Morgan Lewis

COMPANION DIAGNOSTICS

REGULATORY, INTELLECTUAL PROPERTY AND BUSINESS DEVELOPMENT STRATEGIES

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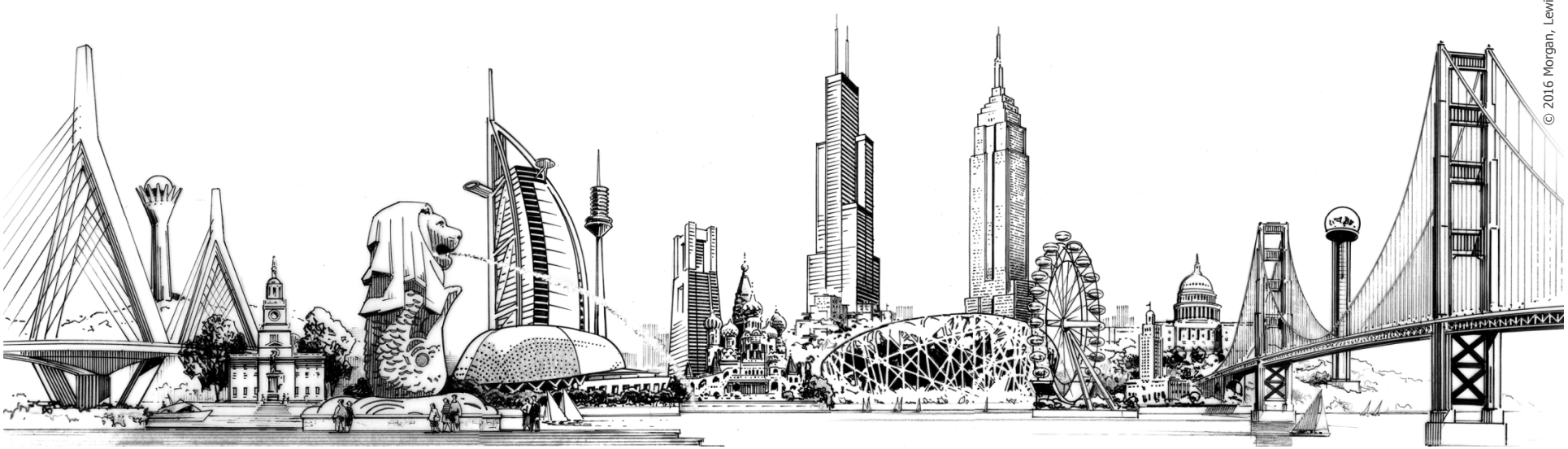

Companion Diagnostic

What is it?

FDA's definition

- Medical device provides information essential for safe and effective use of a corresponding therapeutic product (drug or biologic)
- Use of a therapeutic product depends on the use of an In Vitro Diagnostic Device (IVD)
- Companion IVD intended to be used with corresponding therapeutic product
  - Innovator and generic/biosimilar

Companion Diagnostic

What is it?

- Companion IVD used to identify appropriate patient for prescribing a specific therapeutic agent
- Required when drug/biologic has specific genetic or biological target not present in all patients with particular disease

- Personalized medicine
  - Patients most likely to respond to therapeutic drug or biologic
  - Patients at lower or higher risk for a particular side effect

Companion Diagnostic

Why is it important?

- FDA requires the identification of the appropriate subpopulation for prescribing the therapeutic agent
- Results of the IVD relied upon by health care professionals for safe and effective use of therapeutic agent
  - More than helpful information
  - Determining factor in safe and effective use of the therapeutic product

What is Not a Companion Diagnostic?

- **Combination Product**
  - 21 C.F.R. § 3.2(e) A product composed of 2 or more regulated components combined or mixed and produced as a single entity
- **Lab Developed Test**
  - A type of IVD that is designed, manufactured and used within a single laboratory
- **Drug Development Tool**
  - FDA Qualification Process for biomarkers or materials to aid drug development
- **Qualification of genomic biomarkers**
  - Support use and regulatory decision making during development

What is Not a Companion Diagnostic?

