University and Life Science Patents in the US

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Outline

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2. *Stanford v Roche* (ownership/Bayh-Dole)
3. *In re Gleave* (novelty)
4. *In re Fisher* (utility)
5. *Prometheus v Mayo* (§101 diagnostics)
6. *Diamond v Chakrabarty* (§101 life forms)
7. *Ass of Mol Path v Myriad* (§101 gene patents)

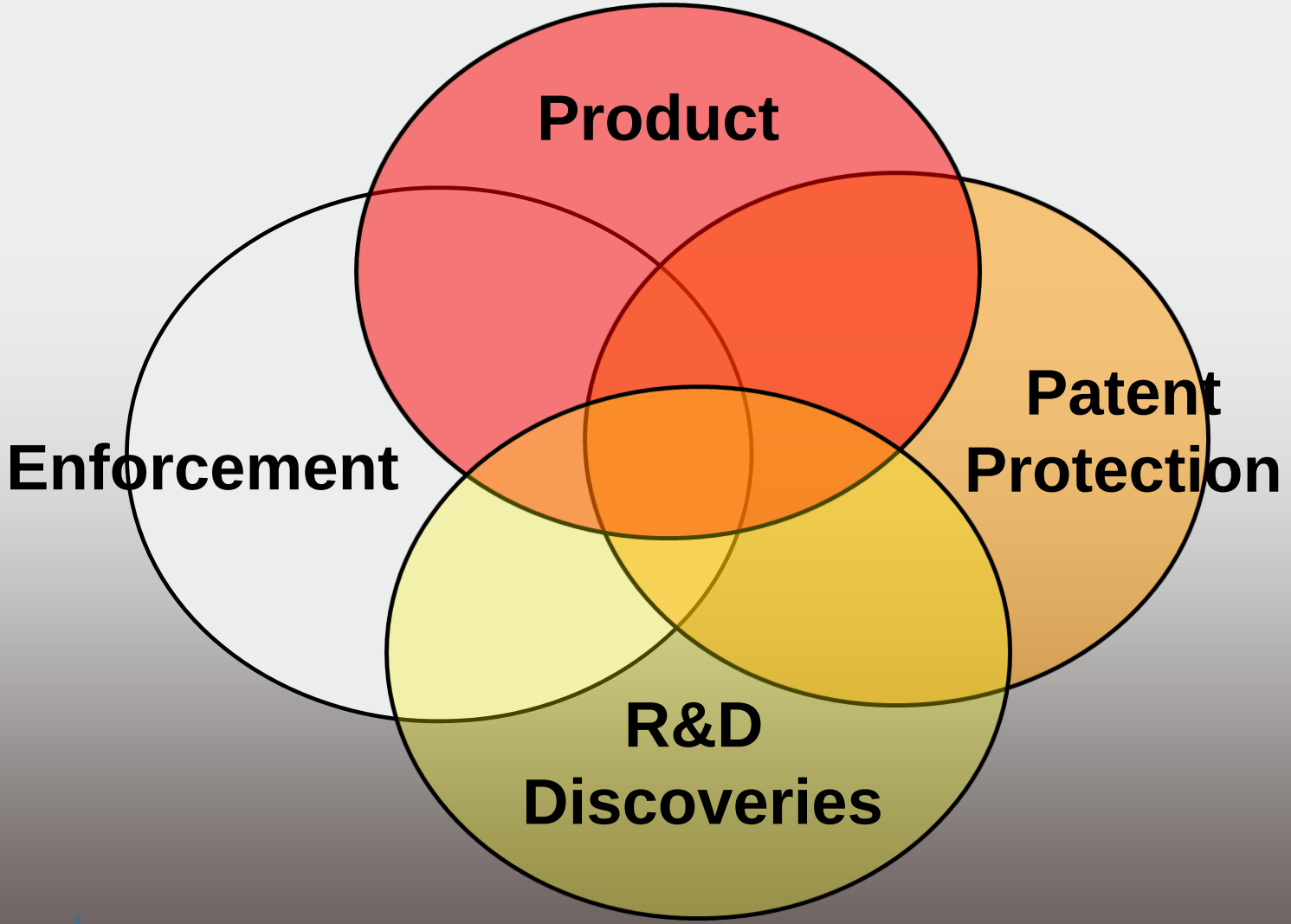
US Copyrights & Patents

- US law originates in the Constitution, Article 1, Section 8, Clause 8.
- "Congress shall have the **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."

