Slide 1

EXCLUSIVITY AND PATENT INVALIDATION: WHAT THE MEDICINAL CHEMIST SHOULD KNOW

Manfred E. Wolff, Ph.D.
USPTO Reg. No. 43,282
Lecture at Drew University
Madison, NJ (2003)

Slide 2

FOCUS OF THIS LECTURE

- IMPORTANT CONCEPTS THAT YOU, AS A MEDICINAL CHEMIST, SHOULD KNOW ABOUT PATENTS SO THAT YOU CAN HELP TO PROVIDE BULLET-PROOF PATENTS FOR YOUR EMPLOYER.

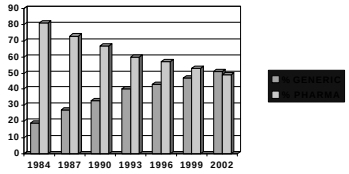
Slide 3

Outline of This Presentation

- General Discussion of Patents (Written Materials Part II, Pp. 1-8)
- Detailed Description of Parts of a Patent (Part II, Pp. 9-13)
- Discussion of Patent Records (Pp. 14-15)
- Exceptions to Infringement (Pp. 16 ff.) (K. Williams)
- Copy of US Patent 4,914,096 (Appendix I)
- Patent Forms (Appendix II)
- Exclusivity, Hatch-Waxman, and Patent Invalidation

Slide 4

Loss of Market Share by Pharma to Generics



Slide 5

EXAMPLE OF THE LOSS OF MARKET SHARE AFTER LOSS OF PATENT PROTECTION

- When Glucophage (metformin), with sales of $2 B, lost patent protection in January 2001, more than 85% of its market was taken over by generics within 30 days.

Slide 6

REGULATORY EXCLUSIVITY

- A fixed period of time within which a regulatory authority will not allow approval of a generic ANDA (abbreviated/abridged application) of an approved drug.

Slide 7

5-YEAR NCE EXCLUSIVITY

- No ANDA for a generic equivalent can be submitted until 5 years from the NDA approval date for the NCE (reduced to 4 years if accompanied by ¶ IV certificate).

Slide 8

3-YEAR NEW USE OR FORMULATION EXCLUSIVITY

- No ANDA can be approved until after 3 years from approval of non-NCE, e.g. for new use or formulation. The 3-year exclusivity period attaches only to the use of the product supported by new clinical studies.

Slide 9

3-YEAR SINGLE ENANTIOMER EXCLUSIVITY

- 3-Year exclusivity attaches to single enantiomers of a previously approved racemate:
  - For same indication as racemate, but improved safety or efficacy as shown by additional clinical trials
  - For new indication exclusive of original indication of racemate, as shown by additional clinical trials

Slide 10

6-MONTH PEDIATRIC STUDY EXCLUSIVITY

- The Best Pharmaceuticals for Children Act permits the FDA to grant a drug manufacturer an additional six months of market exclusivity for a drug if the manufacturer conducts acceptable pediatric studies.

Slide 11

Hatch-Waxman: "Drug Price Competition and Patent Term Restoration Act" (1984)

- Intended to help generics to enter market but still provide inducement for innovation.
- Applies to all pharmaceuticals except antibiotics produced by microorganisms and approved prior to 1999.
- Enables ANDA based only on bioequivalence after data exclusivity period.

Slide 12

Hatch-Waxman

- Types of ANDA certification:
  - ¶ I certification: …no patent listed
  - ¶ II certification: …listed patent(s) expired
  - ¶ III certification: ..approval sought only after patent expiry
  - ¶ IV certification: ..listed patent(s) invalid or not infringed

Slide 13

HATCH-WAXMAN ¶ IV CERTIFICATION 180 DAY EXCLUSIVITY

- Goes to first ANDA applicant for particular form of ANDA
- Delays approval of subsequent ANDA applicant for that form(s) for 180 days from (1) earliest marketing by first ANDA applicant or (2) adverse District Court decision to patentee (invalidation)

Slide 14

VALUE OF 180 DAY EXCLUSIVITY

- $365 M/YR SALES = $1 M/DAY
- LEGAL FEES FOR CASE = $2-10 M

Slide 15

LESSON OF HATCH-WAXMAN FOR THE MEDICINAL CHEMIST

- The value of 180-day exclusivity is great
- The cost of litigation to invalidate a patent is small by comparison
- Hence, an aggressive campaign to invalidate pharmaceutical patents is underway
- Medicinal Chemists MUST understand the basis of patent invalidation and help to ensure the preparation of bulletproof patents.

