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# Patent Litigation Issues

2010 Life Sciences Summit

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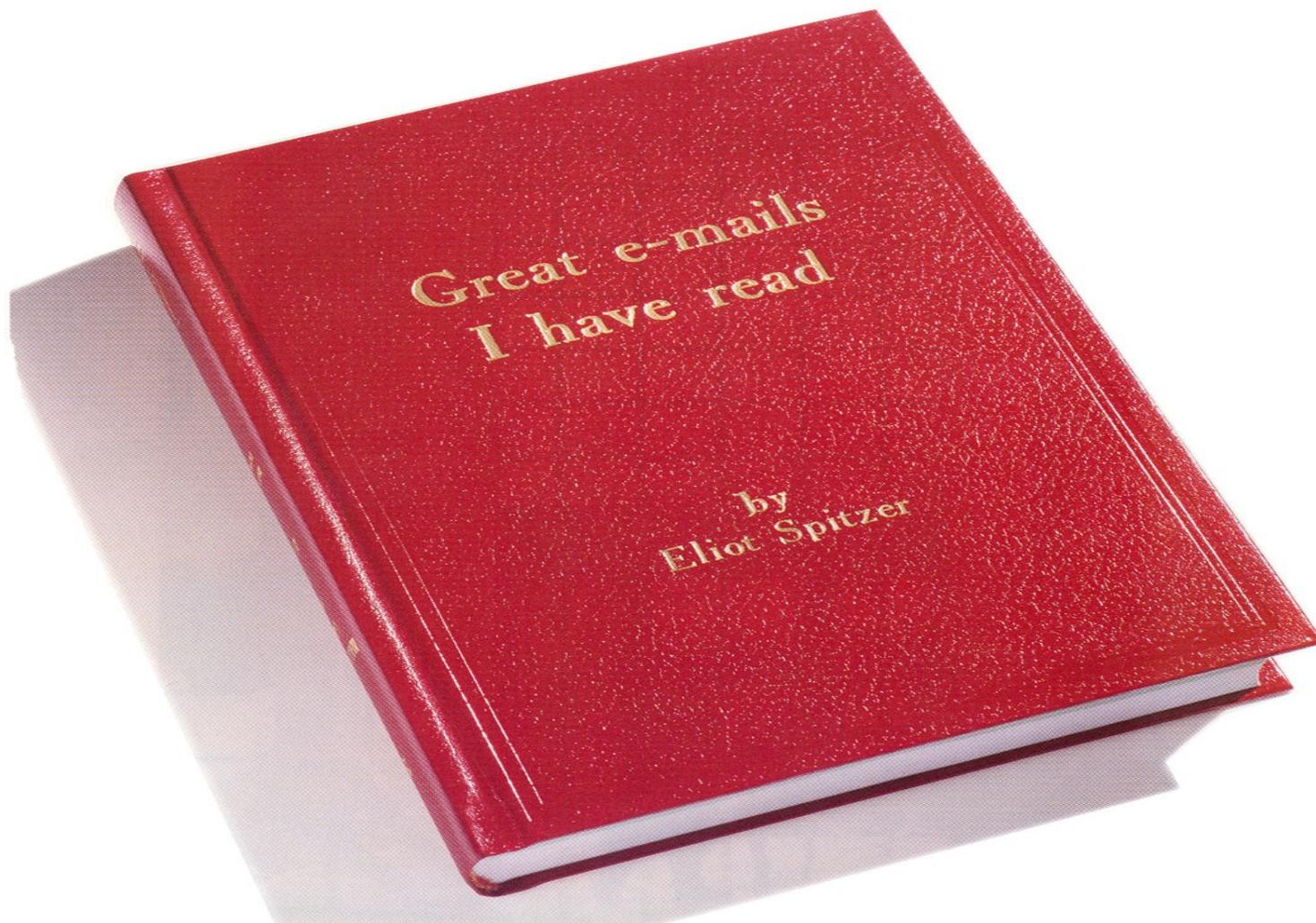
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# University as Licensor of Patents

- All patent infringement cases are brought in federal court
- All owners and exclusive licensees must be named parties
- Inventors and tech transfer office as witnesses
  - Depositions, trial
- Importance of record-keeping
  - Confidentiality agreements
  - Invention disclosures
  - Lab notebooks, samples, photos, prototypes
  - Emails
- Document retention policy



## I wish I hadn't said that.....

- Inventor re: his patent application: “[W]hy is this not obvious?”
  - *Purdue Pharma v. Par Pharma*(D.Del. 2009)
- Bill Gates to AOL execs: "How much do we need to pay you to screw Netscape?"

