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RECENT DEVELOPMENTS IN CHEMICAL, PHARMA AND BIO PATENTS

Craig A. McRobbie (BSKB)
MJ Edwards (Gilead Sciences, Inc.)

PRACTISING LAW INSTITUTE
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Hour 2

Hour 2 – Overview: PTO & Related Appeals

- PTO Guidelines on 101 (July 2016)
- CRISPR Interference – (2017)
- Improper Markush Groups - *Huberschwerlen* – (2016), *Ren* (2016), *Chettier* (2016, 2017)
- *Par-Amneal v. Jazz Pharma* (2016) - public accessibility of prior art.
- *Genzyme v. BioMarin* (Fed. Cir. 2016) – Claim interpretation & evidence to support non-obv.

Hour 2 – (Continued)

- Obviousness – *Ariosa v. Verinata* (PTAB 2016); *Coalition v. COSMO* (PTAB 2016); *Coalition v. NPS* (PTAB 2016); *Fresnius-Kabi v. Cubist* (PTAB 2016); *LA Biomedical v. Eli Lilly* (Fed. Cir. 2017)

MEMORANDUM

DATE: July 14, 2016

TO: Patent Examining Corps

FROM: Robert W. Bahr
Deputy Commissioner
for Patent Examination Policy

SUBJECT: Recent Subject Matter Eligibility Rulings (*Rapid Litigation Management v. CellzDirect* and *Sequenom v. Ariosa*)

Conclusion - The USPTO's current subject matter eligibility guidance and training examples are consistent with the Federal Circuit's panel decisions in *Rapid Litigation Management* and *Sequenom.* Life sciences method claims should continue to be treated in accordance with the USPTO's subject matter eligibility guidance (most recently updated in May 2016).

PTO Memo

- The end result of the claims at issue in *Rapid* is not simply an observation or detection of the ability of hepatocytes to survive multiple freeze-thaw cycles, but instead the claims recite a number of process steps (*e.g.*, fractionating, recovering, and cryopreserving) that manipulate the hepatocytes in accordance with their ability to survive multiple freeze-thaw cycles to achieve a desired outcome (a preparation of multi-cryopreserved viable hepatocytes).

- Because these claims were focused on a process for achieving this desired outcome, the court determined that they, like thousands of other claims that recite methods of producing things or methods of treating disease, were not directed to a judicial exception.

USPTO issued additional Examples - May 4, 2016

- Example 28 – Vaccines
- Example 29 – Diagnosing and Treating Julitis
- Example 30 – Dietary Sweeteners
- Example 31 – Screening For Gene Alterations
- Example 32 – Paper-Making Machine
- Example 33 – Hydrolysis of Fat

