

DRUG DISCOVERY MODEL

Tasnuva Airen

tasnuva.airen@hotmail.com

Drug discovery is a process of developing drugs by either identifying the active ingredient from traditional remedies or by a sudden positive discovery of long term research. The basic approach of drug discovery is to understand how diseases and infections are controlled at the molecular (interaction between cells) and physiological level and to target specific entities based on this knowledge. The challenge in the drug discovery process is to find the exact causes of an underlying disease and find a way to negate them or bring them to normal levels. The process involves the identification of candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. Despite advances in technology and understanding of biological systems, drug discovery and development is an expensive process due to the high costs of R&D and human clinical tests. The average total cost per drug development varies from US\$ 897 million to US\$ 1.9 billion depending on the therapy or the developing firm.ⁱ The typical development time is 12-15 years. R&D of a new drug involves the identification of a target (e.g. protein) and the discovery of some suitable drug candidates that can block or activate the target. Clinical testing is the most extensive and expensive phase in drug development and is done in order to obtain the necessary governmental approvals. In the U. S. drugs must be approved by the Food and Drug Administration (FDA).^{ii, iii}

Two methods of drug discovery involve

A. Virtual screening is an integral part of the drug discovery process. It is an automatic evaluation process of large libraries of compounds that is filtered down to a manageable number by using computer programs and can be synthesized, purchased, and tested. The main advantages of this method compared to laboratory experiments are low costs, no compounds have to be purchased externally or synthesized by a chemist.^{iv}

B. Normal Screening such as high-throughput screening (HTS) experimentally tests the activity of hundreds of thousands of compounds against the target each day. High-Throughput Screening or HTS allows a researcher to quickly conduct millions of biochemical, genetic or pharmacological tests. Through this process one can rapidly identify active compounds, antibodies or genes which modulate a particular bimolecular pathway. This method provides real results that are used for drug discovery. However, it is highly expensive; more than virtual screening.^v

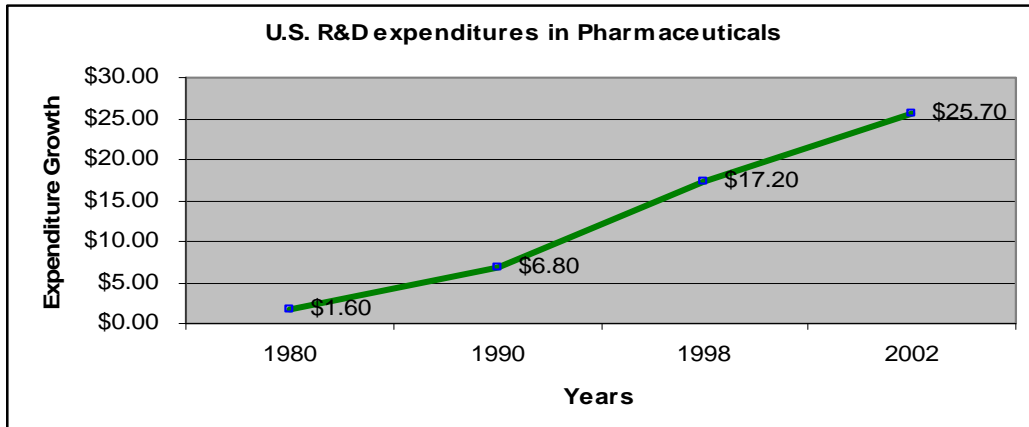
The entire “drug discovery” process takes an average of 12 – 15 years to complete.^{vi}

Research Stages	Time	Description
1. Basic Research Stage	Years 0-3	During this time period, thousands of substances are being developed, examined and screened.
2. Development Stage	Years 4-10	<ul style="list-style-type: none"> ▪ During this time, 10-20 substances are tested, both in vitro (within an artificial environment) and in vivo (within a living body). ▪ Preclinical Testing conducted using animals for years 4-6 ▪ Clinical Testing conducted using humans for years 7-10
		Phase I-clinical testing on 5-10 substances Phase II-clinical testing on 2-5 substances Phase III-clinical testing on 2 substances
3. Registration of the drug with the U.S. Food and Drug Administration		
4. Introduction of the drug to the public	Years 11+	Product Surveillance done on people for years 11,12,+
		Phase IV - observations/monitoring the product

While three dimensional structures have long been used to search for new drug targets, only a fraction of new drugs coming to the market has been developed with the use of a structure-based drug discovery approach.

