FDA History and Intellectual Property

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Reminders

- Updated syllabus online:

http://bit.ly/NUSLDrugLaw

- Trouble with access to edX courses?

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Online Resources

- HarvardX massive open online course (MOOC), "#HarvardXFDA: The FDA and Prescription Drugs—Current Controversies in Context," available at: http://bit.ly/HarvardXFDA.
- For the IP session, videos are available from the PennX MOOC, "Intellectual Property Law and Policy: Part 1," available at: http://bit.ly/PennXIP.
- For the Opioids sessions, videos are available from the HarvardX MOOC, "The Opioid Crisis in America," http://bit.ly/OpioidX.

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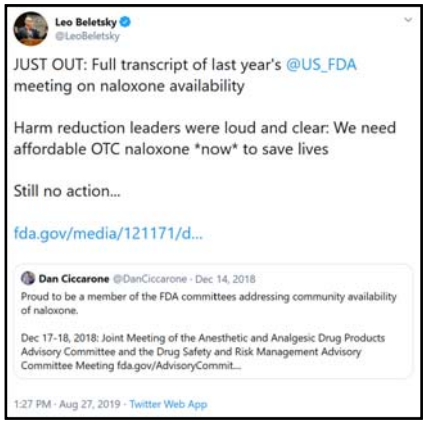

Current Events in Drug Law

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Debates

- Debate 1: Prescription Drug User Fees (September 11, 2019)
- Debate 2: Off-Label Promotion (September 23, 2019)
- Debate 3: OTC Naloxone (October 16, 2019)
- Debate 4: Should the FDA be independent? (October 28, 2019)

- All students should come to class prepared to debate if called upon

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Current Events in Drug Law

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Public Comment Brief

- Review the docket announcement and related materials for the Proposed Rule, "Tobacco Products; Required Warnings for Cigarette Packages and Advertisements." (Docket No. FDA-2019-N-3065-0001).
- Consult relevant legal, regulatory, and public health material to educate yourself about the context and implications for the proposed action.
- A structured "public comment" brief (5-6 pages) will be due before the start of class on Wednesday, October 2, 2019.

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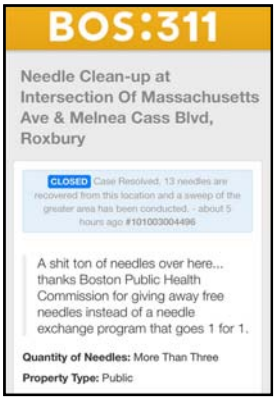

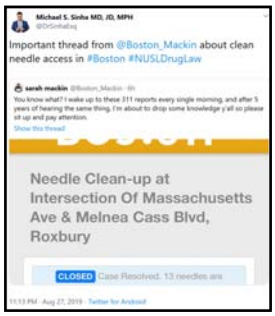

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#NUSLDrugLaw on Twitter

2. Attendance and Engagement: This component of the evaluation is based on: A. class attendance and punctuality (5%), B. contribution to in-class structured policy debates (10%, more information here); and C. participation and demonstrated engagement with the subject matter as evidenced by participation during class, during office hours, and at least twice weekly on Twitter (at #NUSLDrugLaw [optional but encouraged]) (5%).

- Be sure to tag the following in your tweets: @DrSinhaEsq #NUSLDrugLaw
- Need help getting started on Twitter? Schedule time during office hours!

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Final Paper

- The final paper on a pre-approved topic should be 18-24 pages in length and contain appropriately formatted BlueBook references.
- A proposal outlining the topic significance, key questions, expected outcomes and preliminary sources will be due before class on Thursday, September 12, 2019. Please clear the topic with Dr. Sinha prior to beginning the proposal. Use the Hutt book as a resource for project ideas—a lot of great topics not covered in this class.
- *The final assignment will be due before 3PM on Friday, November 15, 2019.*

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Historical Background

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Any questions from the FDA videos?

