Lecture # 9 -- Strategic Patenting/Medical Biotechnology

I. Strategic Uses of Patents (continued)

- *NY Times* article on Apple provides a good example of patent thickets
  - After paying royalties to a company that held a broad patent for a "portable music playback device" similar to the iPod, Apple adopted a strategy of filing patents whenever possible
    - Number of patents filed per year by Apple increased by factor of ten over the past decade.
    - It wasn't necessary to have a finished product, but just an idea.
    - Raises the question of what should be patentable?
      - Should a concept, rather than a tangible product, be patentable?
      - What are the boundaries on a patent of an idea?
        - There are many similar ways to write a program? If the idea is patented, are alternative ways all infringements?
      - Note that the patent application for Siri was rejected and revised 10 times before grant in December 2012
        - When first file, it was just an idea. Even the iPhone itself did not exist.
        - Apple continually made small adjustments to the wording to keep the application in force
          - By doing so, these continuations allow Apple to keep the initial priority date from 2004.
        - Apple sued Samsung for violating this patent in February 2013
          - Note that, since the patent wasn't granted until December 2012, Samsung's research on similar technologies would have predated the patent
          - By keeping the application pending, Apple provides uncertainty for inventors working on competing technology.
- Question: how do patent thickets affect small firms?
  - Enforcement costs are high
    - Over $20 billion spent on litigation in smartphone industry in 2012-13
    - Lawsuit by company that had a patent on voice recognition technology challenged cost $3 million.
    - For a small firm with few patents, difficult to defend them
  - Large firms use patents defensively
    - Apple acknowledges not all applications will succeed
    - But, if filed, keep others from filing similar patents

        - Note that, if Apple is granted a bad patent, it needs to be challenged to be overturned.
            - Can small companies afford to do that?
- Case study: the semiconductor industry
    - Semiconductor patents have increased rapidly.
    - A study by Bronwyn Hall and Rosemarie Ham Ziedonis suggests that "patent portfolio races" are a primary cause.
        - Although patents up, investment in R&D not up as much.
        - Patent/R&D ratio rose from 0.3 patents per $1 million R&D to 0.6 patents per $1 million R&D.
            - This could mean that the industry is patenting more, or that their research is becoming more productive.
                - Using patent citations to check quality, they find that citations per patent fall since 1984, although not by much once self-citations are removed.
                - Field interviews with employees also suggest research productivity has fallen.
- Complex Industries
    - An important feature of the semiconductor industry is complexity.
        - For complex technologies, a patent is not valuable unless you also have access to related technologies.
        - Thus, firms patent to gain access to related technologies.
            - For example, IBM, Motorola, and Sun Microsystems frequently cross-license patents.
                - Such agreements may hinder competition.
            - Similarly, some companies have created patent pools, in which groups of patents from two or more companies are grouped together and licensed.
                - DOJ looks suspiciously at this.
    - Although patents are used for defensive purposes, they are less likely to spur innovation in complex industries.
    - What does spur innovation?
        - Benefits of lead time
        - R&D tax credits
        - Special treatment from government
            - E.g. government sponsored collaborative research, non-tariff barriers to protect strategic industries.
- Standard essential patents
    - Standards are important for technologies such as Wi-Fi
        - Allow devices to communicate, even if made by different companies
    - Once a standard is set (by bodies such as the Institute of Electrical and Electronics Engineers), patent holders are in position to demand royalties
    - To avoid "hold up", companies are obliged to license at reasonable rates
        - Known as "Reasonable and non-discriminatory" (RAND)

        - E.g., charge a few cents per unit of product using the technology (e.g. per cell phone)
    - However, RAND is not defined
        - Has led to suits about what is reasonable
        - A federal judge recently considered the following criterion:
            - What royalties are already being paid by others?
            - What royalties are being paid for similar patents
            - What is the patent holder's normal royalty policy
            - What is the value of the technology to its users

