Patent Issues in NDAs

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OBJECTIVES

- To advance the knowledge of patent issues pertinent to drug development among pharmaceutical scientists

- To promote effective communication between pharmaceutical scientists and patent attorneys

OUTLINE

- PATENTS
  - A Very Brief Introduction
    - What is Patentable?
    - Meaning of Words
- HATCH-WAXMAN ACT
  - INTRODUCTION
  - ¶ 4 CERTIFICATIONS
  - Infringement Cases
    - Fluoxetine (PROZAC®)
    - Buspirone (BUSPAR®)
    - Omeprazole (PRILOSEC®)
  - CONCLUSION

1. INTRODUCTION

Scientists Invent

Lawyers Patent

“Because there is a general lack of understanding of each culture, these interactions often lead to a cognitive friction that is both disturbing and costly to society.”

A Convergence of Science and Law (National Academy Press, 2001)
http://books.nap.edu/html/science_law/report.pdf

Constitutional Basis for Patents and Copyrights

Article I, § 8, cl 8

To promote the Progress of Science and useful Arts by securing for limited Times to

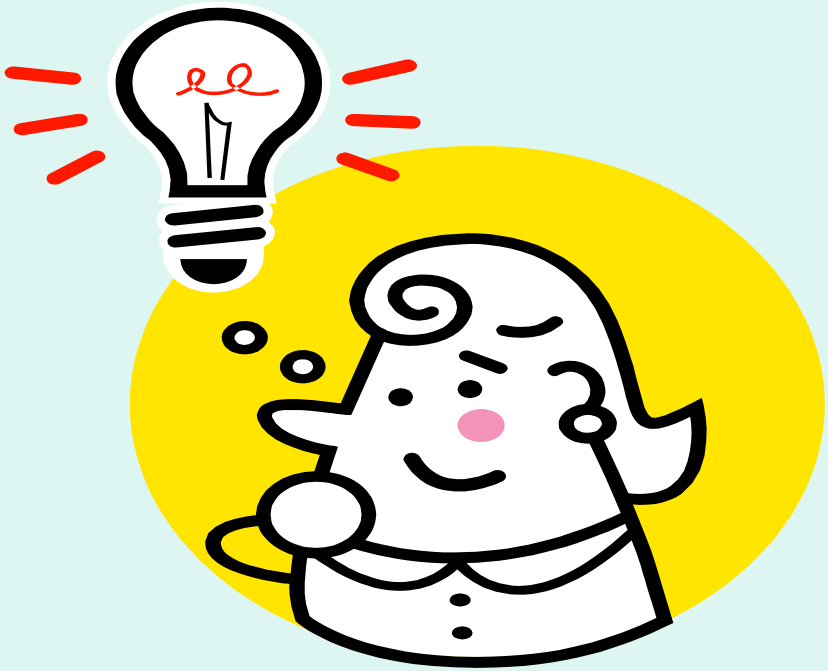
Authors and Inventors

the exclusive Right to their respective Writings and Discoveries

In other words, a patent is a

limited monopoly

Patents are about



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Patent "Economics"

- **Patents on 65 "blockbuster" drugs expired in 2003**
  - **Revenues of $2 to $10 million per week (per drug)**
- **Drugs commonly lose 40% of market share to competitors within one year after patent expiration**

(http://www.mondaq.com/article.asp?articleid=22997)

Meaning of words often the grounds for patent dispute

Which word is open to interpretation?

Claim 2.

A touch probe . . . the probe generating a trigger signal when said sensing tip contacts an object . . .

(Touch Probe, US patent 5,491,904)

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Claim 2.

A touch probe . . . the probe generating a trigger signal **when** said sensing tip contacts an object . . .

[Renishaw PLC v. Marposs Societa' Per Azioni 158 F.3d. 1243(Fed. Cir. 1998)]

What can be patented?

Is there any thing whereof it may be said, See, this is new? It hath been already of old time, which was before us.

Eccles, i. 10.

What can be patented?