Slide 16

Constitution of the United States § 8 Article 1

- The Congress shall have power * * * 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.

Slide 17

35 U.S.C. §112 ¶ 1

- The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Slide 18

DECISION IN UNIV. OF ROCHESTER V. SEARLE

- Claim 1 of US 6,048,850: A method of selectively inhibiting PGHS-2 activity…comprising administering a non-steroidal compound that selectively inhibits activity of he PGHS-2 gene product to a human host in need of such treatment.

Slide 19

DECISION IN UNIV. OF ROCHESTER V. SEARLE

- A mere wish or plan is not enough to satisfy written description requirement
- "Invention" of a method meaningless if lacking substance essential to its practice.
- A description of what a substance does, rather than what it is, is not sufficient.
- To practice this method, person of ordinary skill in the art requires undue experimentation

Slide 20

UNDUE EXPERIMENTATION

- Scope of claims is not limited to only those embodiments disclosed in the specification as long as one of ordinary skill would be able to make and use the invention without undue experimentation (i.e, technological problems can be solved in a reasonable time).
- A broad claim may be supported without even a single disclosed embodiment.

Slide 21

PREDICTABLE v. UNPREDICTABLE

- Fisher: In cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement. Once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known physical laws. In cases involving unpredictable factors, such as most chemical reactions and physiological activity, the scope of enablement varies inversely with the degree of unpredictability.

Slide 22

UNPREDICTABLE ART

- In re Wands: Applicant claimed immunoassay methods using MAb's.
- Of 143 hybridomas, only *4* fell within the claims. A 3% success rate mandates undue experimentation to make claimed Ab's
- Patent denied.

Slide 23

SOME REASONS FOR PATENT INVALIDATION

- NOT USEFUL
- NOT NOVEL
- OBVIOUS
- WRONG INVENTR
- NO PRIORITY
- DEFINES SUBSTANCE BY FUNCTION
- NOT DILIGENT
- NOT ENABLED
- UNDUE EXPERI-MENTATION
- NO BEST MODE
- INEQUITABLE CONDUCT

Slide 24

NOVELTY AND UNOB-VIOUSNESS REQUIREMENT

- Novelty: Invention must be different from what is known to the public. Any difference, however slight, will suffice.
- Unobviousness: At the time of invention, the invention must have been considered unobvious to a person skilled in the art. Shown by new, unexpected, or far superior results.

Slide 25

PRIOR ART: WHAT IT IS AND WHAT IT ISN'T

•THE MEDICINAL CHEMIST IS THE EXPERT IN THIS AREA

•IT IS VERY IMPORTANT FOR THE MEDICINAL CHEMIST TO ADVISE THE PATENT PROFESSIONAL ON THIS TOPIC FOR EACH PATENT

Slide 26

NOVELTY: DESIGNATION BY FORMULA OR WORDS

- Mere disclosure of formula or sequence of words used to designate a compound not enough. If prior art fails to provide method for producing compound, and no method is known or obvious, compound is not anticipated.
- Anticipating reference need not disclose utility.

Slide 27

TEST FOR OBVIOUSNESS

- Test for determining obviousness is whether prior art, taken as a whole, would have suggested invention to one of ordinary skill in the medicinal chemical arts at time invention was made, rather than "obvious to try" standard.

Slide 28

OBVIOUSNESS

- Consider invention as a whole: Structure, Uses, Properties.
- Similar properties are expected from structurally similar compounds.
- Obviousness does not require absolute predictability; only reasonable expectation that beneficial result will be achieved.

Slide 29

OBVIOUSNESS: HOMOLOGS

- Homology is not automatically equated with obviousness.
- If similar properties are not predicted, there is no obviousness.
- If observed properties are superior, obviousness is rebuttable.