Brief Overview of the Pharmaceutical Industry^{vii}

The highly innovative and technologically advanced U.S. pharmaceutical industry has consistently maintained a competitive edge in international markets. According to the U.S. Department of Commerce, the industry is expected to experience continued growth. Much of this growth is the result of substantial investment in research and development. According to the Pharmaceutical Research and Manufacturers of American (PhRMA), U.S. R&D expenditures (domestic and foreign firms) have increased substantially during the following time period. As a result of this investment, approximately 1,000 new pharmaceuticals are currently in the process of being brought to the marketplace.



viii

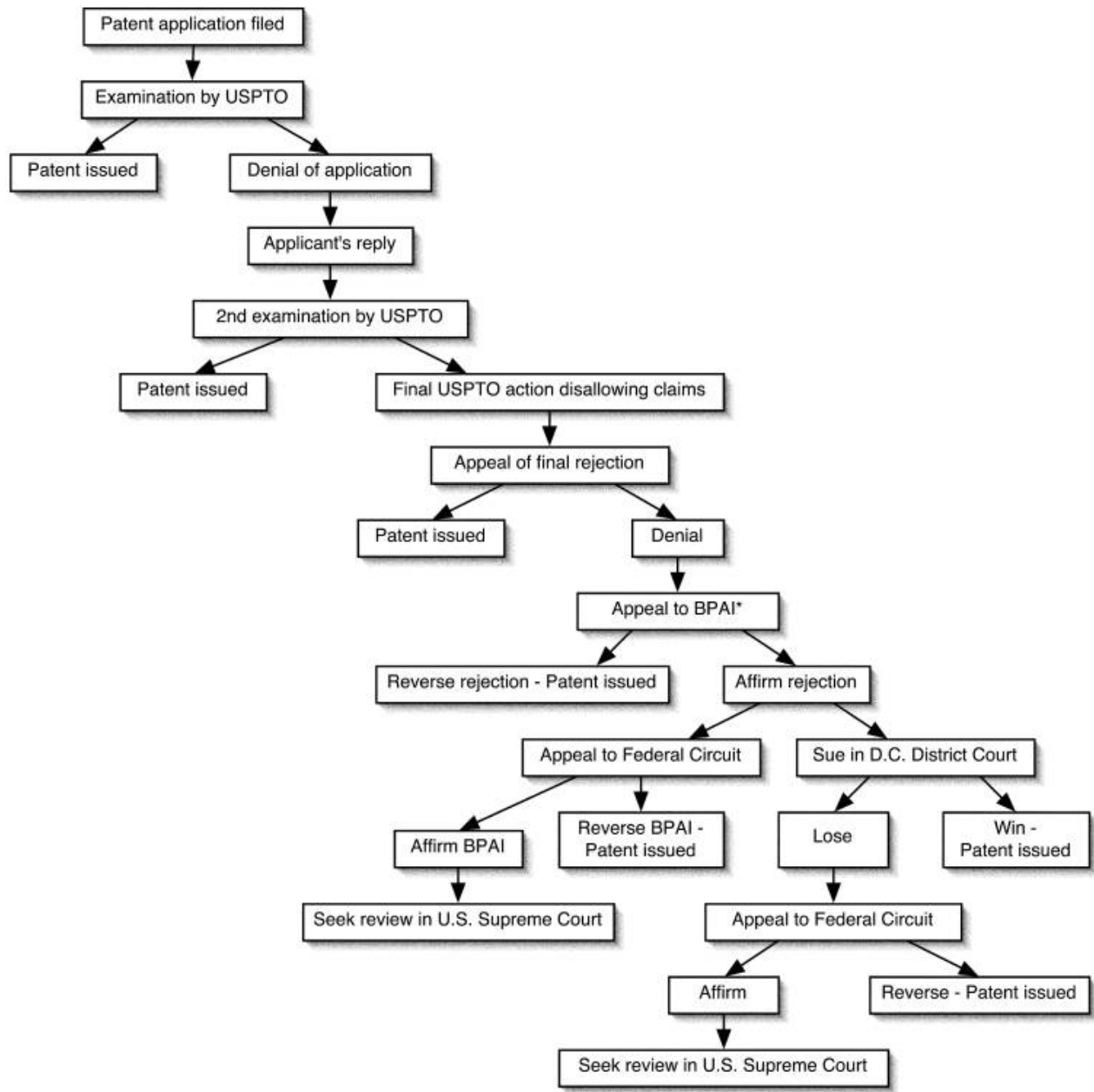
Patent Protection and Market Exclusivity:^{ix, x}