CRISPR Interference

Broad Institute

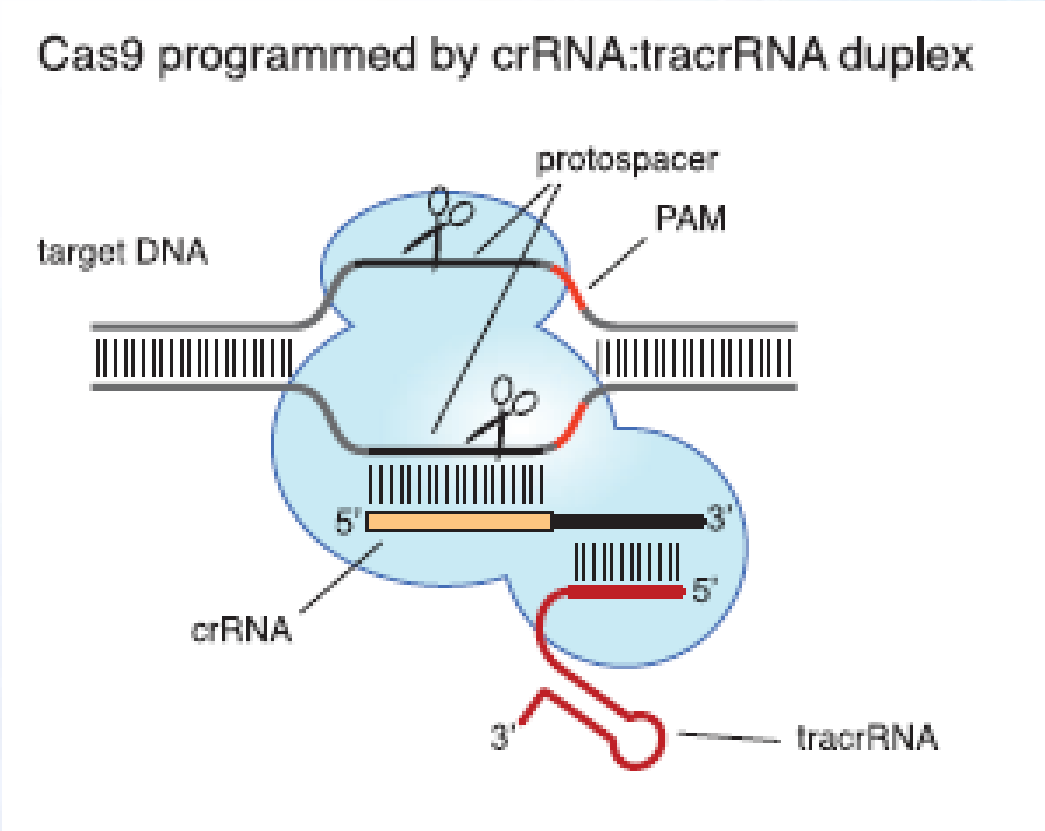
v.

University of California

Interference No. 106,048

(PTAB Feb. 2017)

Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)



Claims

- **UC**: A method of cleaving comprising contacting a target DNA with a CRISPR associated system comprising: Cas9 protein and a single-molecule DNA-targeting-RNA … (reads on cell-free or any other environment)
- **Broad**: A method of altering expression of at least one gene product comprising introducing into a eukaryotic cell… first and second regulatory elements on vectors…

No Interference-in-Fact: The Law

- Essentially an obviousness analysis
- 2 way test (like obviousness type double patenting)
- Are the claims of Broad that are limited to eukaryotic systems patentably distinct from UC generic claims in view of the state of the art at the time?

Holding – No Interference-in-Fact

- "Although [prior art] statements express an eagerness to learn the results of experiments in eukaryotic cells… none … express an expectation that such results would be successful".
- Dr. Carroll's "stay tuned" conclusion indicates that he expected it would be tried but not necessarily a reasonable expectation of success.
- Carroll highlighted some reasons it might fail.
- Other motions dismissed.

Federal Circuit Appeal

- UC, Berkeley and the University of Vienna have appealed the PTAB decision finding no overlap between their CRISPR patents and those of the Massachusetts-based Broad Institute.