❖Complementary Diagnostic

- Not required by FDA for drug/biologic approval
- Cross-labeling of IVD not required
- Provides additional information relevant to drug/biologic use, *e.g.*, pharmacogenomic biomarkers, to guide treatment strategies
- Broader applicability to a class of drugs/biologics
- Personalized medicine
  - Diagnosis
  - Differentiate patient risk
  - Monitoring patient response

What is Not a Companion Diagnostic?

❖ **Complementary Diagnostic** **Approved October 2015**

➢ **Dako's PD-L1 IHC 28-8 pharmDx**

Used in Opdivo® pivotal trial

PD-L1 expression defined as percentage of positive membrane staining tumor cells at any intensity

Assess survival benefit associated with Opdivo®

➢ **BMS's Opdivo® (anti-PD-1 nivolumab)**

Advanced NSCLC progressed after platinum-based chemotherapy

OS benefit across PD-L1 expression levels

Indications for use does not reference PD-L1 expression

Examples of Companion Diagnostics

- Currently FDA has listed 28 approved companion diagnostic tests
  - Class III (**PMA**) and Humanitarian Device Exemptions (**HDE**)
  - Multiple approvals for the same biomarker
  - Next generation tests
  - Detection of gene/mutation
  - Detection of target protein

Examples of Companion Diagnostics

- Herceptin® BLA → PMA HER-2 detection
  Breast cancer
- VENCLEXTA® NDA → PMA 17p Deletion
  Chronic Lymphocytic Leukemia
- Gleevec® NDA → HDE D816V Mutation
  Aggressive Systemic Mastocytosis
- Erbitux® and Vectibix®
  BLAs → PMA KRAS detection
  Colorectal Cancer
- KEYTRUDA® BLA → PMA PD-L1 detection
  Non-Small Cell Lung Cancer

Examples of Companion Diagnostics

- Herceptin® HER-2 detection FISH, IHC, CISH
  Aid in assessment of patients for whom Herceptin treatment is being considered

- VENCLEXTA® 17p Deletion FISH
  Aid in identifying CLL patients for whom VENCLEXTA treatment is indicated

- Gleevec® D816V Mutation PCR
  Aid in selection of ASM patients for whom Gleevec treatment is being considered

- Erbitux® and Vectibix® KRAS detection PCR, IHC
  Aid in identification of CRC patients for whom treatment with Erbitux or with Vectibix may be indicated based on a no mutation detected result

- KEYTRUDA® PD-L1 detection IHC
  Aid in identifying NSCLC patients for treatment with KEYTRUDA

Companion Diagnostics

Regulatory Strategies

- Requires contemporaneous approval of NDA or BLA with approval of a PMA or clearance of a 510(k)
- Co-development partners for pharma/biotech and diagnostic device expertise
- Regulatory pathway issues
  - Investigational New Drug application (IND)
  - Investigational Device Exemption (IDE)
- FDA intercenter consultations
  - CBER/CDER and CDRH

Companion Diagnostics

Regulatory Strategies

- Clinical trial design
- Specimen collection and analysis
- Cost of simultaneous product development
- Labeling/IFUs stipulate use of diagnostic device and drug or biologic
  - or develop complementary diagnostic
- Post-marketing distribution
- Post-marketing promotion

INTELLECTUAL PROPERTY CONSIDERATIONS

Three Biggest IP Considerations

- Issue: purpose of evaluation
  - "Audit" of own IP/evaluation of strength of own portfolio/ability to cover technology
  - Freedom to operate (FTO) analysis for validity of third party IP (need to license or design around)
- In the U.S., patentable subject matter considerations under 35 U.S.C. §101 is perhaps the biggest concern
  - Supreme Court law of *Myriad*, *Prometheus*
  - *Sequenom* as an answer?
- In the U.S., "divided infringement", wherein methods claims may involve more than one actor, are of concern
  - Supreme Court law of *Akamai*
- Differential treatment of "patentable subject matter" in foreign jurisdictions leads to different IP outcomes
  - Address in agreements?