US Fed. Court System

- Patents are governed by Fed. law, although related issues, e.g., contract or antitrust may involve application of state law.
- Patent disputes originate in the state District Courts (DC).
- All patent appeals are consolidated in the Court of Appeals for the Federal Circuit (CAFC)
- The Supreme Court (SCt) is the ultimate arbiter.

Proprietary Product Wheel



Pharma, Biotech, Diagnostic IP

- The cost of goods to manufacture is low;
- Often easy to reverse engineer;
- Commercial barriers to entry may be low;
- Upfront R&D, regulatory costs may be large;
- Investors are looking to reduce risk. They need comfort that the innovator will have a monopoly reap the fruits of their discovery; and
- Before investing the time and effort to develop, validate, commercialize, and build a market for a novel innovation, are there IP barriers to entry?

Patent Requirements

- USEFUL? Generally easy, but for nucleic acid related inventions utility must be specific AND substantial.
- NEW? Easy, it can't be known. In US 1 year grace period.
- UNOBVIOUS? Typically, use an indirect proof, commercial success, long felt need, failure of others, unexpected results.
- ENABLEMENT/WRITTEN DESCRIPTION? Actual examples are not required. Must be sufficient for a person in the field to make and use the invention. In US must disclose the best mode.

Perfect World Patents?

- COMPOSITION OF MATTER
  - **Small molecules, new chemical entities (NCEs)**
  - **Antibodies**
  - **Proteins (native/recombinant)**
  - **Enzymes**
  - **Nucleic acids (genomic, synthetic, DNA, RNA…)**
- METHODS OF USE
  - **Therapeutic**
  - **Diagnostic**
- METHODS OF MANUFACTURING

Ownership vs. Inventorship

- US rewards inventors. If there were no other contractual obligations, a sole inventor would own the entire patent and a joint inventor is part owner of the entire patent.
- To be an inventor you must contribute to either the CONCEPTION or the REDUCTION TO PRACTICE of an invention. Someone following a protocol to validate will not be an inventor.
- Most employers and universities require general assignment of future inventions made in the course of employment and assignment of specific patents.

US Gov't Funding

- Most academic/university discoveries are supported in part by federal funds.
- Prior to 1980, in a slow process institutions could obtain rights under varied NIH/NSF/DOE procedures.
- In 1980, Bayh-Dole Act passed granting nonprofit and small business recipients… a means to retain rights to federally-funded inventions. In exchange:
  - **US gov't gets (march-in rights, research non-excl., patent notification, annual updates regarding commercialization *i-edison*…).**
  - **Commercial preference for small businesses, US manufacturing.**

Bayh-Dole (Key terms)

- "CONTRACTOR" means any …party (univ.) to a funding agreement.
- "SUBJECT INVENTION" means any invention of the contractor conceived or first reduced to practice under a funding agmt.
- TITLE: §202(a) nonprofit "may elect to retain title to any subject invention"
- INVENTOR RIGHTS: §202(d) "agency …after consultation with contractor may grant requests for retention of rights by inventor subject to provisions of this Act"
- SUPREMACY: §210(a) "shall take precedence over any other Act which would require disposition…inconsistent with this Chapter [NSF, DOE, NASA]"

Stanford v Roche (1)

- Stanford sued Roche for infringement of several patents on PCR-based HIV diagnostics for treatment monitoring.
- 1988 Stanford fellow Holodniy signed employment agmt "I agree to assign…such inventions as required by contracts or grants."
- 1989 signed a Visitor's Confidentiality agmt "**will assign and do hereby assign** to CETUS…as a consequence of" his work with Cetus.

Stanford v Roche (2)

- 1991 Cetus reviewed internal invention disclosure and decided not to file & Roche bought Cetus.
- 1992 Stanford filed appn for HIV diagnostic.
- 2000 Stanford offered Roche a license to series of HIV patents.
- 2005 Stanford sued Roche in CA District Court.
- 2007 DC denied Roche's motion to dismiss as co-owners, finding Holodniy had not regained title under Bayh-Dole.