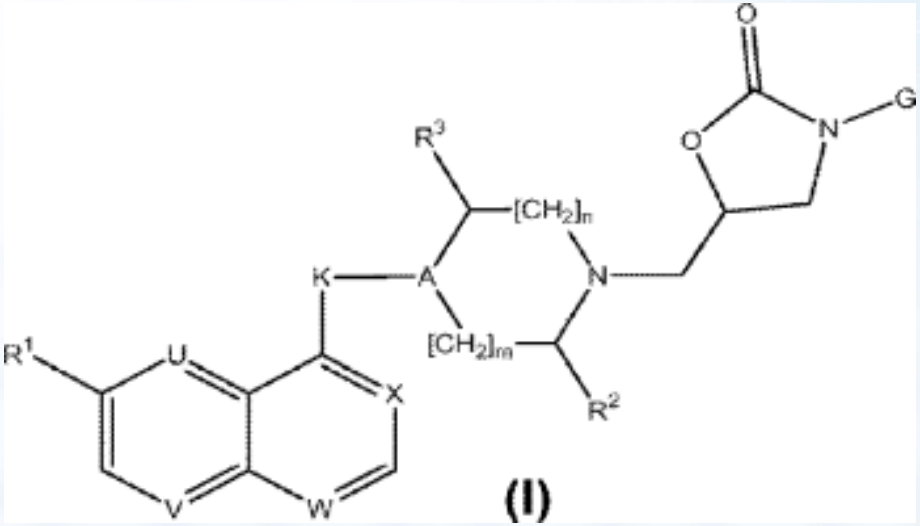
EX PARTE HUBERSCHWERLEN

Appeal No. 2014-000307

(PTAB July 2016)

Claim

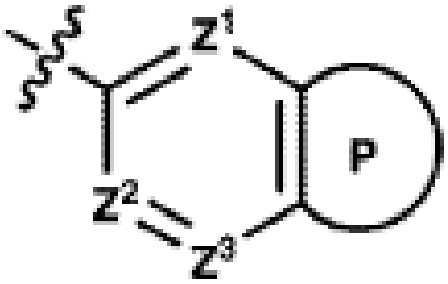
- A compound of the formula:



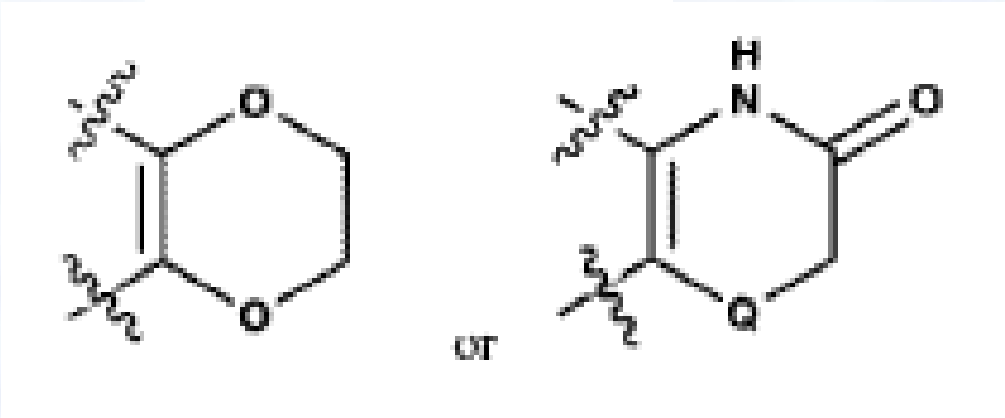
- Wherein …..

Substituents on the Basic Formula

- G is



- And P is



Test/Holding

- Is Markush group “repugnant to scientific classification”
- Must look at the claim as a whole
- Rejection reversed

Ex parte Chettier

Appeal No. 2016-003639

(PTAB August 2016)

(reh'g denied January 2017)

Facts/Holding

- Claim: 133 SNPs
- All SNPs have same use for diagnosing and treating degenerative disc disease
- No common structure
- Rejection for improper Markush group affirmed

Ex parte Ren

Appeal No. 2015-004371
(PTAB December 2016)

Claims/Rejection

- Claim 1 (rejected for lack of enablement and written description) - Method for silencing at least one target comprising (a) replacing at least one phase region of said ta-siRNA …; (b) replacing the at least one micro RNA binding site…
- Claim 4 (and others) Rejected for improper Markush group – Markush group of ta-siRNAs
- Ex. stated: "… different structures, and thus, are presumed to have different functions"

Case Summary

- Claims – trans-acting small interfering RNAs (ta-siRNAs)
- Sequences “all belong to the same recognized class of a ta-siRNA sequences that share a nucleic acid backbone ... [and] differ because drawn to different genes or different plants”
- Rejection reversed because compounds (1) share a common utility and (2) share a substantial feature essential to that utility.

Genzyme

v.