1. Allowed by Statute
2. Useful
3. Novel
4. Non-Obvious

INTELLECTUAL PROPERTY

1. PATENTS
2. COPYRIGHT
3. TRADEMARK
4. TRADESECRETS

ANTISENSE DRUG REP
HI, I'M BOB.
Cooney

HATCH-WAXMAN ACT

DRUG PRICE COMPETITION AND PATENT TERM RESTORATION ACT OF 1984

H-W POLICY ISSUES

To Protect Intellectual Property

– ***Encourage Innovation***

Foster Competition

- ***Consumer Benefit***

Patents and H-W ACT

- NDAs are required to include:
  - patent number and
  - expiration date of any patent that claims either
    - the drug (active ingredient and/or composition or formulation) or
    - method of use (i.e., indication)

Patents and H-W Act (cont'd)

- **FDA required to list the submitted patent information in its "Orange" book**

- **Approved Drug Products with Therapeutic Equivalence Evaluations**

ANDA and Paper NDA

ANDA [FDCA 505 (j)]

NDA under H-W for generic copies of FDA-approved drug products ("listed drugs")

Not required to contain safety and effectiveness data

ANDA and Paper NDA (cont'd)

Paper NDA [FDCA 505 (b)]

NDA under H-W for generic copies of FDA-approved drug products

Required to contain full safety and effectiveness data

- may rely on published reports ("not conducted by or for the applicant…")

FDAs Role in ¶ 4 certification issues

- **None (essentially)**
  - **FDA does not examine the propriety of the patent(s) listed by the innovator**
  - **Upon complaints by generic company about improper patent listing, FDA makes mere inquiry of innovator regarding propriety of patent(s) listed**

H-W Certifications

A generic company (the ANDA/503(b)2 applicant) must certify that drug :

- **I) has not been patented;**
- **II) patent has expired;**
- **III) patent will expire on a given date and that generic will not be marketed prior to that date; OR**
- **IV) patent is not infringed or invalid**
  - **»Most complicated of the 4 certifications**

Paragraph IV Certification

- **Generic Company Must Notify Innovator (Pioneer) about its Filing**

- **Describe Reasons why Patent**
  - **Will Not be Infringed**
  - **Is Invalid**

Paragraph IV Certification (cont'd)

- Innovator has 45 days after notice to file an infringement suit*
- **FDA stays ANDA for 30-month if suit filed, unless**
  - **- Patent Expires**
  - **- Patent Found Invalid by Courts**

***ANDA submission with ¶ 4 certification creates grounds for infringement action by patent holder**

EINSTEIN SIMPLIFIED

Case Study 1

- The "Prozac" case (decided August 9, 2000)
  - 272 F.3d 973

- Facts
  - fluoxetine (active ingredient of Prozac)
  - Barr Labs submitted ANDA in December 1995 for generic fluoxetine with ¶ IV certification
  - Lilly brought action alleging Barr's ANDA application infringed its patents

“Barr”argued that claim 7 of the “549” patent was invalid for double patenting

Double Patenting

"[T]he extension of exclusive rights through claims in a later patent that are not patentably distinct for claims in an earlier patent"

(222 F.3d at 985)

Issue for Court

To determine whether Claim 1 of the “895 patent covers subject matter claimed in claim 7 of the “549” patent (the later patent)

A method of blocking the uptake of serotonin by brain neurons in animals comprising the administering to said animal of fluoxetine (claim 7, “549” patent)

A method of treating human suffering from depression which comprises administering to said human of an effective antidepressant dose of fluoexitine (claim 1, “895” patent)

Case Study 2

- The "Prilosec" case (decided 10/11/02)
  - 222 F. Supp. 2d 423
- Facts
  - Omeprazole – active ingredient of Prilosec (Acid Labile)
  - KUDCO submitted ANDA for generic omeprazole with ¶ IV certification
  - Patent Holder Astra Aktiebolag filed infringement suit ("505" patent)

Omeprazole Case (cont'd)

- **The main issue:**
  - **Did the Kremers Urban Development Co. (KUDCo) formulation contain an alkaline reacting compound (ARC)?**

Omeprazole Case (cont'd)

- **Claim 1 ("505"Patent)**
  - **An oral pharmaceutical preparation comprising:**
  - **(a)** **a core region comprising effective amount of a material selected from the group consisting of omeprazole plus an alkaline reacting compound (ARC), an alkaline omeprazole salt plus an ARC and an alkaline omeprazole salt alone**

Omeprazole Case (cont'd)