A patent is a legal tool that grants an inventor market exclusivity over a new invention or medication. It facilitates the owners' right to exclude others from making, using, or selling the patented material for a limited time. In exchange, the patent owner must surrender to the public a detailed description of the product in a manner sufficient enough to allow a knowledgeable person to make or use the invention. In the pharmaceutical industry, interpretation and application of intellectual property laws is very important because obtaining patents fully protect their innovations. Patents provide important incentives for biomedical innovation and economic growth and also serve to facilitate scientific advancement. Over the past 100 years, pharmaceutical research has helped transform health care, contributing substantially to an increase of over 30 years in life expectancy (from 47.3 years in 1900 to 77.5 years in 2003).^{xi}

Intellectual Property rights are important throughout the innovation cycle in 4 ways.

- a. Strong IP rights in the earliest stages of drug development encourage research-based companies and other researchers to invest in early-stage innovation, a foundation for the development of new treatments and cures.
- b. Many drug products contain the potential for further innovation, and IP protection of a marketable product encourages not only development of that product but also further development of related innovations to expand and improve therapies and cures.
- c. IP protection of marketed products gives their manufacturers the opportunity to benefit financially from the potential commercial advantage created by the innovation. This provides the necessary incentive to promote further investment to support the research, development, and refinement needed for future treatments and cures.
- d. Promoting the innovation needed for the pharmaceutical industry to provide cures and treatments, IP protection plays an integral role in the creation of a pharmaceutical market in which generic companies can compete with basic research companies following the expiration of IP rights.

Market exclusivity is the tremendous economic reward for the patent holder. It provides the inventor with a monopoly over the invention for the 20-year patent term. These two decades of market exclusivity provides huge economic rewards for any inventor, and are extremely critical to the success of biotechnology companies in both profitability and recuperating invested capital. Market exclusivity also provides a vital incentive for continued development of new inventions.



*Board of Patent Appeals and Interferences

Patent application process flow chart. ^{xii}

Hatch-Waxman Act:^{xiii xiv}

The Drug Price Competition and Patent Term Restoration Act of 1984, is known as the Hatch-Waxman Act. Hatch-Waxman and related legislation established a broad array of regulations governing how the pioneer pharmaceutical industry interacts with the generic pharmaceutical industry. The Act has made several significant changes to patent laws in order to encourage innovation in the pharmaceutical industry while facilitating the rapid introduction of lower-cost generic drugs. These changes include

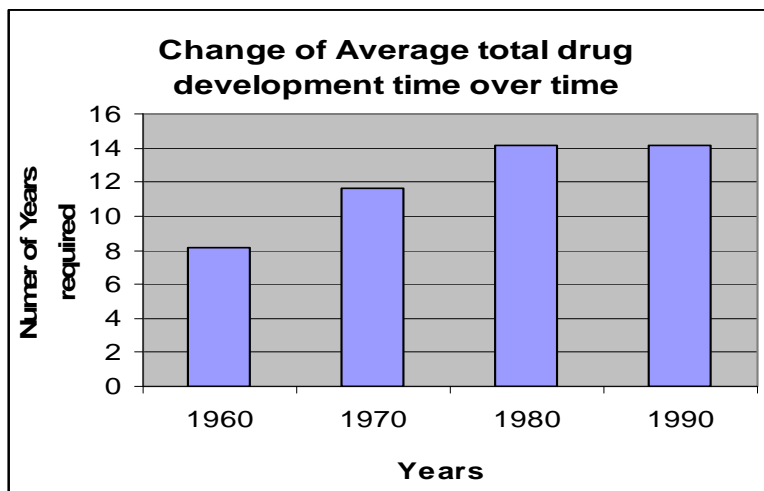
- A statutory exemption from patent infringement
- Establishment of mechanisms to challenge the validity of a pharmaceutical patent
- A reward for disputing the validity, enforceability, or infringement of a patented and approved drug
- Authorities to offer periods of marketing exclusivity for a pharmaceutical independent of the rights conferred by patents.