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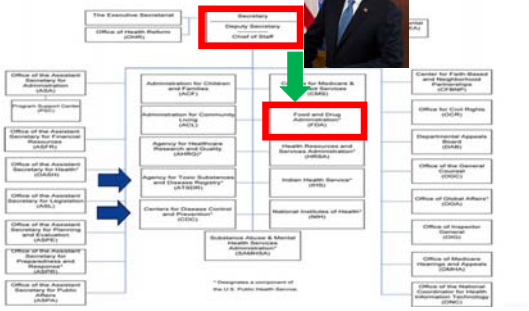
HHS Organization



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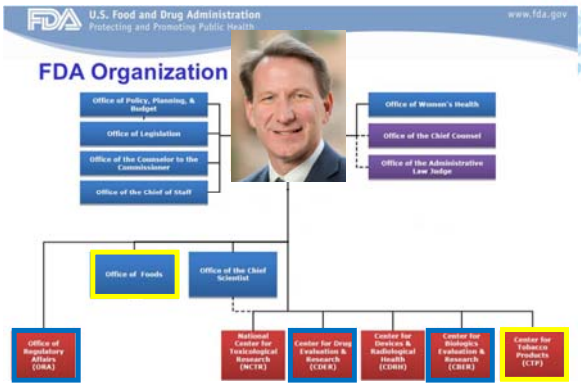

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Some important laws related to the FDA

- Pure Food and Drug Act (1906) – "snake oil salesmen"
- Food Drug and Cosmetic Act (1938) – elixir sulfanilamide
- Kefauver-Harris Amendment (1962) – thalidomide
- Orphan Drug Act (1983) – rare diseases
- Hatch-Waxman Act (1984) – pathway for generic drugs
- Prescription Drug User Fee Act (1992) – "regulatory capture"
- FDA Modernization Act (1997) – pediatric research
- FDA Amendments Act (2007) – postmarket research (Vioxx)
- Biologics Price Competition and Innovation Act (2009) – biologics

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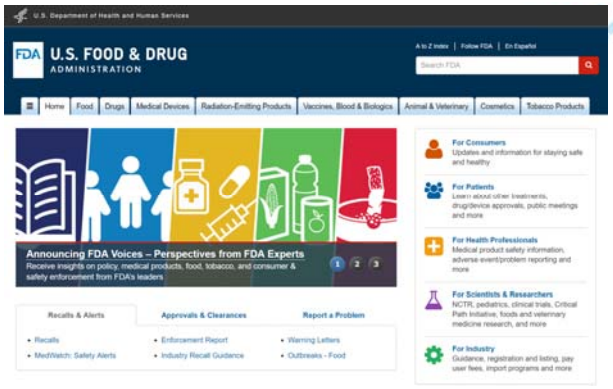

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Clinical Review & Education

JAMA Internal Medicine | Special Communication | HEALTH CARE POLICY AND LAW

Determinants of Market Exclusivity for Prescription Drugs in the United States

Aaron S. Kesselheim, MD, JD, MPH; Michael S. Sinha, MD, JD, MPH; Jerry Avorn, MD

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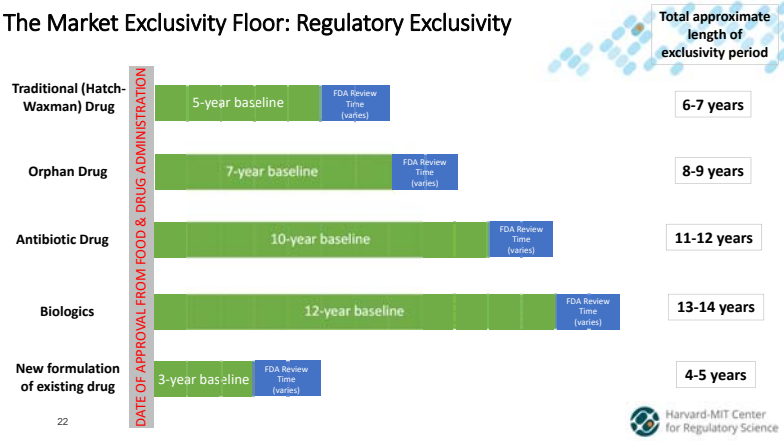
The Market Exclusivity Floor: Regulatory Exclusivity