II. Biotechnology and the Drug Industry

- Biotechnology refers to techniques that use living organisms to make or modify products. Examples include:
    - Genetically modified crops
        - Includes both older varieties such as hybrid rice and corn modified to increase productivity, and newer modifications designed to be resistant to pests and disease.
    - Pharmaceuticals
    - Food processing
- In this lecture we'll primarily look at issues raised by the development of new drugs and research on the human genome. We'll hold off on discussion of pharmaceuticals in developing countries until the policy simulation.
- Biotechnology is an important industry to study because:
    - Biotechnology in the U.S. is the result of both policy choices and institutional environment that enabled U.S. success
    - There are close links between advances in science and advances in the industry.
        - As a result of this link, issues about what should be considered "intellectual property" are prominent.
            - Should the human genome be patented?
            - Should medicines derived from plants be patented?
    - Links between the public and private sector are important
    - There are many ethical issues
        - Is it right to patent genes?
        - Should stem cell research be allowed?
- Technological change in R&D has evolved through the "technology of R&D."
    - The process of doing the R&D itself has changed over time.
- The U.S. Life Sciences Innovation System
    - An innovation system includes the various institutions and actors leading to the creation and development of new technology.
    - Early history (1850-1945) – the pre-R&D period
        - Pharmaceuticals initially developed in dyestuff industries of Switz. and Germany
        - Soon, independent pharmaceutical companies grew in U.K. and U.S.

        - Little formal effort on R&D.
    - Little testing for safety done
    - Post WWII – shift to in-house R&D.
- Pre 1970s
    - Molecular biology and pharmaceutical industry were largely separate
    - Pharmaceuticals used a “random screening” research approach
        - Pharmaceutical companies developed “libraries” of compounds that they tested for promising effects.
        - Note that still happens at times today: Viagra was initially developed for hypertension.
        - Commercialization of penicillin showed that drug development could be profitable.
            - Innovation was highly profitable during this period.
            - Reasons for success
                - Research successful because:
                    - Large untapped opportunities
                    - Large unmet needs
                - Research profitable because:
                    - Difficult to imitate random screening=>1st mover advantage
                    - Patent protection was strong
                    - Vertical integration of research, manufacturing, and marketing kept everything in-house.
    - Molecular biology focused on fundamental theoretical and empirical research, such as the structure of DNA
        - Research took place in academic departments with little connection to industry
- 1970-1980s: Foundations of biotechnology
    - From the mid-1970s on, developments in physiology, enzymology, pharmacology & cell biology led to better understanding of how drugs worked.
        - Made more sophisticated screening possible.
        - Processes often based on tacit skills
            - Therefore difficult to copy
            - Enhances first mover advantage and discourages copying.
    - Note that the molecular biology process for screening a drug is different
        1. Search
            - Biotech => rational drug design
                - Focusing on knowledge of biochemical pathways of disease.
                - Similarly, genomics focuses on genetic causes
        2. Synthesis

        - Until recently, treatments depended on substances that could be identified and separated from natural sources, or which could be chemically synthesized.
        - Now, new substances can be created.
        - Begins with discovery of rDNA
        - Similarly, gene therapy focuses on identifying a defective gene and fixing it with healthy copies of the same gene.
    3. Screening
        - Mapping the genome has expanded the number of potential targets.
            - However, validating these targets is harder.
        - Now, computers are used to simulate how compounds work together.
        - High costs of development led to partnerships with large existing firms.
            - Prior to this time, the industry was vertically-integrated, and composed of large firms.
            - By the mid-90s, over 1200 small to medium sized research dedicated biotech firms (DBFs) were in place.
                - Note importance of IP is important here. DBFs product is knowledge, rather than the drug.
        - One-third of new molecules currently in development are from biotech companies.
        - Once reaching this stage, these molecules have a better chance of success, because they undergo screening from the large companies before a licensing agreement is reached.
- Key events
    - Development of recombinant DNA technology in 1973
        - Gave researchers ability to change genetic codes
        - Made more sophisticated screening possible.
    - Policy decisions
        - 1980 Diamond v. Chakrabarty Supreme Court decision upheld patents for genetically engineered organisms
        - 1980 Bayh-Dole Act encouraged university patenting, enhancing potential for technology transfer
        - 1979 rule change allowed pension funds to invest in venture capital, increasing the amount available
        - Increased NIH funding
    - Effects of increased scientific funding
        - Began with 1970s War on Cancer