# Key Considerations for License Agreements

- How is infringement monitored and reported?
- What is the process for deciding to sue?
- Who controls litigation strategy?
- Who pays?
- How is counsel selected? One firm representing all?
  - Duty of loyalty and conflicts of interest
- Any change to royalties during litigation?
- Who decides settlement?
- How are recoveries split?

# Hatch-Waxman Act Patent Litigation Statistics

Source: RBC Capital Markets Industry Comment, January 15, 2010

- Patent challenges remain on the rise with a record 65 new lawsuits in 2009, up from 51 in 2008 and more than double the number 3 years ago
- For cases that have gone to trial, generics won 48%
- When settlements are included, success rate increases to 76% for generics
- More than half of cases are settled or dropped
- Top 3 courts by volume—NJ, DE, SDNY—accounted for 70% of all decisions

*KSR, Int'l Co. v. Teleflex, Inc.*, 127 S.Ct. 1727 (2007)  
U.S. Supreme Court Refines What's Obvious

- Three categories of post-*KSR*pharma cases:
  - Stereoisomeric purification
  - New chemical entities
    - Derived from the modification of structurally similar compounds
  - Pharmaceutical formulations

# MOTIVATION FOR PURIFICATION OF STEREOISOMERS AND OTHER MIXTURES

- Two factors for determining obviousness of a purified active ingredient:
  - Unexpected properties of the isolated stereoisomer
  - Amount of experimentation required for the separation and purification of the desired stereoisomer

## CASE STUDY - LEXAPRO®

*Forest Labs. v. Ivax*, 501 F.3d 1263 (Fed. Cir. 2007)

Lexapro®	Prior Art
S-citalopram	S/R-citalopram

- Purified S-enantiomer held **NONOBVIOUS**:
  - S-enantiomer unexpectedly had twice the activity of the racemic mixture (i.e., the R-enantiomer had no therapeutic activity)
  - The stereoisomers were difficult to separate as evidenced by the failure of others to do so

## CASE STUDY - PLAVIX®

*Sanofi v. Apotex*, 550 F.3d 1075 (Fed. Cir. 2008)

Plavix®	Prior Art
D-clopidogrel bisulfate	D/L-clopidogrel bisulfate

- Prior art disclosed that the racemic mixture exhibited both therapeutic activity and neurotoxicity
- Plavix® held **NONOBVIOUS**:
  - Unexpectedly, dextrorotatory enantiomer exhibited only therapeutic activity whereas the levorotatory enantiomer exhibited only neurotoxicity
  - Separation technique was not simple or routine
  - Reaction of sulfuric acid with active ingredients to form bisulfate salts was known to cause racemization (i.e., prior art taught away)

## MOTIVATION TO PURIFY MAY COME FROM STRUCTURALLY SIMILAR COMPOUNDS

Altace® (ramipril)	Prior Art
[SS]SSS isomer	Mixture of [SS]SSS and [SS]SSR isomers

- Prior art also taught that in enalapril, a structurally similar compound, the SSS isomer had 700 times the therapeutic activity as the SSR isomer
- Altace® held **OBVIOUS**:
  - POSITA would expect the [SS]SSS isomer to have higher activity than the [SS]SSR isomer given the knowledge of greater activity of the SSS isomer in enalapril
  - Separation technique was known and routine

*Aventis v. Lupin*, 499 F.3d 1293 (Fed. Cir. 2007)