Stanford v Roche (CAFC)

- In 2009 CAFC reversed the lower court ruling regarding ownership and held:
  - **Under "do hereby assign" contract language, Cetus rights vested first.**
  - **As a matter of law, Roche is a co-owner.**
  - **Bayh-Dole only governs btn contractors and gov't NOT btn inventors and contractors.**
  - **Stanford's rights under Bayh-Dole were only residual.**
  - **Bayh-Dole does not void the Holodniy/Cetus agmt.**

Stanford v Roche (SCt)

- DOJ petitioned for SCt review arguing:
  - **Calls to question gov't ability to manage funded inventions for public benefit;**
  - **Gov't owns all funded research, Bayh-Dole creates at presumption of nonprofit ownership;**
  - **Gov't funded invention ownership cannot turn on the timing or vagaries of contract language;**
  - **Inventor Holodniy could not assign to Cetus rights greater than he himself possessed; and**
  - **Upsets massive number of employment agmts, contracts w/ companies.**
- **Oral arguments in Feb. and a decision by summer 2011.**

Stanford (SCt outcomes)

- Reverse CAFC, restore status quo.
- Uphold the CAFC, big effect on universities, new ways to challenge licensed patents.
  - **Congress may change the law to undo SCt ruling**
- Remand for additional fact finding.

Stanford v Roche (lessons)

- Include present assignment language "do hereby assign" in employment agmt;
- Have an agmt with institution, *e.g.*, materials transfer agmt (MTA), to assure clear flow of rights.
- Review agmts associated with valuable inventions.
- Some suggest requiring all agmts btn researchers and 3rd parties be submitted for univ. lawyer review. Practical?

In re Gleave (novelty)(1)

- 2003 Gleave filed for several specific 18-22 bp antisense oligonucleotides to that bound two different types of Insulin Dependent Growth Factor Binding Protein (IGFBP2 & 5)
- 2000 Wraight PCT published with
  - **Sequence of IGFBP2 gene &**
  - **1400 15 bp sequences spanning entire gene!**
- PTO rejected as not novel (§102) given Wraight

In re Gleave (novelty)(2)

- 2008 the BPAI upheld the Examiner determination.
- CAFC Issue: Does a long laundry list anticipate the specific oligos with specific properties? Or is it just a genus disclosure?
- 2009 CAFC held though sequences were not actually made and tested, Wraight anticipates Gleave's specific antisense oligos.

In re Fisher (utility)

- Monsanto researchers Dane Fisher & Raghunath Lalgudi filed appn with 32,000 corn ESTs.
- Examiner rejected claims to ESTs Seq ID No. 1-5 associated with anthesis under §101/112.
- Fisher argued useful as (1) molecular markers, (2) microarrays, (3) PCR primer source, (4) tool for polymorphism, (5) tool to isolate promoters, (6) control protein expression, or (7) comparative plant research.

In re Fisher (utility CAFC)

- Substantial utility: a significant and presently available benefit to the public.
- Fisher admitted at the time filing the genes had no known functions.
- No data to support any of 7 uses.
- Specific utility a use which is not so vague as to be meaningless.
- Fisher's uses could be for any EST from any organism.

Mayo v Prometheus (1)

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 $8x10^8$ 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 $8x10^8$ red blood cells indicates a need to decrease the amount of said drug subsequently administered to said subject.

Mayo v Prometheus (2)

- DC ruled invalid under Sec. 101, merely "correlating" natural phenomena because administering and determining were just data collection steps. ↓
- CAFC I ruled Prometheus met the Machine or Transformation (MoT) test. ↑
- SCT remanded because of *Bilsky* ruling (MoT) is not the only test. ↓
- CAFC II ruled again for Prometheus, method met MoT and involved meaningful transformations. ↑

Diamond v Chakrabarty (SCt 1)

- In 1972 Ananda Mohan Chakrabarty working for General Electric filed for a patent on a genetically engineered bacteria to eat crude oil and uses of the bacteria to clean up oil spills, etc.
- The US patent office granted claims to uses but denied the bacteria *per se* because it was a life form.
- The SCt ruled that one may patent "anything under the sun that is made by man" and made-made life forms are patentable subject matter.

Chakrabarty (SCt 2)

- Laws of nature, physical phenomena, and abstract ideas are NOT patentable, e.g., $E=mc^2$, a new element, a new mineral, or a new plant found in the wild.
- Here, the new bacteria is a non-naturally occurring manufacture or composition, with "markedly different characteristics from any found in nature."
- The statute encourages innovation broadly (i) does not provide a basis to bar patents on new life forms, and (ii) public policy concerns should be addressed to Congress and the Executive.