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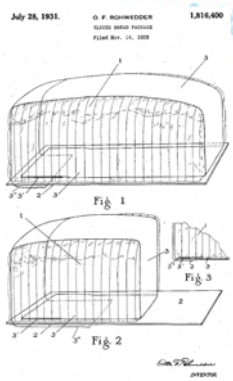
The Market Exclusivity Ceiling: PATENTS!

- Issued by the US Patent and Trade Office (USPTO)
- 20 years for inventions that are novel and non-obvious
- Allows inventors to EXCLUDE others (unlike trade secrets)
- Requires COMPLETE DISCLOSURE of invention on the patent itself
- Drug companies often add to their portfolio by evergreening
  - Secondary patents (e.g., salts, metabolites)
  - Tertiary patents (parts of a device)



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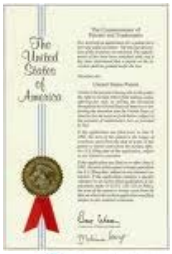
Patents

- Right to exclude others from making, using, or selling the invention without inventor's permission
  - **NOT a right to make, use, sell, offer for sale or import!**
- Time limitation
  - Utility patents → 20 years from filing
  - Design and Plant patents → 14 years from issue
- Geographic limitation to right
  - Patent is effective only in country that grants the patent



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Why Grant Patent Rights?

- Provide incentives for innovation
  - Reward invention and success
  - Provide financial compensation to cover R&D, opportunity costs, etc.
  - Encourage future investment
- Encourage public disclosure of innovations

Inventor

- Must have contributed to the subject matter of the claims
- Joint inventors – each inventor must have contributed to the subject matter of a claim
- Inventorship ≠ Authorship
- Only individuals (not corporations) can be inventors for U.S. patents
  - But rights can be assigned away

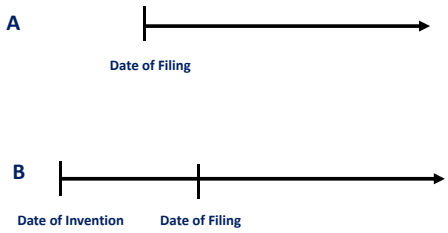
First to Invent v. First to File

Inventor with earliest date of invention is entitled to patent (old U.S. system)

vs.

Inventor with earliest patent filing date is entitled to patent (rest of world, now current U.S. system)

First to Invent v. First to File

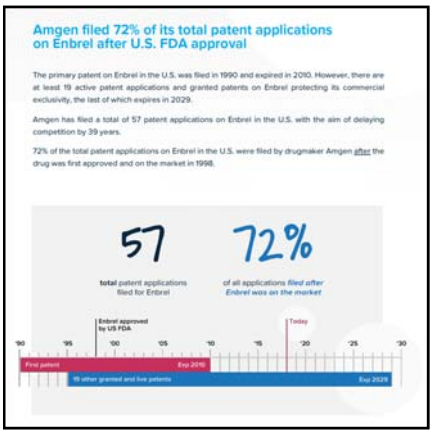


Filing Date

- Filing Date – earliest date that the application for patent was filed
  - Important for determining what counts as prior art
  - Important for securing rights to patent
  - Important for determining date that patent expires
    - For applications filed on or after June 8, 1995, the patent term is 20 years from the filing date
    - For applications that were filed before June 8, 1995, the patent term is 17 years from the issue date

Filing Date

- Enbrel's main patent has already expired. But the drug is now protected by two "submarine patents," so called because they winded their way through the patent office over a long period of time, hidden from view.
- Even though the inventions involved were made in the early 1990s, the patents were not granted until 2011 and 2012 and last until 2028 and 2029.
- If those patents hold, by 2029, Enbrel will have been on the market without generic competition for 31 years.