## NEW CHEMICAL ENTITIES – MODIFICATION OF STRUCTURALLY SIMILAR COMPOUNDS

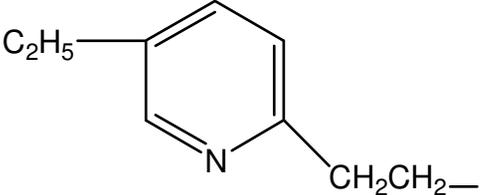
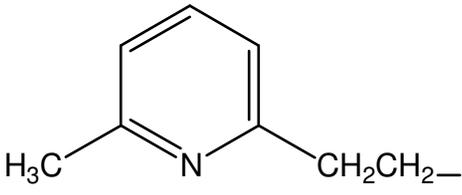
- CAFC has explicitly held that *KSR* did not change its prior analysis with respect to new chemical entities
- Obviousness still requires that the prior art would have suggested making or motivated a POSITA to make the specific modifications necessary to achieve the claimed invention

# NEW CHEMICAL ENTITIES

- Obviousness of new chemical entities made from the modification of a structurally similar compound requires:
  - Motivation to select the lead compound
    - How many viable alternative lead compounds exist?
  - Motivation to modify the lead compound to achieve the claimed compound
    - Did the modification of the lead compound produce a compound with expected properties?
    - Was the modification simple and accomplished by standard techniques?

# MOTIVATION TO SELECT A LEAD COMPOUND

*Takeda v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007)

Actos® (pioglitazone)	Lead Compound in prior art
 <chem>CCN(CC)C1=CC=CC=C1</chem>	 <chem>CC1=CC=CC=N1CCC</chem>

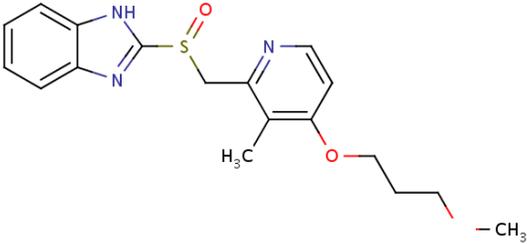
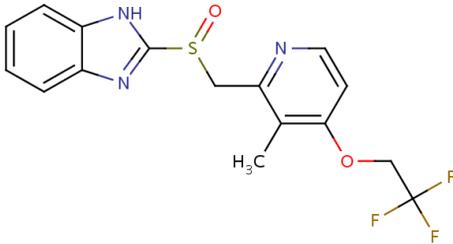
- Claimed invention requires two modifications:
  - Substitution of ethyl for methyl; AND
  - Relocation of the ethyl group from the  $\alpha$ -position to the  $\beta$ -position of the pyridine ring

## ACTOS® WAS HELD NONOBVIOUS

- There was no motivation to select the lead compound
  - There were at least three other compounds in the prior art with properties superior to the lead compound
- Prior art taught away from starting with the lead compound
  - Lead compound was known to cause weight gain, which would be undesirable for diabetics being treated with Actos®
- Unlike the lead compound, Actos® was unexpectedly non-toxic

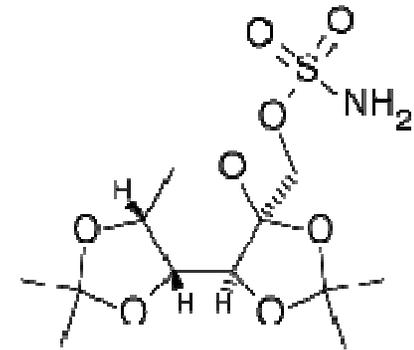
# MOTIVATION TO MODIFY LEAD COMPOUND

*Eisai v. Dr. Reddy's*, 520 F.3d 1353 (Fed. Cir. 2008)

<p>Aciphex® (rabeprazole)</p>	
<p>Lead Compound (lansoprazole)</p>	

- Aciphex® held **NONOBVIOUS** because the desirable lipophilic properties of the lead compound was attributed to the -CF<sub>3</sub> group. Thus, a POSITA would not be motivated to alter the -CF<sub>3</sub> group.