Assn Mol Path v Myriad

- 2009 under the aegis of the ACLU several medical groups file suit against Myriad and the US PTO to invalidate BReast CAncer (BRCA1/2) gene patents and uses as not patentable subject matter (§101).
- The question before the court: Are isolated human genes and diagnostic methods of gene comparison patentable?
- Or unpatentable material from cells in nature?

Myriad (history)

- 1990 Linkage analysis connects chromosome region 17q21 (6-10M bp) with familial breast cancer.
- 1994 Myriad and others sequenced and filed patents on the BRCA1 gene (~6 kb).
- 1995 Myriad filed patents on the BRCA2 gene from chromosome 13.
- 1996 commercial launch of Myriad BRCA test.
- 2009 ACLU group sued in SD NY district court.

Myriad (Claims 1)

Composition of Matter claims, US 5,747,282

1. An isolated DNA coding for a BRCA1 polypeptide, said polypeptide having the amino acid sequence set forth in SEQ ID NO:2.

2. The isolated DNA of claim 1, wherein said DNA has the nucleotide sequence set forth in SEQ ID NO:1. (cDNA)

Myriad (Claims 2)

- Diagnostic method claim U.S. 5,709,999

1. A method for detecting a germline alteration in a BRCA1 gene, said alteration selected from the group consisting of the alterations set forth in Tables 12A, 14, 18 or 19 in a human which comprises analyzing a sequence of a BRCA1 gene or BRCA1 RNA from a human sample or analyzing a sequence of BRCA1 cDNA made from mRNA from said human sample with the proviso that said germline alteration is not a deletion of 4 nucleotides corresponding to base numbers 4184-4187 of SEQ ID NO:1.

Myriad (DC)

- Judge Sweet ruled composition claims (isolated DNA encoding BRCA1/2) invalid under §101 because they are products of nature and not "markedly different."
- He held isolated genomic DNA is merely purification, like a newly discovered element, not a source of patentability.
- Isolated DNA molecules: (1) same information and (2) the same use as the naturally-occurring DNA.
- Method claims invalid because "analyzing" or "comparing" are not patentable under §101 merely abstract mental steps.

Myriad (DOJ)

- DOJ filed briefs on appeal arguing isolated, genomic DNA are products of nature, like cotton, and NOT patentable.
- Identifying genes is like discovering new plants or purifying an element, not a source of patentability.
- Footnote that case would be different if "chemically modified."
  - **Issue: Myriad's "isolated DNA" was, in fact, chemically modified by restriction enzyme cleavage of phosphodiester bonds.**

Myriad (DOJ 2)

- DOJ argued (1) extracting DNA from a cell, (2) excising genes such as BRCA 1/2, (3) splicing exons, are not material changes to naturally occurring chemical structure.
- However, cDNA, vectors, probes, primers are engineered (man-made, modified), thus may patentable.

Myriad (CAFC)

- Over 25 Amicus Briefs were filed.
- Oral arguments were held 4 April 2011.
- Standing? Myriad argues that Assn. of Mol. Pathology etc. lack standing to challenge. While ACLU, others want to invalidate these patents, not clear if there is an actual party who wants to practice BRCA testing. Thus, no actual case or controversy.
- Redressibility? Plaintiffs are challenging only claims for broad composition, isolated BRCA1/2, broad method, not specific probe/primer claims. Even if they won on challenged claims, they couldn't actually practice the invention. Issue: 1st raised at CAFC.

Myriad (consequences)

- Big issue for biotech companies, Amgen, etc.
- US PTO policy is currently unchanged and continue to issue “isolated genomic DNA.” But DOJ/US gov’t position?
- Is reversal of >20 years US PTO practice a taking?
- What about chemical differences between “isolated DNA” and “native chromosomal DNA”?
- If DC upheld, how will US PTO and courts evaluate obviousness of cDNA, vectors?
- Regardless of CAFC outcome, SCt review likely.