§101 Patentable Subject Matter

- Compositions: Supreme Court holding in *Myriad*
  - Exemplary Claims
    - Claim 1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.
    - Claim 5. An isolated DNA having at least 15 nucleotides of the DNA of claim 1.
  - Holding:
  - Isolated naturally occurring nucleic acids, including fragments of genes (e.g. primers, probes) are not patentable subject matter
    - And remember, SNPs are naturally occurring as well
  - cDNA is patentable subject matter

Evaluation of Composition Claims

- "A set of primers to amplify the SNP at position +316 of Gene X"
  - Not patentable subject matter in US under Myriad
    - Fragments of naturally occurring genes are not patentable subject matter
- "A set of primers to amplify the SNP at position +316 of Gene X, wherein at least one primer comprises a covalently attached label/fluorophore"
  - Should be patentable subject matter in US under Myriad
    - "Non-naturally occurring" because of exogeneous label
    - "well, known conventional techniques" is in the context of methods, not compositions
  - May have other patentability issues, including novelty or obviousness

§101 Patentable Subject Matter, cont.

- Methods: Supreme Court holding in *Prometheus*
  - Exemplary Claim:
    - 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 8×10^8 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 8×10^8 red blood cells **indicates a need** to decrease the amount of said drug subsequently administered to said subject.
  - Holding:
    - A combination of the natural law (e.g. the relationship between concentrations of metabolites in blood and the likelihood that the drug will cause harm) with "well understood, routine, conventional activity" (e.g. measuring metabolites in blood or doing PCR) is not sufficient to transform an unpatentable law of nature into patent eligible application of the law.

Exemplary Companion Diagnostics Claims

- A method of treating disease X in a patient, comprising testing for the presence of biomarker group Y in a biological sample from the patient and administering a therapeutically effective amount of Drug to the patient if the sample tests positive for biomarker group Y.
  - From the perspective of the drug manufacturer
- A method of identifying patients with disease X eligible for treatment with Drug Z comprising testing a biological sample from the patient for the presence of biomarker Y, wherein the patient is eligible for treatment with Drug Z if biomarker Y is present.
  - From the perspective of the diagnostic client
- Likely *Prometheus* evaluation for both:
  - "Natural law" is the correlation of the presence of the biomarker to efficacy of drug
  - "identifying patients" and "administering efficacious drugs" are "well-known, conventional steps
  - Invalid claims as lacking patentable subject matter

Hope on the Horizon?

- Petition for certiorari pending at Supreme Court in *Sequenom* case
  - Sequenom is the Non-Invasive Prenatal Testing (NIPT) case
  - Discovery: fetal DNA in maternal blood
  - Claim:
    - 1. A method for detecting a paternally inherited nucleic acid of fetal origin performed on a maternal serum or plasma sample from a pregnant female, which method comprises amplifying a paternally inherited nucleic acid from the serum or plasma sample and detecting the presence of a paternally inherited nucleic acid of fetal origin in the sample.
  - Prior to this, serum and plasma thrown out
  - NDCA and Federal Circuit didn't like it, but felt they had to reject claims for lack of patentable subject matter
  - Many, many amicus briefs filed on Sequenom's side
    - And the petition for cert is a legal thing of beauty
  - Resolved next term?

Divided Infringement Considerations

- Context: how will these claims be infringed, such that we can get money (client as patentee) or avoid paying money (client as possible infringer)?
- *Akamai* (the simplified version)
  - Claims: A method comprising
    - A) distributing web material [Limelight does this step]
    - B) tagging web material [customer does this step]
    - C) doing some other stuff. [Limelight does this step].
  - Issue: is there direct infringement when divided infringement?
  - Holding: An entity is responsible for others' performance of method steps when either (1) the entity directs or controls the others' performance, or (2) where the actors form a joint enterprise.
    - A joint enterprise requires proof of four elements:
      - (1) an agreement, express or implied, among the members of the group;
      - (2) a common purpose to be carried out by the group;
      - (3) a community of pecuniary interest in that purpose, among the members; AND
      - (4) an equal right to a voice in the direction of the enterprise, which gives an equal right of control.

Divided Infringement, cont.

- Sample claim for consideration:
- A method comprising:
  - A) taking/providing a patient sample;
  - B) doing a test [SNP, protein level];
  - C) making a call for treatment;
  - D) administering a drug.
- Who does each step?
- Relationship between them?
- What if drug is oral? Intravenous?