            - Announced in Nixon's 1971 State of the Union address
            - Requested $100 million for cancer research
            - 1971 National Cancer Research Act established the Frederick Cancer Research and Development Center
        - Government R&D supported the development of university departments focused on biosciences
            - Note role of policy shaping institutions
        - In 1970s, only a few researchers had the skills needed to take advantage of rDNA.
        - Since 1970s, PhDs in life sciences have doubled
        - In 1990s, life sciences passed engineering as top field of study in hard sciences
- 1980-1985: Emergence of Life Sciences Innovation System
    - As noted above, life science workforce increased as a result of new funding
    - New blockbuster drugs demonstrated commercial potential of biotech
    - Genetech exemplifies the links between academics and industry that emerged
        - Genetech was founded by a University of California, San Francisco researcher (Herbert Boyer) and venture capitalist.
            - Two early successes were human growth hormone (HGH) and human insulin manufactured using rDNA, rather than extracted from animals
            - Commercialization done through partnerships with private firms (Eli Lily for insulin)
            - Kabi provided $1 million to Genentech support the research, and agreed to pay a percentage of U.S. sales to Genentec
                - Genentech shared this percentage with UCSF and City of Hope hospital.
                - Kabi could send its scientists to Genentech to learn about bacteria expression.
        - In the end, returns on venture capital were low, as only a few researchers were skilled enough to create new products
    - Large academic medical centers also emerged at this time
    - Institutional structures encouraging collaboration between universities and firms began to emerge
    - Why are collaborations (between existing and start-up firms) so important?
        - New drugs require knowledge in many different subfields. It is hard for one firm to internalize all the knowledge
        - Leads to the development of a specialized workforce

        - Also, new knowledge bases are different than medicinal chemistry, so older firms didn't have the institutional capability to work in these areas.
- Because biotech builds on the results of basic science, linkages between university and industry research are particularly strong.
    - Many of the early genetic engineering companies were founded by academic researchers.
    - Many early biotech start-ups closely linked to universities
    - Tacit knowledge was important
        - Proximity is important for the diffusion of tacit knowledge
- Note also that there are many fixed costs to drug development. A small firm would not be able to compete, because of the costs of clinical testing.
- The Role of Regulation
    - Food and Drug Administration (FDA) controls introduction of new products
    - Before clinical trials, firms apply to the Food and Drug Administration (FDA) for permission to begin human testing.
        - Three stages of clinical trials:
            - Stage I focuses on toxicity
            - Stages II and III focus on effectiveness
            - Stage III includes more patients.
        - Once a drug passes the clinical trials, companies apply to the FDA for permission to market the drug.
            - The FDA can accept or reject the application, or can also require more trials.
            - The average time from initial synthesis of a drug to approval is 100 months (8.33 years).
        - Data on success rates:
            - 10,000 molecules screened => average of 250 for pre-clinical testing => 10 to clinical trials => 1 approved
            - Recently more have been rejected at the later stages, after most of the costs have occurred.
        - Regulation both raises costs and lowers returns from a new drug (because of delays getting to market), but also creates barriers to entry

        - These barriers may deter competition.
- 1990s- Mature Life Sciences Innovation System
    - By early 2000s, 25-40% of pharmaceutical sales came from biotechnology
    - Cost per base synthesized fell, partially as a result of polymerase chain reaction (PCR) technology improvements
        - Cost of sequencing genome now below $50,000
    - Complex network structure among research organization. Three key features:
        - University research central
            - Focus on rational drug design
        - Development of specialized biotech firms
            - Mapping the genome has expanded the number of potential targets.
                - However, validating these targets is harder.
            - Now, computers are used to simulate how compounds work together.
            - High costs of development led to partnerships with large existing firms.
                - Prior to this time, the industry was vertically-integrated, and composed of large firms.
                - By the mid-90s, over 1200 small to medium sized research dedicated biotech firms (DBFs) were in place.
            - One-third of new molecules currently in development are from biotech companies.
                - Once reaching this stage, these molecules have a better chance of success, because they undergo screening from the large companies before a licensing agreement is reached.
                - Because of complexity, biomedical research clusters in a few locations: e.g. Boston, Bay Area of CA, San Diego
- Current state of the industry
    - In recent years, pharmaceutical industry R&D expenditures have been rising, while the number of new drugs introduced has been falling.
        - Moreover, few of the drugs introduced are novel.
        - Many are simply “me-too” drugs that address a disease in ways similar to existing drugs.
            - Note that these may still be beneficial, as they provide consumers with choices and lower prices.
                - Patent protection does not prevent similar “me-too” drugs from entering the market.
    - The patents of many profitable drugs are set to expire