About the Presenter

Dr. Nathan Letts has nearly 20 years of experience in life science patent law. Dr. Letts is admitted to practice before the US PTO, NY, NJ and NC Bars. He currently works as a Sr Counsel at The Eclipse Group in North Carolina. He received a PHD in organic chemistry from Columbia University under Ronald Breslow. He received JD from Fordham Law School. He has worked at Cooper & Dunham LLP as a Scientific Advisor and Pennie & Edmonds (now Jones Day) as a Sr Associate in their biotech/pharma group. From 2001-2007 he was sole in-house counsel at diaDexus, Inc. in S. San Francisco where he was VP IP & Licensing. Contacts: 919.313.6167 or npl@eclipsegrp.com

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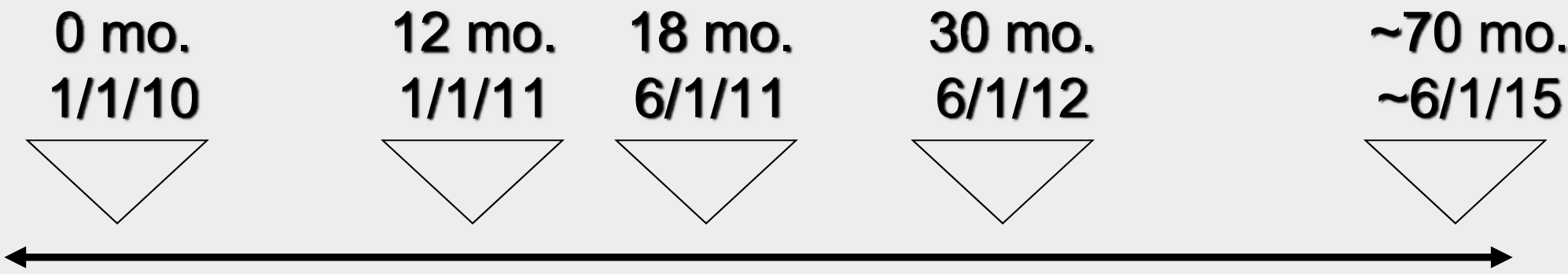
Slides on US PTO process/costs

Patent Timeline/Costs



	Prov.	PCT	Pub.	Nat. Stage	Issue
Govt fees	$220	$3-7K		$2/25/35K US/EP.JP/Maj markets	$2-250K
US Legal fees	$5-15K drafting			$5-10K amending	