It was designed to promote generics while reserving a financial incentive for research and development by allowing generics to win FDA marketing approval by submitting bioequivalence studies. It also grants a period of additional marketing exclusivity to make up for the time a patented pipeline drug remains in development. This extension cannot exceed five years, and it is in addition to the 20 years exclusivity granted by the issuance of a patent.

Prior to 1962, drugs were approved for safety only. Hatch-Waxman made changes to drug approval process in the early 1960s. In 1962, amendments to the Federal Food, Drug, and Cosmetic Act (FDCA) added efficacy as an approval requirement that changed average total drug development time in the following way:

Time	Year
8.1 years	1960s
11.6 years	1970s
14.2 years	1980s and 1990s

xv



xvi

Since 1980, the average number of clinical trials conducted prior to filing a new drug application (NDA) was more than doubled, and the number of patients in clinical trials has tripled. Safety and efficacy approval requires a shorter duration of effective patent protection; it also ensures

generics not to enter the market without repeating the safety and effectiveness studies. Though straightforward in principle, Hatch-Waxman operates through a series of regulatory tradeoffs that can seem complex. We review here the basic operation of Hatch-Waxman and these tradeoffs.

Approval Process

There are 3 possible avenues under Hatch-Waxman, for the approval and marketing of drug products:

1. The full, formal process for approving a new drug requires submission of a new drug application (NDA) and reports of investigations demonstrating a drug's safety and effectiveness with the patent numbers and expiration dates of any patent claiming the drug or a method of using the drug. After an NDA has been approved, the applicant must confirm submission of the patent information and must submit the same subsequently issued information for patents. These patents are listed in the FDA publication known as the "Orange Book."

2. This approval is a more streamlined process, created by Hatch-Waxman. An applicant company must submit reports of safety and effectiveness but may also rely on information required for approval that comes from studies "not conducted by or for the applicant and for which the applicant has not received a right of reference." Examples of such modifications are changes in dosage form, strength, or route of administration; substitution of an active ingredient in a combination product; or changes in formulation, dosing regimen, active ingredient, or indication.

3. Another related streamlining process is called abbreviated new drug applications (ANDAs) designed primarily to allow a generic manufacturer to copy an NDA holder's drug product. This applicant is required to show that the drug product is the same in active ingredient, route of administration, dosage form, and strength as the product in the full NDA.

There are 4 types of patent certification:

I: Patent information on the drug has not been filed.

II: The original patent has expired.

III: The patent is about to expire and the generic will not enter the market until the date on which the patent will expire.

IV: The patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.

Role of Patents in Pharmaceutical Innovation^{xvii}

The patent system is intended to stimulate new discoveries. The award of a patent permits the creator to exclude others temporarily from use of that concept without compensation (currently 20 years from the date of filing) and also places the information associated with an invention within the public domain. The publication of the patent requires stimulating additional innovation and other creative means to meet similar and expanded demands in the marketplace. However, innovation typically is costly and resource intensive. Patents permit novel concepts or discoveries to become property and therefore allow for control over their use.

Effects on Generic Drugs

Many experts agree that the Drug Price Competition and Patent Term Restoration Act have had a significant effect on the availability of generic substitutes for brand name drugs. As a result,