BioMarin

(Fed. Cir. June 2016)

Facts

- Method of treating Pompe Disease
- Reuser – treatment of Pompe with same drug
- Duke Press Release (1997) – Orphan Drug Designation Approved and Duke announced that it would begin testing on human patients.
- Instituted art relied on *in vitro* data.
- Genzyme argued that should not be able to consider art showing successful *in vivo* tests

Claim Interpretation - BRI

- **Claim**: whereby concentration of accumulated glycogen in the patient is reduced and/or further accumulation is arrested.
- Genzyme argued must reduce in skeletal muscle
- PTAB and CAFC noted that Examples stated "increase of activity in the liver and spleen and decreased levels of glycogen in liver and perhaps in heart"
- PO is stuck with broad claim interpretation

Evidence Relevant to Obviousness

- "… introduction of new evidence in the course of the trial is to be expected … as long as the opposing party is given notice and opportunity to respond."
- "Genzyme had ample notice that the references were in play"
- References were cited in Petition, albeit in a different context
- Board can cite evidence to show state of the art

Practice Tips for Patent Owner

- Unless you are sure of your claim interpretation, argue in the alternative and explain why claims are patentable under both interpretations.
- In IPR, PO should not ignore evidence discussed in Petition but not cited in ID.
- It is dangerous to take a position that is inconsistent with other evidence in the record without explaining why you are still correct even if that evidence is considered.

Par-Amneal v. Jazz Pharma

IPR2015-00546

(PTAB July 2016)

Also, five related proceedings between the same parties on five other patents.

Invention

- **1.** Therapeutic method for treating a patient comprising: receiving prescriptions into a central computer; requiring entering the information into exclusive database; controlling distribution; ….
- **2.** Method of claim 1, wherein the controls for distribution are … identifying the physician's name, license, and DEA registration information …
- **POSA**: pharmacist or computer science plus familiarity with drug distribution procedures

Prior Art

- XYREM – date-rape drug GHB
- Advisory Committee Art (ACA)
- https://www.fda.gov/ohrms/dockets/ac/01/briefing/3754b1.htm first 1 minute 19 seconds
- Exs. 1003 – FDA Adv. Committee Transcript; 1004 – Prel. Clinical Safety Review; 1005 – Briefing Booklet prepared for Xyrem Advisory Committee Meeting in accordance with FACA; 1006 – Xyrem Video and Transcript

Summary of Dates of Prior Art

- *May 3, 2001:* FDA Safety Review of Xyrem completed (Ex. 1004, 1)
- *May 3, 2001:* Sponsor's Xyrem Briefing Booklet submitted to Advisory Committee (Ex. 1005, 1)
- *May 3, 2001:* Sponsor's video of Xyrem prescription process submitted to Advisory Committee (Ex. 1005, 2 ¶ 5, 14, 312; Ex. 1006)
- *May 14, 2001:* Federal Register Notice of Xyrem Advisory Committee Meeting (Ex. 1015, Col. 2–3)
- *June 6, 2001:* Xyrem Advisory Committee Meeting (Ex. 1003)

Holding

- POSA is “interested in drug distribution, safety, and abuse prevention would have had reason to look to the Federal Register and FDA Advisory Committee meeting notices”. p 38.
- ACA was “publically accessible to an interested POSA exercising reasonable diligence more than one year before [filing date].” p. 39
- All limitations and steps disclosed in ACA.
- Obvious to combine ACA art

Practice Tips

- Patent and regulatory people need to communicate.
- Make patent filings before meetings with FDA
- Duty of disclosure comes into play.

Coalition for Affordable Drugs

v.