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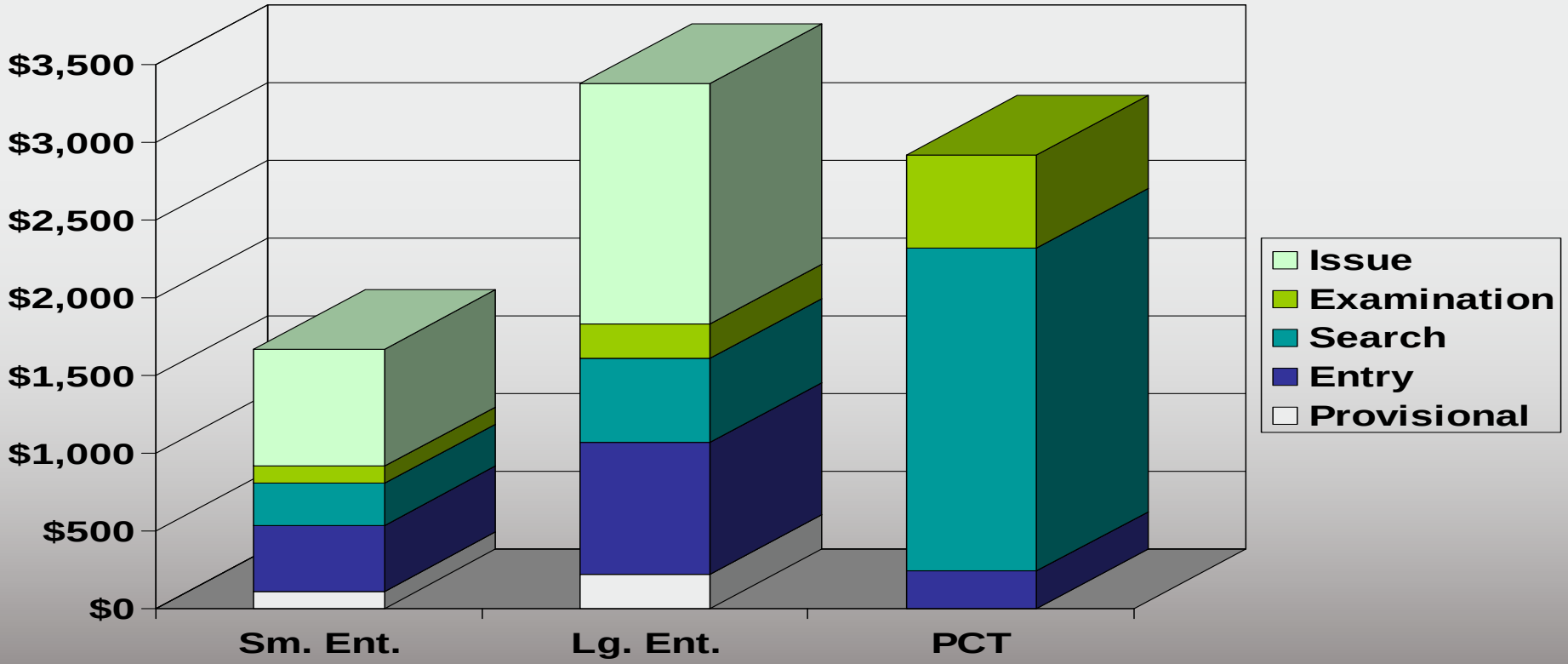
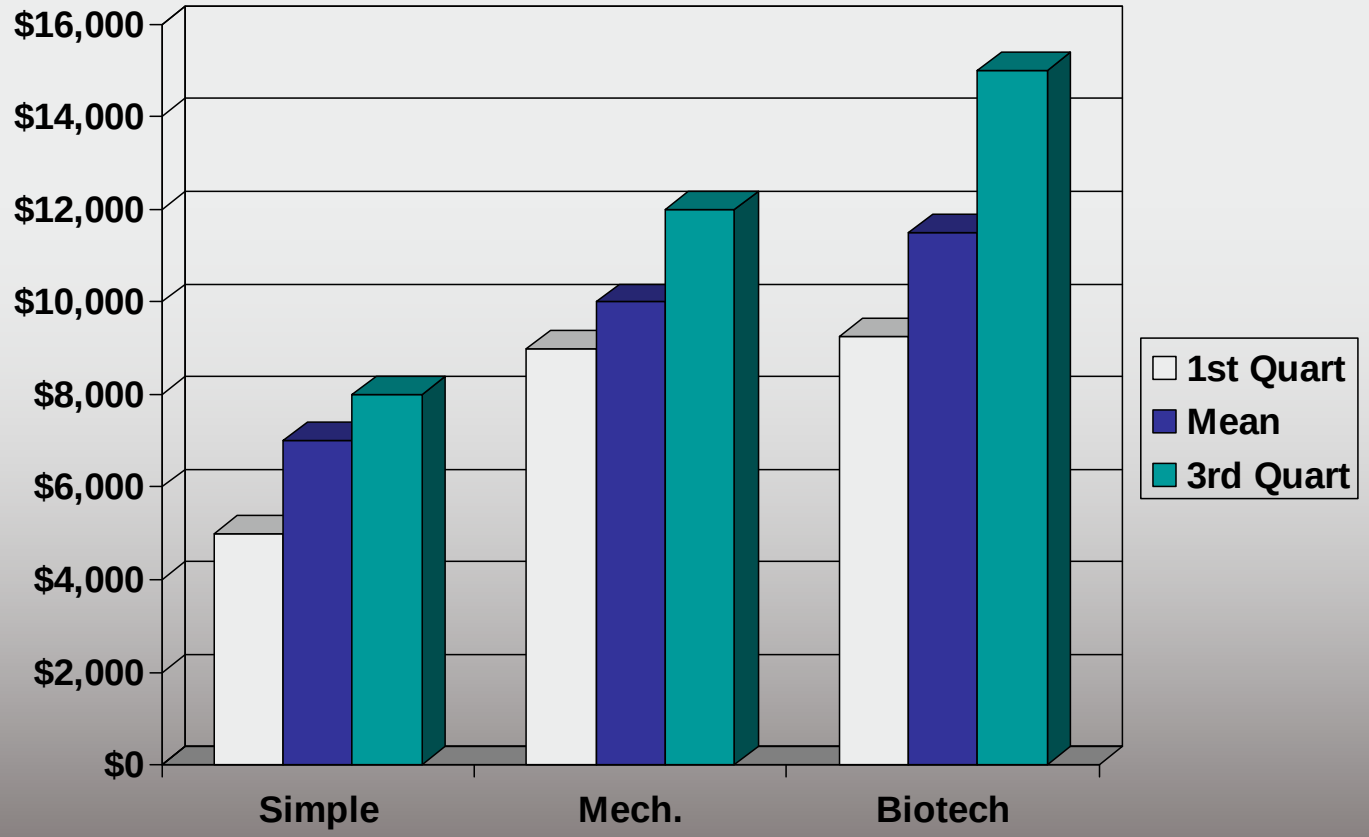
PATENT COSTS: US PTO fees