Anatomy of a Patent – Front Page

US005443036A

United States Patent [19]
Amiss et al.

[11] **Patent Number: 5,443,036**
[45] **Date of Patent: Aug. 22, 1995**

[54] **METHOD OF EXERCISING A CAT**

[76] **Inventors: Kevin T. Amiss**, 255 S. Pickett St., #301, Alexandria, Va. 22304; **Martin H. Abbott**, 10549 Assembly Dr., Fairfax, Va. 22030

[21] Appl. No.: **144,473**
[22] Filed: **Nov. 2, 1993**
[51] **Int. Cl.**[6] **A01K 29/00**
[52] **U.S. Cl.** **119/707**
[58] **Field of Search** 119/702, 707, 174, 905; 446/485

[56] **References Cited**
U.S. PATENT DOCUMENTS

3,877,171	4/1975	Stoop et al.	446/485
4,208,701	6/1980	Schock .	
4,231,077	10/1980	Joyce et al. .	
4,757,515	7/1988	Hughes .	
4,761,715	8/1988	Brooks .	
4,926,438	5/1990	Maes et al. .	
4,985,029	1/1991	Hoshino .	
5,036,097	10/1991	Meyers .	
5,194,007	3/1993	Marshall et al. .	

OTHER PUBLICATIONS

Carayan et al., "Effects of tianeptine on the Performance of a reaching movement in a cat", *Psychopharmacology*, vol. 104, Issue 3, Berlin, 1991, pp. 328–336.
Levesque et al., "Visual 'cortical-recipient' and tectal-recipient pontine zones play distinct roles in cat visuomotor performance", *Behavioral Brain Research*, vol. 39, Netherlands, 1990, pp. 157–166.

Primary Examiner—Todd E. Manahan

[57] **ABSTRACT**

A method for inducing cats to exercise consists of directing a beam of invisible light produced by a hand-held laser apparatus onto the floor or wall or other opaque surface in the vicinity of the cat, then moving the laser so as to cause the bright pattern of light to move in an irregular way fascinating to cats, and to any other animal with a chase instinct.

4 Claims, 1 Drawing Sheet

Anatomy of a Patent – Figures

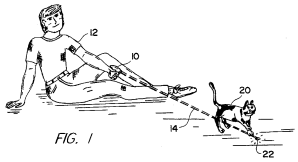


FIG. 1

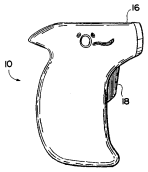


FIG. 2

Anatomy of a Patent

GOAL: provide the reader with enough information to enable one skilled in the art to understand the invention

Background of the Invention

Summary

Description of the Figures

Description of the Preferred Embodiments

Anatomy of a Patent - Claims

- Define the scope of protection of the patent
- Can be amended during prosecution of the patent, but only with support from the detailed description and drawings
- 2 types of claims
  - Independent
  - Dependent

Anatomy of a Patent - Claims

What is claimed is:

- A method of inducing aerobic exercise in an unrestrained cat comprising the steps of:
  - directing an intense coherent beam of invisible light produced by a hand-held laser apparatus to produce a bright highly-focused pattern of light at the intersection of the beam and an opaque surface, said patter
  - selectively redirecting said beam out of the cat's immediate reach to induce said cat to run and chase said beam and pattern of light around an exercise area.
- The method of claim 1 wherein said bright pattern of light is small in area relative to a paw of the cat

Requirements for Patentability

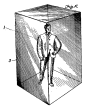
- **Patentable subject matter**: (35 U.S.C. § 101)
- **Utility**: usefulness (35 U.S.C. § 101)
- **Novelty**: not anticipated in "prior art" (35 U.S.C. § 102)
- **Non-obviousness**: non-trivial extension of the known (35 U.S.C. § 103)
- **Disclosure and enablement**: must describe invention with sufficient particularity to enable one skilled in the art to "practice" it (35 U.S.C. § 112)