- **Formulation Differences**
  - **Core Composition**
- **KUDCo microtablet has 3 parts:**
  - **a core, a subcoat and enteric coat**
  - **The Court concluded that the subcoat and the enteric coat of the microtablet do not differ from the "505" patent**

Omeprazole Case (Cont'd)

DECISION

- **The Court held that there was no infringement of "505" patent by the KUDCco microtablet because "[KUDCo]… designed around the "505"… patent by developing a formulation that did not require an ARC in its core"**
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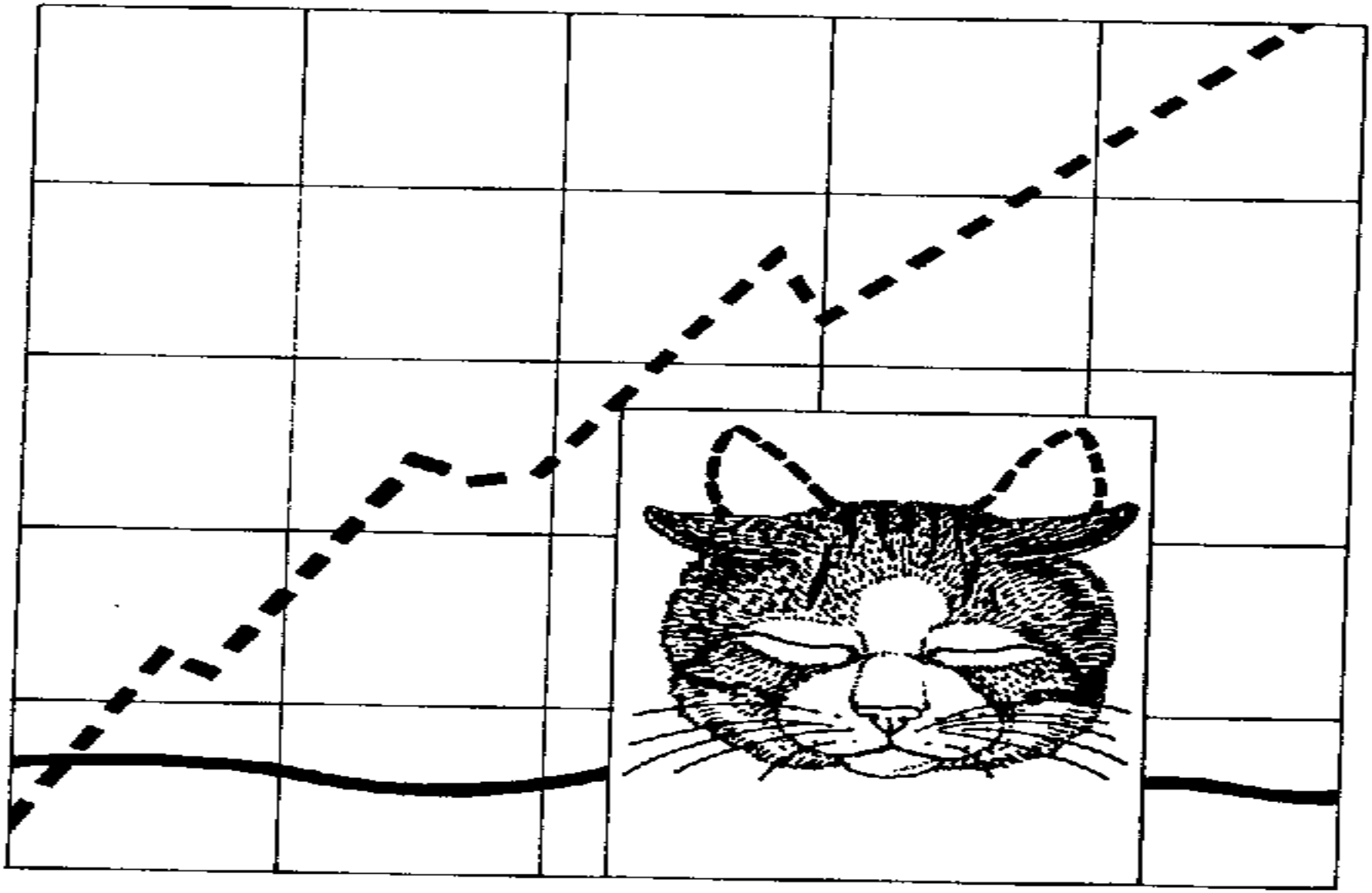
Omeprazole Case (cont'd)

- **There were 3 other generic companies that had also filed ANDAs**
  - **Andrx Pharmaceuticals, Cheminor Drugs, and Genpharm, Inc.**

They all were found to infringe on several of the claims of the Astra patent(s)



Cats are able to prick up their ears while keeping their eyes firmly closed. This enables them to sleep soundly while appearing to pay attention.

