.
  - Does it involve transformations? Maybe/Maybe Not.

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 1

- The claim does recite that the expression level of a particular tissue test sample is measured.
- But compare to claims in *Myriad* that were deemed to not involve transformations:
  - 1. A method for detecting a[n] . . . alteration in a BRCA1 gene, . . . which comprises analyzing a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or analyzing a sequence of BRCA1 cDNA made from mRNA . . .
  - 1. A method for screening a tumor sample . . . for a[n] alteration in a BRCA1 gene in said tumor which comprises . . . *comparing* a first sequence . . . from said tumor sample with a second sequence . . . from said nontumor sample, wherein a difference in the sequence . . . indicates a somatic alteration . . .
- And what about divided infringement - is the lab going to measure the test sample **and** compare to a reference?

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 1

- One potential re-draft of the claim:
  - 1. A method of detecting, in a tissue test sample, an expression level of RNA encoding a polypeptide comprising the sequence of SEQ ID No. 2 that is indicative of disease X or a predisposition to disease X comprising:

    determining the expression level of RNA encoding a polypeptide comprising the sequence of SEQ ID No.2 in a tissue test sample;

    wherein an increased expression level of said RNA, relative to a normal tissue sample, is indicative of disease X or a predisposition to disease X.

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 1

- The re-drafted claim likely satisfies the transformation prong of the Machine or Transformation Test (by including a "determining" step). Dependent claims could be drafted that further specify the determining step (probe hybridization, PCR, etc.)
- The re-drafted claim also likely resolves the divided infringement issue by focusing specifically on the activity handled by the diagnostic lab.
- However, depending on the state of the art, the claim may be vulnerable to a prior art attack given that it only includes a single "active" step.

Drafting Biomarker Method Claims - Example 2

- **2. A method for diagnosing a subject having or at risk of having disease X comprising:**

  contacting a target nucleic acid isolated from a specimen of a subject with a reagent that detects polymorphism Y in gene A; and

  detecting the presence or absence of polymorphism Y, wherein the presence of the polymorphism is indicative of disease X.

  - Does it involve a particular machine? No.
  - Does it involve transformations? Yes.

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 2

- The body of the claim includes two active steps, both of which would be practiced by the diagnostic lab.
- However, a court might construe the preamble as a limitation, as was done in the *Prometheus* case, and that step of "diagnosing a subject" is unlikely to be done by the lab.
- A re-draft that will likely resolve this issue is:

> **2.** A method for detecting the presence or absence of polymorphism Y indicative of disease X comprising:
>
> contacting a target nucleic acid isolated from a specimen of a subject with a reagent that detects polymorphism Y in gene A; and
>
> detecting the presence or absence of polymorphism Y, wherein the presence of the polymorphism is indicative of disease X.

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 3

- **3. A method of treating disease X in a subject having polymorphism Y, wherein polymorphism Y is indicative of therapeutic responsiveness by said subject to compound Z, comprising:**

  administering a therapeutically effective amount of compound Z to said subject.

- Does it involve a particular machine? No.
- Does it involve transformations? Yes.

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 3

- The body of the claim includes an active administration step, which are "always transformative."
- Divided Infringement is not an issue as the only active step is the administration step.
- However, consider "inherency" issues - particularly if treatment with compound Z is known but the correlation with polymorphism Y is not.

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 3

- **One potential re-draft of the claim:**
  - 3. A method of treating disease X in a subject comprising:

    administering a therapeutically effective amount of compound Z to said subject,

    wherein said subject, prior to administration of compound Z, has tested positive for polymorphism Y, and

    wherein polymorphism Y is indicative of therapeutic responsiveness by said subject to compound Z.

Drafting Biomarker Method Claims - Example 3

- The active step remains an administration step ("always transformative").
- No divided infringement issue (although the claim targets the doctor and not a diagnostic lab).
- No inherency issue with regard to administrations that occurred prior to identification of the polymorphism.

Drafting Biomarker Method Claims - Example 4

- 4. A method of treating disease X in a subject having polymorphism Y, wherein polymorphism Y is indicative of therapeutic responsiveness to compound Z comprising:

  administering a therapeutically effective amount of compound Z to said subject, until such time that the subject tests positive for polymorphism B, wherein polymorphism B is indicative of a lack of therapeutic responsiveness by said subject to compound Z; and thereafter

  administering a therapeutically effective amount of compound A to said subject.

- Does it involve a particular machine? No.
- Does it involve transformations? Yes.

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 4

- The claim includes active administration steps, which are "always transformative."
- Divided Infringement is questionable, while the administration steps are active steps, identification of the second polymorphism could also be construed as active.
- Again consider "inherency" issues - particularly if treatment with compound Z is known but the correlation with polymorphism Y is not.

BAKER BOTTS LLP

Drafting Biomarker Method Claims - Example 4

- **One re-draft of this claim is:**
  - 4. A method of treating disease X comprising:

    administering a therapeutically effective amount of compound Z to said subject,

    wherein said subject, prior to administration of compound Z, has tested positive for polymorphism Y, wherein polymorphism Y is indicative of therapeutic responsiveness by said subject to compound Z, and thereafter

    administering a therapeutically effective amount of compound A to said subject,

    wherein said subject, prior to administration of compound A, has tested positive for polymorphism B, wherein polymorphism B is indicative of a lack of therapeutic responsiveness by said subject to compound Z.

BAKER BOTTS LLP

Taking Advantage of These Lessons

- **Drafting new applications**
  - When drafting new applications do not only focus on preparing patent-eligible claims - also focus on including disclosure in the specification that supports the eligibility of your claims.
- **Review pending applications**
  - While the specification cannot be updated, claims should be reviewed and amended to ensure compliance with the Machine or Transformation Test.
- **Audit of commercially-relevant issued cases**
  - To the extent a case remains pending, new claims could be pursued.
  - In the absence of a pending case, consider filing a reissue to add claims.

BAKER BOTTS LLP

BAKER BOTTS LLP