Patentable Subject Matter § 101

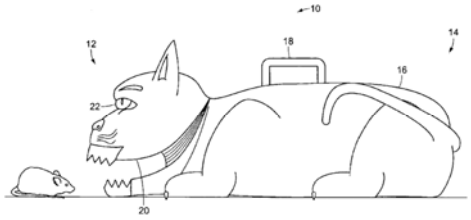
- 35 U.S.C. § 101: Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
- "Anything under the sun that is made by man"
  - Patentable if made, modified, or transformed by man
  - No morality component in US

What *can* be patented (utility)

- Process (method)
- Machine
- Manufacture (article)
- Composition of matter (chemical)
- A new use or improvement for any of the above…

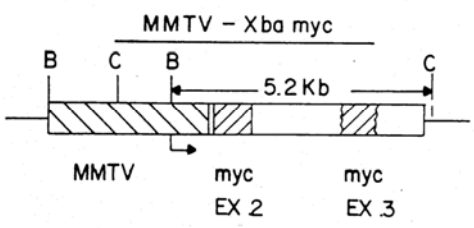


A better mousetrap



U.S Patent No. 6,865,843 (2005)

A better mouse



U.S Patent No. 4,736,866 (1988)

What *cannot* be patented

- Purely mental processes
- Mathematical Algorithms
- Scientific Principles
- Naturally Occurring Things
- Human Beings

Utility § 101

- 35 U.S.C. § 101: Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and **useful** improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.
- Test: must be practical and specific, not merely of scientific interest
  - A new compound, gene, or antibody, without any known pharmacological activity or other practical utility, will not normally be patentable.

Novelty § 102

- A single "prior art" reference
  - "prior art" - any information that has been made available to the public in any form (e.g., patented, described in a printed publication, or in public use, on sale, or otherwise available to the public) before the filing date that might be relevant to a patent's claims of originality
- Test: is every element of your invention in the prior art reference

Obviousness § 103

- One piece of prior art or combination of 2 or more
- Combination is obvious to one skilled in the art
- Test:
  - Determine scope and content of prior art
  - Determine level of ordinary skill in the art at time the invention was created
  - Determine difference between prior art and claimed invention

Disclosure & Enablement § 112

- Must describe invention with sufficient particularity to enable one skilled in the art to "practice" the invention
- Description defines the invention, providing as much information as possible
- The more detail, the better!

Patentability v. Infringement

- Test for patentability:
  - Patentable subject matter
  - Utility
  - Novel
  - Non-obvious
  - Disclosure and enablement
- Test for infringement: Whether your invention satisfies each and every element of an issued patent claim

Patentability v. Infringement

- Basic idea: as long as your invention has each limitation/element of the prior art reference, it infringes
- Remember, a patent right is a negative right – it is a right to exclude others from making, using or selling your invention
  - It is not a positive right
- Possible solution:
  - Design around
  - Licensing

Consequences for Patent Infringement

- Money Damages

- Injunction

- U.S. Court of Appeals

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Defenses To Patent Infringement

- Non-infringement: accused product does not literally possess each and every claimed element or its equivalent
- Invalidity: patent is invalid if its claims are unpatentable
- Unenforceable: inequitable conduct
  - Intent to deceive USPTO
  - Material information

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Exceptions

- **Experimental Use**: "For amusement, to satisfy idle curiosity, or for strictly philosophical inquiry" *(Madey v. Duke)*
- **Safe Harbor**: 35 U.S.C. § 271(e)(1) "solely for uses reasonably related to the development and submission of information under a Federal law" *(Merck KGaA v. Integra Lifesciences)*
- **Exhaustion**: *(Bowman v. Monsanto)*
- **Medical Practitioner**: 35 USC 287 (c)(1) with respect to a medical Practitioner's performance of a medical activity