US PTO website www.uspto.gov (accessed Aug. 2010)

PATENT COSTS:

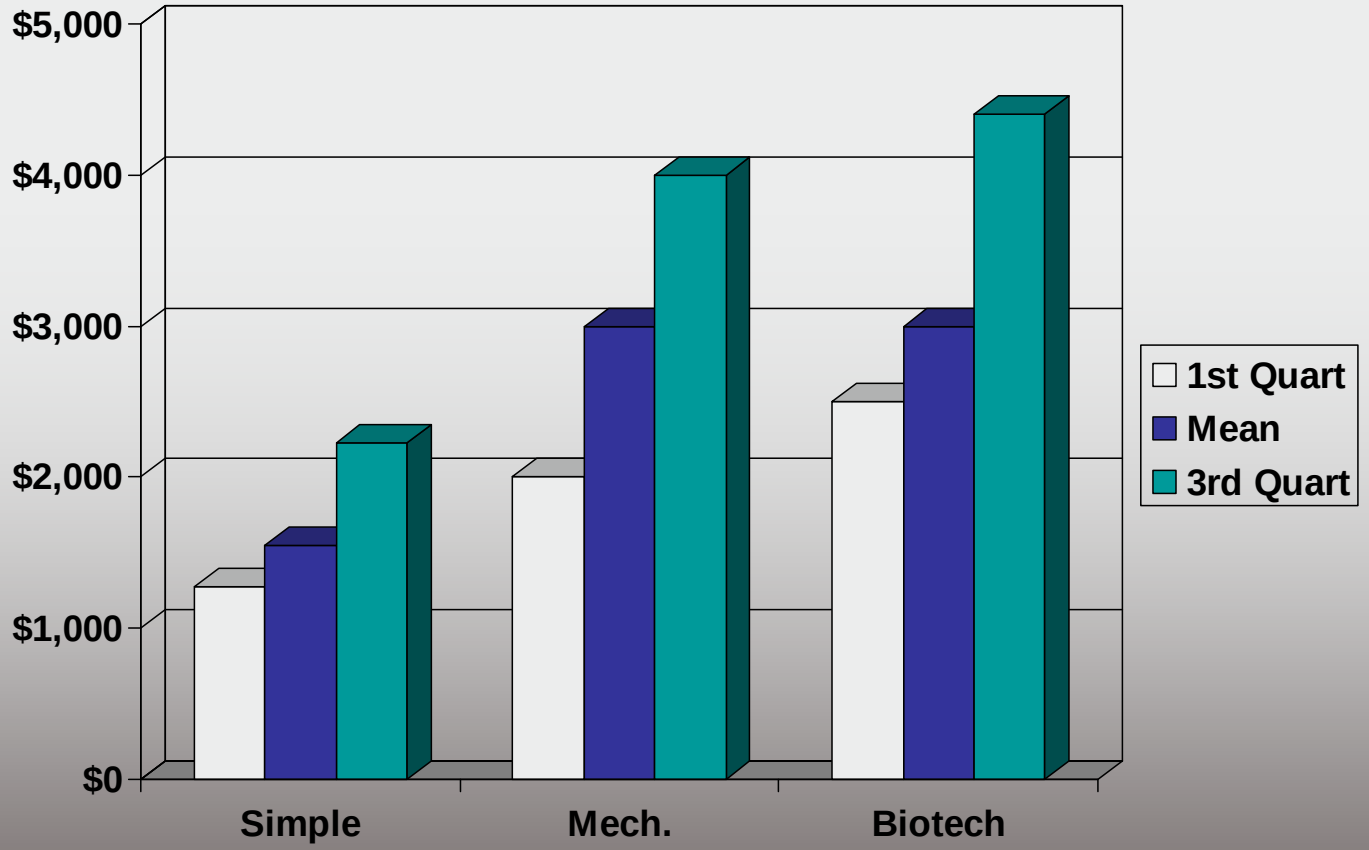
Preparation & Filing



Source: American Intellectual Property Law Assn.
"Report of the Economic Survey 2009" pages I-110-112