COSMO Technologies

FWD, IPR2015-00988

(PTAB October 5, 2016)

Claims

1. Controlled-release oral pharmaceutical compositions containing as an active ingredient 5-amino-salicylic acid (5-ASA), comprising:
   a) an inner lipophilic matrix consisting of substances selected from the group consisting of…
   b) an outer hydrophilic matrix, the lipophilic matrix is dispersed and consists of compounds selected from the group consisting of…
   c) optionally other excipients
   d) wherein the 5-ASA is present in an amount of 80 to 95%

Claims

4. A process for the preparation of the compositions of claim 1, which comprises:
   a) Melt granulation of at least on portion of the active ingredient with the lipophilic excipients with melting point lower than 90 C.;
   b) Mixing the granules from step a) with the hydrophilic excipients and subsequent tableting or compression

Claim Interpretation – Plural terms

- Petitioner argued that although “substances” and “compounds” are written in the plural form, the BRI also includes the singular form where, as here, the plural merely refers to a group of objects.
- Patent Owner did not challenge this point
- PTAB agreed with Petitioner.

What is a Wax (Petitioner)

- Petitioner: “waxes” are lipophilic and that a higher aliphatic alcohol is lipophilic and therefore higher aliphatic alcohols such as cetyl alcohol (CA) are waxes.
- Treatise described CA as “waxy, white flakes, granules, cubes or castings”. Expert witness Dr. Palmieri stated CA is a wax.
- Two different patents includes cetyl alcohol as a wax.

What is a Wax (Patent Owner)

- Something “waxy” or having “wax-like properties” too broad and includes substances in other Markush groups.
- Do not look at other patents for interpretation of technical terms.
- Expert says “an ester of a high MW monohydric alcohol and high MW fatty acid”.
- PO interpretation is supported by “numerous treatises, textbooks, and dictionaries”

What is a Wax (PTAB)

- Agreed with PO definition.
- Does not include higher alcohols that are not in ester form.
- Two USPs that support Petitioner are “outweighed significantly by non-patent extrinsic evidence…”
- Used a “chemical definition” rather than “significantly broader group of substances that happen to have wax properties”.

Groenendaal

- Controlled release formulations targeted to intestine, preferably lower parts.
- Solid dispersion
- Amount of active 0.01-99%, preferably 20-90%, more preferably 50-80%.
- Ex. 5 – granules made by mixing 75g ethyl cellulose, 75 g hydrogenated castor oil.

Groenendaal (Cont.)

- Example 5 – granules made by mixing 75g ethyl cellulose, 75 g hydrogenated castor oil, 500 g (22 %) 5-amino salicyclic acid (5-ASA) and 450 g water-insoluble carrier powdered cellulose.
- Figure 3 showed sustained release

Leslie

- Slow release oral composition comprising combination of higher aliphatic alcohol (cetyl and cetostearyl preferred) and hydrated-alkyl cellulose (hydroxy ethyl preferred).
- Combination of above in critical proportions delays release of therapeutic.

Analysis

- Extraordinary variety of pH-independent controlled release compositions known.
- Other approaches to obtain controlled release (reservoir dosage forms, osmotic dosage forms, chemically-modified active ingredients).
- Petitioner failed to provide a compelling reason why POSA would have selected matrices, much less the specific formulation in Leslie.
- Not limited number of predictable solutions, *KSR*.

Analysis (Cont.)

- Merely throwing metaphorical darts at board filled with combinatorial prior art possibilities, *Kubin* (Fed. Cir. 2009).
- Petitioner's manufacturing cost argument not persuasive.
- Evidence of commercial success, once daily dosage and long-felt and unsolved need helpful.
- FWD – Petitioner did not show that claims were obvious.

Practice Tips

- Be careful when using plural form of words in claims. You might get a construction that requires more than one of the element.
- Defining technical terms based on technical references rather than patents is better.
- Be careful when using “consisting of” language.

ARIOSA DIAGNOSTICS

V.

VERINATA HEALTH

IPR2013-00276 (and 00277)

(PTAB August 20916)

(Note: Another Patent on same general technology was subject of *Ariosa v. Sequenom* that was held not patent eligible)

Prenatal Diagnostics

<u>Cellular fraction</u>
(nucleated fetal cells - prior art)
<u>Serum or plasma</u>
(cffDNA – US ‘504)

<u>Amniotic sac fluid</u>
(Amniocentesis – prior art)

<u>Placental tissue</u>
(Chorionic villus sampling – prior art)

Claims

- Method for determining fetal aneuploidy:
- Obtaining fetal and maternal cell-free genomic DNA sample
- Enriching to generate library, pooling libraries
- Massively parallel sequencing to produce reads of at least 100 different sequences
- Comparing sequencing reads.