Slide 30

OBVIOUSNESS: ESTERS

- First Case: In re Carabateas (CCPA 1966a)
  - Piperidine reverse ester ($-O_2CR$) substituents were found to be obvious in light of prior art references generically teaching both normal ($-CO_2R$) and reverse ester piperidines indicating that these structurally similar esters would exhibit analgesic properties.
- Second Case: In re Carabateas (CCPA 1966b)
  - Claimed "reverse" ester was found to be unobvious because of 19-fold increase in activity vs. reverse ester of prior art.

Slide 31

OBVIOUSNESS: ISOSTERES

- In re Merck (Fed. Cir. 1986): Method of treating human depression by oral administration of amitriptyline (a C= bioisostere of imipramine, the corresponding N- compound) was obvious; one of ordinary skill in medicinal chemical arts would have expected amitriptyline to resemble imipramine in alleviation of depression in view of the prior art regarding bioisosterism of such compounds as chlorpromazine and chlorprothixene.

Slide 32

CONCEPTION: THE TOUCHSTONE OF INVENTORSHIP

- Mergenthaler v. Scudder (1897)
  - Conception is the complete performance of the mental part of the inventive act--formation in the inventor's mind of the complete and operative invention.
  - All that remains is to perfect the act of construction, not invention.

Slide 33

JOINT INVENTORSHIP

- Joint Inventorship: "one of the muddiest concepts in the muddy metaphysics of patent law."
- Inventors may apply for patent jointly even if:
  - They did not physically work together or at the same time
  - Each did not make the same type or amount of contribution
  - Each did not contribute to the subject matter of every claim of the patent

Slide 34

JOINT INVENTORSHIP (con.)

- Joint inventor need only contribute to the subject matter of a single claim.
- Joint inventors must be aware of each other; no joint inventorship if totally unaware of each other's work.
- Invention conceived before collaborative work begins is not a joint invention.
- A prior conceived invention modified by collaborative effort may constitute a joint invention.

Slide 35

CONTRIBUTION TOWARD CONCEPTION

- Merely exercising normal skill to reduce an inventor's idea to practice, without an inventive act, does not make one a joint inventor, even if the reduction to practice constitutes the best mode (Ethicon v. U.S. Surgical (Fed. Cir. 1998)).
- Suggesting an idea of a result sought but not the means of accomplishing it does not qualify one as a joint inventor.

Slide 36

Hess v. Advanced Cardio-vascular Sys. (Fed. Cir. 1997)

- Named inventors Simpson and Robert approached Hess about materials for a balloon angioplasty catheter.
- Hess, who had no experience in angio-plasty, suggested an adhesive-free seal made from a product of his company.
- Simpson and Robert tested and refined their catheter without input from Hess, and ultimately filed a patent application.

Slide 37

Hess v. Advanced (con.)

- Co-Inventorship must be proved by clear and convincing evidence.
- Co-inventor must have had some conceptual role in some important element of the claimed invention.
- An inventor “may use the services, ideas, and aid of others in the process of perfecting his invention without losing his right to a patent.”
- Hess was not an inventor, but a skilled salesman who educated the inventors on the state of the art.

Slide 38

What is the Invention?: Brown v. UC (Fed. Cir. 1994)

- Animal tech Brown, brought cats she believed had contracted a new virus similar to HIV to virologists at UC.
- Virologists purified and patented feline virus (FIV), along with method for detecting in cats and method of vaccination.

Slide 39

What is the Invention? (con.)

- Brown sued to correct the inventorship, claiming she made the critical inventive contribution by discovering the virus.
- But FC ruled that patent did not claim discovery--only isolated and purified form, plus method for diagnosing.
- Notwithstanding the leads she supplied, she did not contribute to the conception of the invention.

Slide 40

REDUCTION TO PRACTICE

- Two phases to invention: Conception and Reduction to Practice
- Only inventors conceive; others can reduce to practice
  - Actual Reduction to Practice
  - Constructive Reduction to Practice

Slide 41

ACTUAL REDUCTION TO PRACTICE

- Concrete embodiment of invention shown to work for its purpose
- Composition of matter
  - Synthesis of compound
  - Confirmation of identity of compound (analysis, nmr, mass spec., etc..)
  - Testing to show utility for intended use

Slide 42

ACTUAL REDUCTION TO PRACTICE (con.)