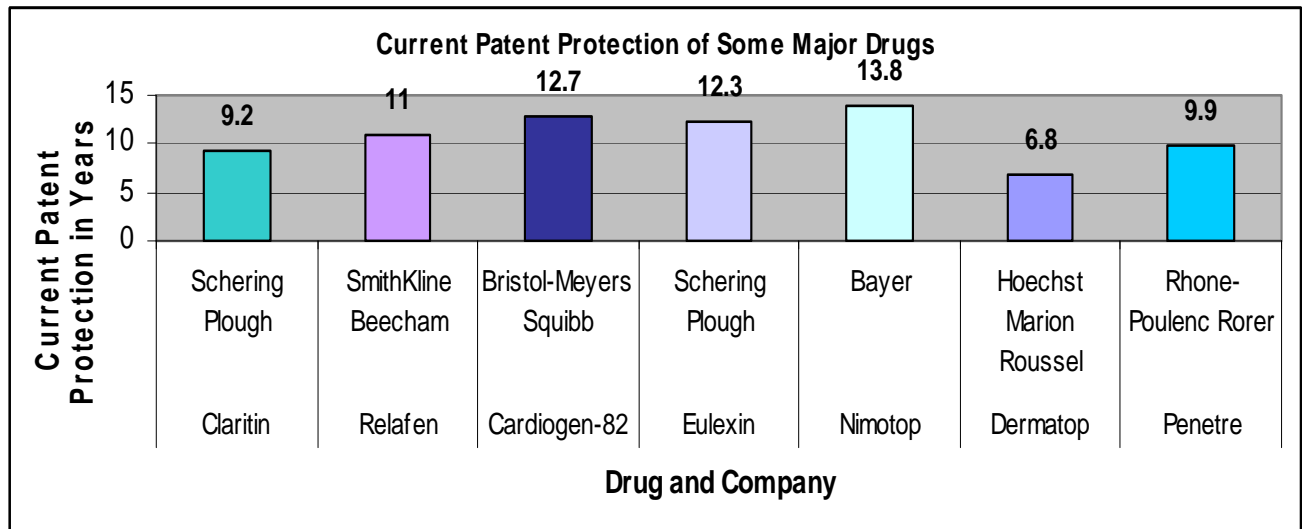
generic firms now enter the market much more rapidly after patent expiration and enter in abundant numbers.

Effects on Brand Name Drugs

The Hatch-Waxman Act has led to the availability of generic drugs but the effects on brand name pharmaceuticals appear more to be complex. The R&D funding and intensity are increasing, there is no direct measures of innovation, along with the number of new drugs approved and those in development do provide indicators of continuing innovation in the industry. Some experts argue that the expiration of patents and the desire to generate new replacement drugs, not the extension of patent ownership, is the stimulus to innovation. A study by the University of Minnesota’s Institute of Pharmaceutical Research in Management and Economics looked at the range of patent protection of several major drugs are as follows:

Drug	Company	Current Patent Protection (Years)
Claritin	Schering Plough	9.2 years
Relafen	SmithKline Beecham	11 years
Cardiogen-82	Bristol-Meyers Squibb	12.7 years
Eulexin	Schering Plough	12.3 years
Nimotop	Bayer	13.8 years
Dermatop	Hoechst Marion Roussel	6.8 years

xviii



xix

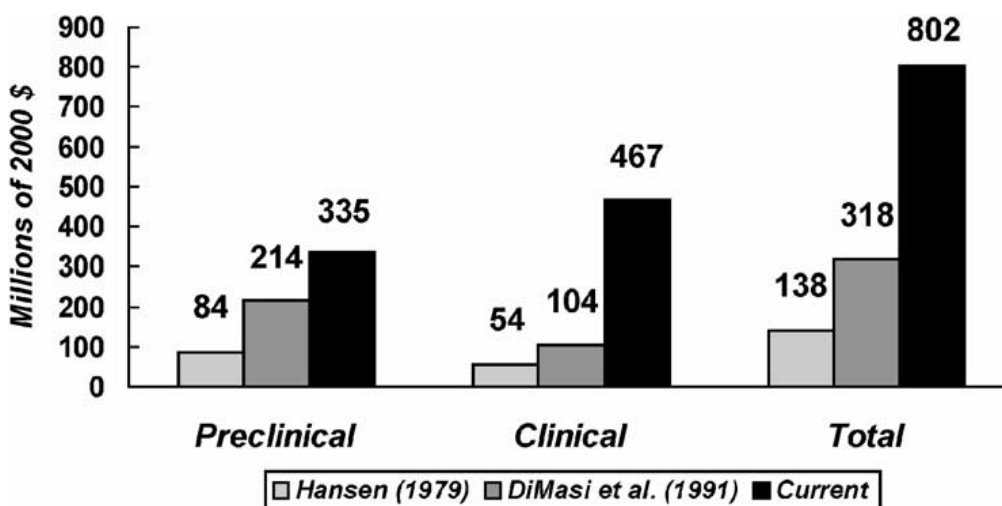
Why Drugs Prices So High?^{xx}

According to the pharmaceutical industry represented by PhRMA (Pharmaceutical Research and Manufacturers of America) drug prices are high because of the huge expenses incurred during the time of research and development (R&D) of new, innovative drugs. Most of this research takes a long time and a lot of money. Much of this research fails at the beginning, middle or at

the end of the drug development process. This means that many drugs do not reach the market nor help to cover the huge cost of the long research process. To cover all these costs each successful drug is priced so that the pharmaceutical companies can protect their patent and generate revenue for new drug development.