Original PTAB & CAFC Decisions

- Fed. Cir. reversed and remanded initial FWD that held that Petitioner failed to show unpatentable because PTAB failed to consider 2nd Morton Declaration filed with Petitioner Reply to show background knowledge.
- 2nd Morton Declaration "in effect, replaces the tagging and sequencing techniques of Dhallan and Binladen with the Illumina indexing kit and sequencing platforms"

Argument on Remand

- “Petitioner now argues if one starts with Shoemaker’s MPS performed on Illumina Genome Analyzer as the base technique, it is readily apparent from the Illumina multiplexing kit brochure that modifying Shoemaker’s MPS technique to include indexing required nothing more than ordering a kit”.

Decision on Remand – Same Result

- Specific argument was not made in the Petition.
- General argument was made in Declaration, but not in context of Shoemaker, Dhallan & Binladen references, upon which trial was instituted.
- Original arguments focused on why a POSA "could have" but did not address why "would have" used in combination of references.
- Did not address "reasonable expectation of success".

Practice Tips

- Need to address “could have” and “would have” made combination separately.
- PTAB suggests providing “a reason, with rational underpinning, as to why the ordinary artisan would have combined the cited teachings to arrive at [claimed invention]”.
- The “reason to combine” should be explained in detail.

COALITION FOR AFFORDABLE DRUGS

V.

NPS PHARMACEUTICALS

FWD, IPR2015-01093 (and 00990)

(PTAB October 2016)

Claim

- 1. Glucagon-like peptide 2 (GLP-2) formulation comprising:
- GLP-2 or analog thereof;
- phosphate buffer;
- L-histidine; and
- a bulking agent selected from the group consisting of mannitol and sucrose.

Ground 1 - Obviousness

- **Drucker '379** – pharmaceutical compositions comprising GLP-2 analog. PBS. Can be lyophilized.
- **Kornfelt** – Stabilized compositions comprising glucagon and stabilizing amount of pharmaceutically acceptable ampholyte, such as histidine. May include "excipient" for facilitating lyophylization and rapid and complete redissolution, such as mannitol and sucrose.

- **Osterberg –**
  - protein drugs unstable in solution and freeze-drying used to get good shelf life.
  - Selection of buffer important. Sugars and amino acids protect during freezing.
  - L-histidine can act as both stabilizer and buffer.
  - The addition of sucrose abolished crystallization of L-histidine. Reduced crystallization of L-histidine is very important for formulation design.

Fwd – Claims Obvious

- Motivation and reasonable expectation of success.
- Osterberg teaches importance of L-histidine and sucrose to make stable storage formulation.
- Kornfelt: L-histidine is one of three preferred AAs.
- Routine experimentation to identify optimal AA and sugar. Successful application with GLP-2 analogs was “routine application of a well-known problem-solving strategy”
- Finite number of AAs and sugars.

Practice Tips

- Difficult to show formulation of drug using conventional excipients.
- Conventional drug formulation and dosing optimization usually obvious.
- To overcome obviousness attack, it is helpful to have strong “teaching away” references, other prior art going in totally different direction with the same drug or strong “unexpected” (not just better) results.

Fresenius-Kabi

v.

Cubist Pharmaceuticals

IPR 2015-00223 (See also 2015-00227)

(May 2016)

Background

- **Daptomycin** – antibiotic against Gram-positive bacteria. Toxicity issues in skeletal muscles.
- **District Court Litigation** – claims held unpatentable by district court. Affirmed CAFC. Now on Appeal to Supreme Court.