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Congressional Legislation

- America Invents Act – signed Sept. 16, 2011
- Biggest change to patent law since 1952
- 2 Main Changes
  - Switch from first-to-invent to first-to-file system
  - Expands post-grant opposition review

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Patents in the Supreme Court

- **Diamond v. Chakrabarty (1980):** "anything under the sun that is made by man" is patentable
- **eBay v. MercExchange (2006):** An injunction should not automatically issue based on a finding of patent infringement (federal court must weigh the four-factor test)
- **KSR v. Teleflex (2007):** obviousness is a matter of common sense
- **Prometheus v. Mayo (2012):** The patent claims say nothing significantly more than "apply the natural laws that they describe" and that simple additional instruction, by itself, is insufficient to transform an otherwise unpatentable claim into a patentable one.
- **AMP v. Myriad Genetics (2013):** Isolated gene sequences (the DNA sequence for the BRCA gene) are not patent-eligible but synthetic sequences (the cDNA sequence) are.

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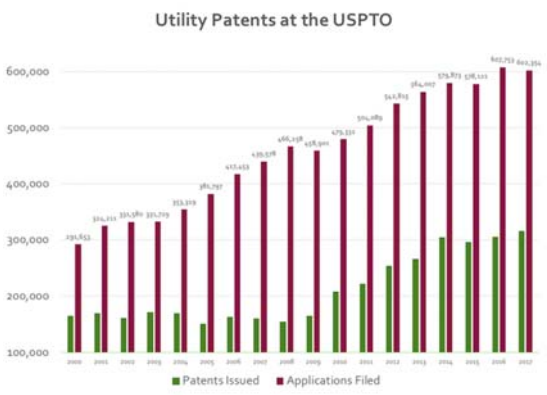

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Bayh-Dole Act

- Allowed Universities to retain title to inventions
- Codified in 35 U.S.C. § 200-212
- Sponsored by:
  - Senator Birch Evan Bayh of Indiana
  - Senator Bob Dole of Kansas

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Requirements

University must:

- Provide the federal government with a free license to the invention
- Pursue patenting and commercialization of inventions
- Share a portion of any revenue received from licensing the invention with the inventor
- Give licensing preference to small companies (later modified)
- Requires that the product must be substantially manufactured in the U.S.

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Goals of Bayh-Dole

- Promote use and development of federally funded inventions
- Encourage creation and growth of small businesses
- Promote U.S. manufacturing
- Promote and protect government rights in federally funded inventions

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Results of Bayh-Dole

- Impact on university patenting/licensing
  - Over 21,856 invention disclosures received by U.S. Universities in 2011
  - Over 19,905 patent applications filed for U.S. Universities in 2011
  - Over 4,700 patents issued by 2011 (compared to 250 before 1980)
  - Over 4,899 license agreements executed in 2011
  - License agreements with 141 different institutions
  - Over $1.8 Billion dollars annually in gross license income received
- "Most inspired piece of legislation to be enacted in America in over a half-century" – The Economist

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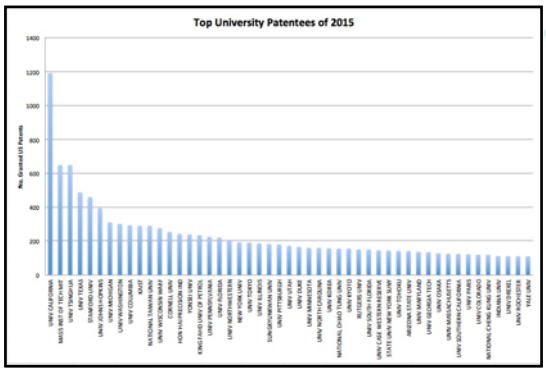