# NEW CHEMICAL ENTITIES - UNEXPECTED PROPERTIES AND COMPLICATED DEVELOPMENT PATHWAYS



- Topomax<sup>®</sup> (topiramate) was held **NONOBVIOUS**
  - Drug was initially studied for its antidiabetic properties but was found to be an effective anticonvulsive drug (secondary consideration of nonobviousness)
  - POSITA would not have chosen the starting material used by the inventor to synthesize topiramate
  - The number of possible synthetic routes from the starting material to the claimed compound were numerous, “not the small and finite number of alternatives that KSR suggested might support an inference of obviousness”

# PHARMACEUTICAL FORMULATIONS

- Formulations may be more likely to be found obvious where known components or features of the formulations are used to provide predictable solutions to known problems

## NORVASC® (AMLODIPINE BESYLATE)

*Pfizer v. Apotex*, 480 F.3d 1348 (Fed. Cir. 2007)

- The prior art references disclosed (1) other amlodipine salts and (2) that besylate salts were widely used in the pharmaceutical industry
- Norvasc® held **OBVIOUS**:
  - POSITA would have been motivated to make a besylate salt because of their widespread use in pharmaceuticals
  - Accordingly, POSITA would have had a reasonable expectation of formulating a besylate composition with the desired therapeutic activity

# OBVIOUSNESS BASED ON EVIDENCE FROM FDA FILINGS

- Litigation surrounding Norvasc<sup>®</sup> demonstrates that your competitors will continue to seek evidence of obviousness from your statements made in FDA filings
  - Pfizer stated to the FDA that prior besylate compounds approved by the FDA had worked for the same purpose as Pfizer's besylate salt
  - CAFC gave weight to this evidence
- PROCEED WITH CAUTION

## FORMULATIONS - OMEPRAZOLE

*In re Omeprazole*, 536 F.3d 1361 (Fed. Cir. 2008)

- Claimed Invention
  - Enteric-coated omeprazole having a water-soluble subcoating, which was necessary to eliminate undesired reactivity between the enteric coating and omeprazole
- Prior Art
  - Disclosed enteric-coated omeprazole
  - Disclosed the use of subcoatings in pharmaceutical formulations

# OMEPRAZOLE FORMULATION

- Formulation was held **NONOBVIOUS**:
  - Because the prior art did not teach the reactivity problem between the enteric coating and omeprazole, a POSITA would not have appreciated the need to include the subcoating
  - Variety of other solutions were available to POSITA other than using a subcoating (i.e., the number of solutions was not finite)
  - POSITA would not have used a water-soluble subcoating given the desire to deliver omeprazole to the small intestine rather than the stomach

## FORMULATIONS – PK LIMITATIONS

*Abbot v. Sandoz*, 536 F.3d 1361 (Fed. Cir. 2008)

- Claimed Invention
  - Extended release clarithromycin with a PK profile
- Prior Art
  - Disclosed extended release erythromycin formulations
  - Disclosed extended release azithromycin formulations and their PK profiles
  - Disclosed extended release clarithromycin as an alginate salt

## FORMULATIONS – PK LIMITATIONS

*Abbot v. Sandoz*, 536 F.3d 1361 (Fed. Cir. 2008)

- Clarithromycin formulation held **NONOBVIOUS**:
  - Claimed PK limitations were not disclosed in any of the prior art references
  - Claimed invention was not “obvious to try” because the bioavailability of azithromycin was substantially different from clarithromycin
  - Formulation of extended release clarithromycin with the desired PK limitations was not routine experimentation

## PRACTICE SUGGESTIONS IN VIEW OF *KSR*

- For improvement inventions, incorporate claim limitations that result from unpredictable experimentation
  - E.g., PK parameters, dissolution rates, fed vs. fasted bioavailability, etc.
- Adequately document any difficulties in formulating the compositions and synthesizing or purifying the active ingredients

## PRACTICE SUGGESTIONS IN VIEW OF *KSR*

- Base claims on compounds that have unexpected properties over prior art compounds
- Analyze the prior art in advance of patenting to assess viable claims for the protection of important products
- Beware of making statements during other regulatory proceedings that may jeopardize the validity of your patent