Claims

- 47. A method for administering daptomycin, comprising the step of administering … a therapeutically effective amount of daptomycin in a dose of at least 3 mg/kg of … at a dosage interval that minimizes skeletal muscle toxicity, wherein the dose is repeatedly administered at a dosage interval of once every 48 hours.
- 51. …wherein dose is 4 mg/kg.
- 52. …wherein dose is 6 mg/kg.

Prior Art

- **226 Patent** – Preferred about 1 to about 30 mg/kg. Typical daily about 100 mg to about 1.0 g. Single or multiple doses per day.
- **Rotschafer** – Can lengthen dose interval to >1/day for vancomycin. “dosage adjustment necessary in patients with impaired renal function”.
- **Woodworth** – studies with at least 72 hours separating doses of 2, 3, 4 and 6 mg/kg with daptomycin were “well tolerated”.

Claims Obvious

- Although Woodworth is “predictive in nature”, it is based on extensive laboratory research and reasonable expectation that 4 or 6 mg/kg at daily intervals would be successful.
- Rotschater teaches dosage adjustment in renally impaired patients. This provides motivation to extend interval to 48 hours.
- Unexpected results not proven. Art very close

Practice tips

- Claim language should indicate more than mere ‘dosage optimization’.
- Claims that indicate more than mere ‘dosage optimization’ make for a stronger patent that is better able to withstand a challenge in court.

L. A. Biomedical v. Eli Lilly

and

Eli Lilly v. L. A. Biomedical

IPR2014-00752, Appeal No. 2016-1518

IPR2014-00693, Appeal No. 2016-1547

(Fed. Cir. February 28, 2017)

U. S. Patent 8,133,903 Claim

- Method comprising
- administering cyclic guanosine 3', 5'-monophosphate (cGMP) PDE5 inhibitor in continuous long-term regimen to an individual with at least one of a penile tunical fibrosis and corporal tissue fibrosis; and
- Arresting or regressing… wherein PDE-5 inhibitor is administered at a dosage up to 1.5 mg/kg/day for not less than 45 days.

IPRs

- District court litigation.
- One IPR for 102 and another for 103 challenge.
- PTAB, denied benefit of provisional application, interpreted various claim terms and held that claims were anticipated and obvious for various reasons.

Claim Interpretation – Patient Populations

- PTAB – BRI of "an individual with at least one of penile tunical fibrosis and corporal tissue fibrosis" is its plain meaning; "an individual with penile tunical fibrosis and/or corporal tissue fibrosis"
- Board's construction "having symptoms that may be associated with … but not that the patient be specifically diagnosed as having … reads that limitation out of the claim" and thus too broad.
- Reason: symptoms may have other causes.

Other Limitations

- "Arresting or Regressing" limitations require efficacy. Do not merely duplicate wherein clause that specifies dose.
- "Continuous long-term regimen" must be at least 45 days in length. CAFC rejected "constant [blood] level argument". That limitation was in other claims in provisional but not included in allowed claims.

Obviousness – IPR2014-00752

- CAFC reversed & remanded on obviousness.
- Reasonable expectation of success based on overly broad claim construction not limited to patient having symptoms associated with specified cause. Need remand to reconsider.
- Less challenging “goal” (broader claim construction) might have been obvious.
- Some key teachings (suggestions) in prior art based on speculation.

Novelty – IPR2014-1547

- PTAB held that claims not anticipated.
- Lilly argued a POSA would have understood that "chronic administration" in prior art anticipates daily administration for 45 days or more because a POSA would understand ED in absence of therapy can last longer than 45 days.
- Lilly testimony does not address how long ED will last with therapy.
- CAFC affirmed no anticipation.

Practice Tips

- CAFC receptive to “patient population” arguments and that particular symptom is not always associated with particular cause for all patients. If symptoms may have claimed and unclaimed causes, anticipation may be hard to prove.
- Put symptom and cause in at least some claims.
- Wrong claim interpretation can doom your case. May want to argue and submit evidence on alternative claim constructions.

Questions?