PATENT COSTS:

Amendment/Argument



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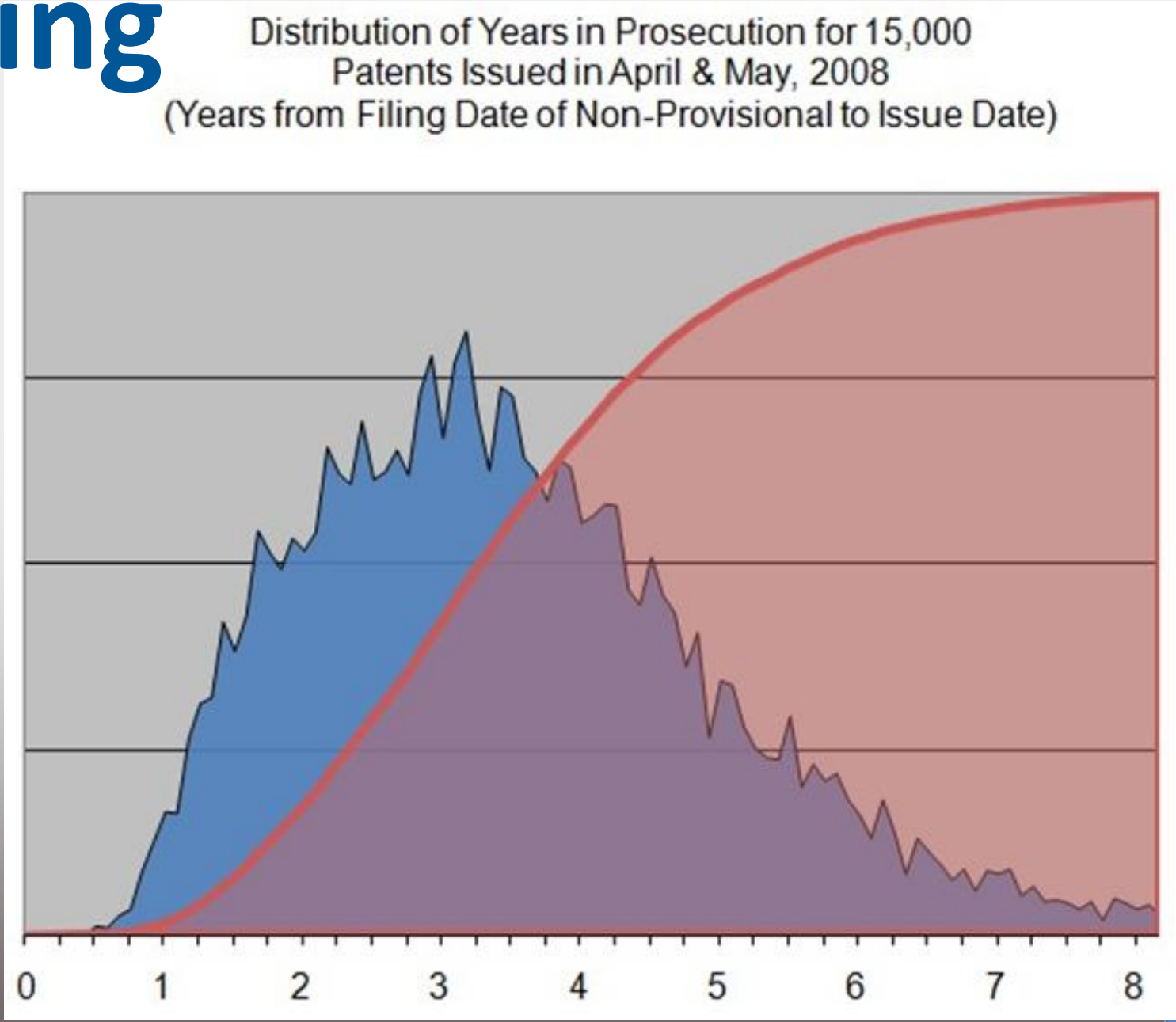
Timing



Source: PATENTLYO Blog (http://www.patentlyo.com/patent/2008/06/patent-prosecut.html)