Case Study 3

- The "Buspirone" Case (decided 2/14/2002)
  - 185 F. Supp. 2d 340
  - Facts
    - Bristol Myers Squibb Listed two patents with respect to their Buspar® NDA
      - "763" expiration date: 7/21/2000)
      - "365" obtained hours before "763" expired
    - Danbury, Watson & Mylan had tentative FDA approval to market generic buspirone on 7/22/00 following expiration of the "763"

Buspirone Case (Contd)

- **Facts (cont'd)**
  - **BMS obtained patent "365" on 7/21/2000 and requested FDA to list this patent in the Orange Book with a declaration that the new patent "is a method-of-use patent covering, among other things, a method of using BuSpar for all its approved indications" (http://www.cato.org/pubs/regulation/regv24n4/v24n4-2.pdf)**

Buspirone Case (Cont'd)

- **Facts (cont'd)**
  - **FDA then informed the three generic applicants that their ANDA was incomplete and needed certification that their generic buspirone will not infringe upon the "365"patent.**
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Buspirone Case (Cont'd)

- Facts (cont'd)
- **A method for the palliative treatment of neurosis in which anxiety symptoms are prominent which comprises administering a non-toxic anxiolytically effective dose of busprione or a pharmaceutically acceptable acid addition salt thereof to a neurotic patient ("763" patent claim)**
- **A process for ameliorating an undesirable anxiety state in a mammal comprising systemic administration to the mammal of an effective but non toxic dose of 6-hydroxy metabolite or a pharmaceutically acceptable acid addition salt or hydrate thereof ("365" patent claim)**

Buspirone Case (Contd)

The 3 generic companies moved for summary summary judgment on BMS allegation of patent infringement based on the argument that:

a) **generic buspirone would not infringe the "365" patent or**

b) **The "365" patent is invalid**

Buspirone Case (Cont'd)

Decision

The Court granted the motion for summary judgment by the 3 generic companies that " the '365' Patent does not cover uses of buspirone"

HATCH-WAXMAN MARKET EXCLUSIVITIES

Clinical Study Exclusivity (3 years)

- **NDA or Supplemental NDA**
- **Reports of new clinical investigations (excludes BA studies)**
  - **Essential For Approval of New Application**
  - **Conducted or Sponsored by Applicant**

[(§§ 505 (c)(3)(D)(iii) and (j)(5)(D)iii & (iv), FDCA]

New Chemical Entity (NCE)

- **NCE - a drug not previously approved by FDA under section 505 (b) (i.e., NDA)**
- **5 years if ANDA or 505(b)(2) ("paper NDA") application does not contain paragraph IV certification to a listed patent**
- **4 years if ANDA or paper NDA application is submitted containing a paragraph IV certification to a listed patent**

Generic Drug ("Early Bird") Exclusivity

180 day exclusivity for the first generic (ANDA) applicant that certifies that pertinent patent(s) is invalid or will not be infringed

- **from start of marketing or**
- **invalidation of relevant patent(s)**

NON HATCH-WAXMAN EXCLUSIVITIES

ORPHAN DRUG

- **Designated and approved to treat diseases or conditions affecting**
  - **fewer than 200,000 patients in the US**
  - **Or more than 200,000 and no hope of recovering costs of developing and marketing the drug**

- **Drug makers get seven-year market exclusivity after market approval.**

Pediatric Exclusivity

- **6 Months of Additional Market Protection**
- **Sponsor Conducts and Submits Pediatric Studies on Active Ingredient**
- **Written Request from FDA**

Mars – the newest IP domain?

CONCLUSION

Creation and Protection of Pharmaceutical Patents Requires that Scientists and Lawyers Work Closely To Develop Strategies for the Life Cycle of the Drug