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Licensing Income

Rank	Institution	2011 Research Expenditures	2011 patents Issued	2011 Licensing Income
1	Northwestern U.	$484,149,349	67	$191,541,162
2	U. of California System	5,418,601,941	343	182,049,620
3	Columbia U.	714,343,087	88	146,319,455
4	New York U.	430,752,000	64	142,202,157
5	Princeton U.	192,940,000	33	115,206,000
6	Massachusetts Inst. Of Technology (MIT)	1,490,429,000	174	76,120,000
7	U. of Washington/Wash Res.	966,817,063	70	67,362,185
8	Stanford U.			66,797,246
9	U. of Texas System	2,546,669,877	156	65,359,377
10	U. of Wisconsin-Madison/WARF	1,111,641,832	156	57,730,000
11	Wake Forest U.	187,598,965	15	45,733,291
12	U. of Rochester	407,244,000	27	41,813,373
13	U. of Utah	410,305,757	47	37,054,745
15	U. of Florida	559,156,034	86	29,493,522
26	Harvard U.	833,200,000	60	13,811,527
All	**Totals**	**$55,074,821,326**	**4,296**	**$1,813,968,412**

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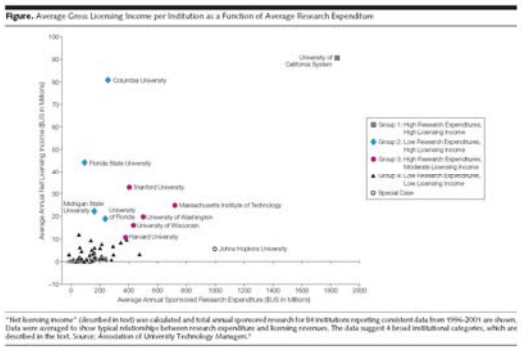
Licensing Income



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Criticisms of Bayh-Dole

- University patenting growing before 1980, and no change in slope after legislation
- May have hastened patenting and licensing by universities that had previously avoided these practices
- Universities patenting less important innovations
- Universities are bad licensers
  - Median income: $1.13 million
  - Licensing returns modest compared to investment

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Stanford v. Roche (2011)

- Facts: Dispute over patents covering diagnostic tests for HIV infection, originally owned by Stanford University, and HIV diagnostic tests sold by Roche.
- When the researcher joined the faculty of Stanford, he, like all scientific personnel at companies and research institutions, signed an agreement in which he agreed that his employer would own any inventions he made.
- Holding: The Supreme Court held that U.S. patent rights have always (since 1790) initially vested in "the inventor" and that the non-specific language of the Bayh-Dole Act does nothing to change the original setup

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March-In Rights

- Government has right to "require the contractor [university], an assignee or exclusive licensee of a subject invention to grant a non-exclusive, partially exclusive, or exclusive license in any field of use to a responsible applicant or applicants, upon terms that are reasonable under the circumstances, and if the contractor, assignee, or exclusive licensee refuses such a request, to grant such a license itself."
- Allows the government to ignore the exclusivity of a patent and practice the invention itself, or have a third party practice the invention on the government's behalf

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Requirements

- Government must justify why action is necessary
  - Contractor or assignee has not taken, or is not expected to take within a reasonable time, effective steps to achieve practical application of the subject invention in such field of use
  - Needed to alleviate health or safety needs
  - Meet requirements for public use specified by Federal regulations

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Examples of March-In Rights

- Government never has exercised its March-In Rights
- Anthrax attacks of 2001
  - Bayer had patent rights to the drug ciproflaxin, which was used to treat anthrax
  - As the anthrax scare continued and fear of a full-blown epidemic increased, the federal government contemplated marching in and acquiring Bayer's patent rights to the drug ciproflaxin in order to benefit the health and safety of the public

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In the Case of Xalatan

- Facts:
  - Pfizer had patent to glaucoma drug
  - Sold in U.S. at 2-5 times the prices in other high income countries
- Result:
  - NIH denied petition; Pfizer has met the standard for achieving practical application
  - No evidence that health and safety were not adequately met by Pfizer
  - NIH should not address the issue of whether drugs should be sold in the U.S. for the same price as they are sold in Canada and Europe, only Congress