        - As an example, Pfizer set to lose $10 billion/year in revenues when Lipitor patent expired in 2011
        - Firms have been struggling to come up with new patented products
            - Firms beginning to lay of R&D workers
            - Will be hard to replace, so that ramping spending back up will be difficult
            - Remaining R&D focused on most profitable options, such as cancer
            - One new area is personalized medicine
        - To adjust, some pharmaceuticals are moving into generics
            - "Branded generics" can be a sign of quality

III. What Led to U.S. Success?

- Key drivers of life sciences innovation system
    - High level and growth of public funding
        - Federal support for life sciences R&D has nearly quadrupled in real terms since 1980s.
            - In contrast, most other funding areas experienced little growth
            - More than 60% of academic R&D expenditures go to life sciences
            - Primarily from NIH and NSF
            - Growth rates were less volatile than other fields during 1990s
                - Allowed for long-term planning
                    - Investment in physical capital, not just short-run expenditures
                    - Sustains upstream science in academics and government labs
            - Growth ended from 1998-2003, began to decline 2003-2008
            - Within NIH, funding targets (e.g. diseases) did vary
    - Slow and steady growth of specialized workforce
        - Increased funding led to more graduate training programs in life sciences
        - Allowed for increased specialization and collaboration
            - Wasn't necessary to master a wide range of skills, allowing for more depth in one or two areas
        - Graduates had diverse employment options, both in academics and private sector
    - Financial rewards for clinical breakthroughs possible
        - Consumers have high willingness to pay for medicine
        - Insurance means that patients don't bear the full cost
        - Long testing periods and patent protection guarantee an exclusive market for successful drugs

        - Returns, however, are skewed
            - A few “blockbusters” earn high sales
            - 2/3 of drugs do not generate enough revenue to recoup development costs.
    - Peer review and open science
        - Three key features
            - Academic freedom
                - Leads to more diverse research
            - Priority-based rewards system
                - Motivates early disclosure of key results
            - Freedom to collaborate
    - Role of intellectual property
        - Problems observed in other sectors less severe in biotech
        - Drugs are simple, not complex
            - Thus, large patent portfolios not needed
        - Chemicals are highly codified
            - Patent rights are straightforward.
            - Easy to delineate and defend
                - Easy to imitate, so patents important
        - While patents remain controversial, there is little evidence that they have limited innovation
            - Controversies are usually over access to medicine (e.g. patenting medical tests)
        - Other laws influence role of patents
            - 1984 Hatch-Waxman Act
                - Provides patent extensions: when a generic company files an application with the FDA, the patent holder is entitled to file an infringement suit that automatically delays release of the generic for 30 months
                - Provides incentives to challenge weak patents
                    - 180 days exclusive generic status to successful challenger
                - Forces disclosure
                    - Innovators must list relevant patents for a drug
                - Lowers testing costs – can use innovator’s health and safety data
    - Competition across multiple dimensions and domains
        - Upstream competition among academic researchers looking to be the first with a new discovery
        - Much competition downstream to acquire (e.g. by licensing) access to most promising discoveries
        - Generics provide competition once patent protection expires
- International differences in biotech industry
    - Japanese firms have played a smaller role
    - IPR

        - Japan and Italy did not patent pharmaceutical products until the 1970s.
        - Strong IPP helps new firms succeed
            - In Europe, cannot patent something that has been published.
                - Thus, private enterprises not appealing to academics who want to publish
            - European Parliament rejected a proposal to strengthen biotech patent rights in 1994, but approved a similar directive in 1998.
                - However, EPO requires an "inventive step", as opposed to US "non-obvious" requirement.
                - Thus, whether something is patentable depends on whether it is an invention or a discovery.
    - Product approval
        - U.S. and U.K. are most stringent
            - FDA regulates clinical testing on human subjects
            - Lead to large development costs (the "D" of R&D) before a product can come to market
                - 70% of the costs of development are on drugs that never get to market. (This is not just on clinical trials)
            - New therapies take longer to come to market in the U.S. than in the U.K. or Germany
            - Until Waxman-Hatch Act of 1984, generics also had to undergo extensive testing, further delaying competition after patents expired.
            - US regulations require tests on 4000 or more patients in clinical trials before approval.
        - In Japan, until 1967, any drug approved elsewhere could be used in Japan.
            - Combined with weak IPP, this gave Japanese firms incentives to license, rather than develop, new technologies.
    - Structure of health care systems
        - More demand for drugs in U.S. than other countries.
        - Prices not negotiated with a government insurer.
- How has Japan begun to emerge?
    - Decreased review time for new drug
        - Prior to 2008, review times were longer than in US or Europe
    - Reviewed pricing system
        - Old system lowered price of drugs every two years
        - Pilot scheme allows prices to be maintained during the life of a patent, to help recoup costs
            - Has led to increased R&D by Japanese firms
        - Note role of complementary policies here – patents don't help if prices are capped
    - Government requiring 30% of drug sales to be generics