- Process
  - Perform all steps of process, including known steps
  - Successfully obtain desired product of process
  - Establish utility of product

Slide 43

CONSTRUCTIVE REDUCTION TO PRACTICE

- File a regular or provisional U.S. Patent Application, or a foreign patent application, complying with the requirements of §112, ¶ 1.
  - Written description of the invention
  - Enable the invention by showing how to make and use
  - Disclose best mode for invention known to inventors at time of filing

Slide 44

WHY DO WE NEED TO KEEP AND CORROBORATE GOOD RECORDS?

- Needed in priority contests and to antedate references:
  - Elements in proving date of invention: Conception→Diligence→Reduction to Practice

Slide 45

GOOD LABORATORY RECORDS

- Permanent and continuous form that gives the chronological history of research leading to the invention
- Date ideas formed or work conducted
- Consecutively numbered, bound books
- Describes design of experiments, protocols, and results
- Defines abbreviations where necessary

Slide 46

GOOD LABORATORY RECORDS (con.)

- Contemporaneously read, understood, and signed
- Sign, date, and witness every entry
- Extrinsic materials like photographs, spectra, copies of protocols permanently affixed in book, signed across page and dated
- Be careful of photocopies of gels--may lose bands!

Slide 47

WHO IS CORROBORATING WITNESS?

- A technician working under inventor's direction
- A co-worker who observed inventor's work
- A supervisor who personally knows inventor's ideas and reduction to practice

Slide 48

VALIDITY OF ELECTRONIC RECORDS

- Must be authentic and reliable
  - Must authenticate who contributed to the record, date, and who witnessed the entry
  - Must ensure that entries not altered or erased

Slide 49

ARCHIVING ELECTRONIC RECORDS

- Periodically archive electronic records with custodian with control over archive
- Alternatively: Print, sign, date and witness hard copies, and bind them permanently as a notebook; or,
- Make repeated electronic copies of work to date and archive the copied disks as a permanent record of work

Slide 50

ENABLEMENT
35 U.S.C. §112 ¶ 1

- The specification shall contain a written description* * * of the manner and process of making and using [the invention], in such full, clear, concise, and exact terms as to enable any person skilled in the art* * * to make and use the same* * *.

Slide 51

BEST MODE REQUIREMENT

- The public is entitled to know the most preferred embodiment of the invention (at the time it is made) in exchange for period of exclusivity granted by patent rights.

Slide 52

IS INVENTOR OBLIGED TO LABEL THE BEST MODE?

- No obligation to label best mode as such
- Best mode can be one of many examples, or doesn't even have to be an example
- Can be disclosed as preferred conditions or reagents

Slide 53

IS INVENTOR OBLIGED TO LABEL THE BEST MODE? (con.)

- Sole issue: If inventors contemplated a best mode, does specification adequately disclose it to enable the skilled person to practice it.

Slide 54

CONCEALMENT AND INEQUITABLE CONDUCT

- Best mode violation doesn't automatically give rise to inequitable conduct (could be unintentional).
- Unintentional violation will invalidate only limited number of claims.
- If violation involves inequitable conduct, entire patent becomes unenforceable.

Slide 55

NOBELPHARMA v. 3i
(*Nature Biotechnology* **16,**587 (1998)

- Nobelpharma licensed patent claiming titanium dental implant with a network of micropits for “osseointegration”.
- 3i used same technology, and Nobelpharma sued for infringement.
- 3i countersued, alleging patent invalid for failure to disclose best mode

Slide 56

NOBELPHARMA v. 3i (con.)

- Court found that inventor Branemark, at the time of filing for patent, possessed a preferred method and knowingly failed to disclose it sufficiently to enable those skilled in the art to practice that method.
- Patent ruled invalid.

Slide 57

TYPES OF CLAIMS

- Processes
- Machines
- Manufactures (e.g. packaged drug)
- Compositions of Matter
- Processes involving new uses of processes, machines, manufactures or compositions of matter
- Improvements in any of the above

Slide 58

TYPES OF CLAIMS FOR NEW CHEMICAL ENTITIES WITH EXAMPLES IN U.S. PATENT 4,914,096

- Composition of matter (Claims 1-10)
- Mechanism of action (Claims 11-12)
- Method of synthesis
- Therapeutic use (Claims 13-22)
- Formulation (Claim 23)
- Article of manufacture (Claim 23)
- Assay method