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In the Case of Norvir

- Facts:
  - Abbott Labs had patent to ritonavir (Norvir), used in treatment of AIDS
  - Abbott raised the price of Norvir by 400% in U.S.
  - Abbott refused to license Norvir to another company for purpose of providing protease inhibitors co-formulated with ritonavir
- Result:
  - NIH denied the petition
  - Abbott has met the standard for achieving practical application
  - No evidence that health and safety were not adequately met by Abbott
  - NIH should not address the issue of drug pricing, only Congress

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PHARMACEUTICALS & PATENTS

By Tahir Amin and Aaron S. Kesselheim

Secondary Patenting Of Branded Pharmaceuticals: A Case Study Of How Patents On Two HIV Drugs Could Be Extended For Decades

EXHIBIT 1

Patents And Applications Covering Ritonavir And Lopinavir/Ritonavir

Patent categories	Ritonavir	Lopinavir	Lopinavir/ritonavir	Ritonavir and/or lopinavir with other compounds	Total
Total	—[a]	—[a]	—[a]	—[a]	210
Base compound or active ingredient	1	1	0	0	2
RELATED CHEMICAL STRUCTURES AND COMPOSITIONS OR FORMULATIONS (61)					
Composition and formulation[b]	18	9	15	7	49
Intermediate compounds	13	9	0	0	22
Polymorphs	2	2	0	0	4
Prodrugs	2	2	1	1	6
MANUFACTURING METHODS AND PROCESSES (68)					
Processes[c]	36	27	5	0	68
METHODS OF TREATMENT OF HIV INFECTION AND OTHER DISEASES (31)					
First method of treatment or administration for HIV	4	4	5	5	18
New uses for HIV or other diseases	6	1	1	5	13
GENERAL PATENTS (28)					
General formulations	—[a]	—[a]	—[a]	—[a]	5
Processes and methods for preparing general formulations	—[a]	—[a]	—[a]	—[a]	11
Other technologies or test systems	—[a]	—[a]	—[a]	—[a]	12

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PLOS

Polymorphs and Prodrugs and Salts (Oh My!): An Empirical Analysis of "Secondary" Pharmaceutical Patents

Amy Kapczynski[1*], Chan Park[2*], Bhaven Sampat[3,4]

Methodology/Principal Findings: We read the claims of the 1304 Orange Book listed patents on all new molecular entities approved in the U.S. between 1988 and 2005, and coded the patents as including chemical compound claims (claims covering the active molecule itself) and/or one of several types of secondary claims. We distinguish between patents with any secondary claims, and those with only secondary claims and no chemical compound claims ("independent" secondary patents). We find that secondary claims are common in the pharmaceutical industry. We also show that independent secondary patents tend to be filed and issued later than chemical compound patents, and are also more likely to be filed after the drug is approved. When present, independent formulation patents add an average of 6.5 years of patent life (95% C.I.: 5.9 to 7.3 years), independent method of use patents add 7.4 years (95% C.I.: 6.4 to 8.4 years), and independent patents on polymorphs, isomers, prodrug, ester, and/or salt claims add 6.3 years (95% C.I.: 5.3 to 7.3 years). We also provide evidence that late-filed independent secondary patents are more common for higher sales drugs.

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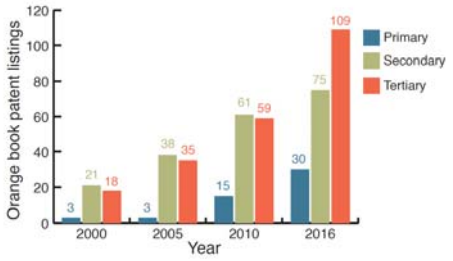
Tertiary patenting on drug–device combination products in the United States

Reed F Beall & Aaron S Kesselheim

Drug–device combination products are becoming increasingly prevalent, with many lasting years beyond the expiration date of primary and secondary patents on the drug itself.



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Any questions?

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