IV. The Human Genome

- Background on the human genome
    - In June of 2000, two groups of researchers announced they had finished sequencing most of the DNA comprising the human genome.
        - One group, the Human Genome Project, was publicly funded.
        - One group, Celera Genomics, was privately funded.
- Patenting has been controversial
    - Examples of patenting activity:
        - In 1991, Craig Venter a biologist at the National Institutes of Health (NIH) filed patent applications for 350 unique clones of human genes.
            - The action was preemptive, to prevent the private sector from patenting genes in the NIH database.
        - Celera Genomics has filed patent claims on over 6,500 gene sequences.
        - The University of California and the National Institutes of Health also hold many gene patents.
        - Since one cannot "invent" a gene, how is patenting possible?
            - Genes used in the laboratory are not in their natural form.
                - They are copied, abbreviated, spliced into bacteria or otherwise altered.
                - Thus, to the patent office, genes are a man-made chemical.
            - Patenting of genes has been allowed since the 1970s.
- *Association for Molecular Pathology v. Myriad Genetics* 2012 US Supreme Court
    - Myriad developed tests for hereditary breast and ovarian cancer based on BRCA genes
        - Tests cost over $3,0000
    - Court ruled that Myriad did not create anything
        - "Separating the gene from its surrounding genetic material is not an act of invention."
    - Distinguished between DNA that appears in nature (and thus tested here) versus creating DNA in the laboratory
- *Mayo vs. Prometheus* 2012 US Supreme Court
    - Prometheus patented a test to determine the correct dosage of drugs used to treat gastrointestinal disorders
        - The effect of these drugs (thiopurines) depends on how each patient processes the drugs
        - The tests determine the best combinations for each patient
    - In 2004, the Mayo Clinic developed a competing test with different recommendations. Prometheus sued for patent infringement.
        - Mayo said Prometheus was claiming the rights to a natural process
        - The biotech industry claimed patenting clever applications of natural laws was permissible
        - Supreme Court ruled 9-0 in Mayo's favor

            - Makes patents for personalized medicine more difficult.
- Are patents for diagnostics involving single genes necessary?
    - Do these patents help or hinder research?
        - Decrease access to tests
            - No second opinions possible, since tests have a monopoly
    - Low barriers to entry and lower fixed costs for developing tests suggest patents not as important to recoup R&D costs

V. Could Open Source Work for Biotech?

- Examples of open source development in medicine.
    - Sequencing the human genome
        - Data were put in public domain.
    - Bioinfomatics
        - Performing biological research on computers
        - Software code and data are often shared
- Other potential areas
    - New uses for non-patentable drugs
        - "If aspirin could cure cancer, would anyone care?"
    - Diseases afflicting a small number of people, such as Parkinson's disease
    - Diseases in developing countries
        - Three researchers proposed the Tropical Disease Initiative, a website to allow biologists and chemists to volunteer their expertise on tropical diseases.
        - Results would be open and available for public discussion.
        - Allows collaboration
            - Nonetheless, drugs would be developed by drug companies, based on competitive bids.
        - What is the motivation here? Is this similar to open-source, or is this a means of charity?
- Comparing biomedical research and software
    - Similarities
        - Both fields attract many young researchers, such as graduate students and young professionals, who will get involved to enhance their reputation.
        - Both include motivations to "make the world a better place."
        - Both are high-paid professions, and respond well to grand initiatives.
    - Differences
        - Financial needs different
            - The big costs for drugs are clinical trials
            - Drugs require expensive equipment
        - For drugs, the things that are easy to share are far upstream from patients, and are less profitable than the final product.
            - Can things closer to the patient be made open-source?
        - Software protected by copyrights, rather than patents.
            - Patents are costly.

- Biomedical research put in the public domain, such as the genome, is often put there to avoid this cost.
- May hurt reciprocal nature of sharing, as the motivations are different.
    - There is no legal obligation to share innovations. There is nothing to stop someone from making an improvement and sending it to the patent office instead of sharing it.