US Versus the Rest of the World

- The current §101 law has put the US at odds with many foreign countries
  - See foreign biotech association amicus filing in *Sequenom*
- Scenario: no valid diagnostic claims in the US, valid diagnostic claims in Europe, Japan, etc.
- New and unique licensing and agreement issues

AGREEMENT CONSIDERATIONS

Diagnostic Agreements

- Context: Company A has a therapeutic product ("Product"), and wants Company B to develop a diagnostic for the Product ("Assay").
- Financials: Company A will typically pay Company B to develop the Assay, which Company B may then manufacture and commercialize while retaining the profits.
- Diligence: Company A will want to know that Company B will manufacture and commercialize adequate supplies of the Assay to match market demand for the Product. Company A will seek back-up rights and standby licenses to ensure that it can take the Assay forward if Company B is failing to do so.

Regulatory Questions

- Is it likely that the Product will come up in discussing the approval of the Assay with regulatory authorities? If so, how involved should Company A look to be in regulatory discussions?
- What information regarding the Product is Company B likely to need for regulatory submissions?
- How coordinated should the parties be in responding to and interacting with regulatory authorities?
- How aligned does the packaging and package inserts need to be for the Product and the Assay respectively?
- How are pricing and reimbursement issues handled?

IP Questions

- Can we generalize regarding the potential for Company B to develop "blocking" IP with respect to the Product in the process of developing the Assay?
- If Company B wanted to file a patent covering the Assay, might there be aspects of the Assay that reveal undisclosed/confidential details regarding the Product?
- Could a patent strategy with respect to the Assay jeopardize the status of the Product's patents? What about any challenges or defenses of the Assay's patents? Or vice versa (the Product's IP jeopardizing the Assay's patents)?
- Is it advisable for the parties to plan on entering a joint defense agreement in the event that one, but not the other, is the subject of an infringement claim?

Today's Speakers

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Biography

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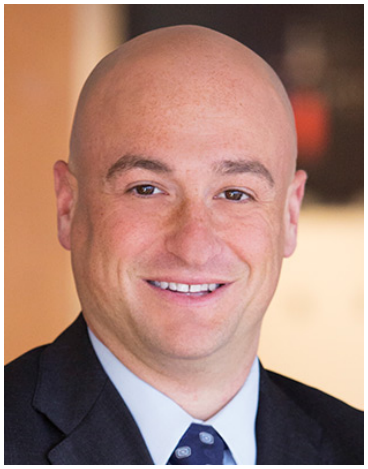
Phoebe Mounts counsels companies developing drugs, biologics, medical devices, and human cell and tissue-based products on US Food and Drug Administration (FDA) regulations. Her scientific background enables her to assist clients with product approvals for emerging technologies, such as combination products and companion diagnostics, including counseling on regulatory pathway issues and developing preclinical and clinical studies. Phoebe prepares submissions to the FDA, including applications for orphan-drug designation, humanitarian device exemptions (HDEs), investigational new drugs (INDs), investigational device exemptions (IDEs), and 510(k)s, as well as meeting requests and background packages.



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Benjamin H. Pensak counsels clients on technology transactions and related corporate matters, primarily in the life sciences industry. Ben represents international and US–based public and private companies and institutions and his clients include biotechnology, pharmaceuticals, medical device, diagnostics, and medical informatics companies. Ben advises clients regarding negotiating and structuring acquisitions, divestitures, joint ventures, corporate partnering, licensing, and other complex collaborations. He also drafts and negotiates day-to-day technical contractual arrangements.

Biography

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With an emphasis on emerging biotechnology and biopharmaceutical companies, Robin M. Silva manages and counsels clients in domestic and international issues, focusing on IP portfolio strategic development. Her background includes patent prosecution, IP due diligence (opinions, financings, evaluating IP portfolios in connection with due diligence for acquisitions, mergers, financings, collaborations, and partnering deals), global portfolio management and mining, technical litigation support, and working with business development personnel and licensing managers to maximize portfolio value.

Thank you!