Drug costs also depend on the doctor who chooses a drug doesn't pay for it. They pick only those brand named drugs which they get from different pharmaceutical companies as samples. Therefore, they may pick a high-priced brand name over a generic version of the drug. Ads aimed at consumers also tout brand names, increasing the demand for more expensive drugs.

Laws governing the drug patents play major a role in how they are priced. Drug patents give companies the exclusive right to manufacture a drug for 20 years; without patents, companies would be unable to protect their products long enough to recoup the huge costs of drug development, and new drug research would suffer.



Trends in capitalized preclinical, clinical and total cost per approved new drug.^{xxi}

Conclusion

Under the current US system of patent protection and regulatory oversight of competition, there are many advances in the fight against disease. The patent approval process can at times fail to recognize genuine novelty and usefulness, and regulations can be misapplied or circumvented. In whatever way the US government chooses to address US pharmaceutical and health care policy, the important interplay of IP rights, regulation, and innovation needs to be addressed if we are to continue to experience the phenomenal advances in medical treatment that physicians and their patients have come to expect. Every single drug discovery opens up the opportunity of new drug development and future advancement besides protecting the currently occurring diseases. Patent protection is needed not only for the advancement of medical treatment, but also to protect our future generation from various known and unknown diseases.

ⁱ Drug Discovery Model: <http://content.healthaffairs.org/cgi/content/abstract/25/2/420>

ⁱⁱ Drug Discovery Model: http://en.wikipedia.org/wiki/Drug_discovery

ⁱⁱⁱ Drug Discovery Model:

http://images.google.com/imgres?imgurl=http://upload.wikimedia.org/wikibooks/en/3/3e/Schem_a.jpg&imgrefurl=http://en.wikibooks.org/wiki/Proteomics/Proteomics_and_Drug_Discovery&usg=__nDFemQfXUHiqnXcSr7cv1khR328=&h=685&w=340&sz=38&hl=en&start=8&um=1&tbnid=7SWGXkIS80LQaM:&tbnh=139&tbnw=69&prev=/images%3Fq%3Ddrug%2Bdiscovery%26hl%3Den%26rls%3Dcom.microsoft:en-us:IE-SearchBox%26rlz%3D117SKPB_en%26sa%3DX%26um%3D1

^{iv} Methods of Drug Discovery: http://en.wikipedia.org/wiki/Virtual_screening

^v Methods of Drug Discovery: http://en.wikipedia.org/wiki/High-throughput_screening

^{vi} Drug discovery” process [American Association for Laboratory Animal Science 2004](http://www.aasf.org/american-association-for-laboratory-animal-science-2004)

^{vii} Overview of the Pharmaceutical Industry:

<http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL3075601102005.pdf>

^{viii} <http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL3075601102005.pdf>

^{ix} Patent Protection and Market Exclusivity :

<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1201316/>

^x Patent Protection and Market Exclusivity <http://www.aapsj.org/view.asp?art=aapsj0903034>

^{xi} <http://www.aapsj.org/view.asp?art=aapsj0903034>

, [NeuroRx. 2005 October; 2\(4\): 572–578.](http://www.aapsj.org/view.asp?art=aapsj0903034)

^{xii} Patent application process flow chart: [NeuroRx. 2005 October; 2\(4\): 572–578.](http://www.aapsj.org/view.asp?art=aapsj0903034)

[Copyright © 2005, The American Society for Experimental neuroTherapeutics, Inc.](http://www.aapsj.org/view.asp?art=aapsj0903034)

^{xiii} Hatch-Waxman Act : <http://www.cptech.org/ip/health/generic/hw.html>

^{xiv} Hatch-Waxman Act:

<http://www.aapsj.org/view.asp?art=aapsj0903034#Business%20Importance%20of%20Patents>

^{xv} <http://www.cptech.org/ip/health/generic/hw.html> ,

<http://www.aapsj.org/view.asp?art=aapsj0903034#Business%20Importance%20of%20Patents>

^{xvi} <http://www.cptech.org/ip/health/generic/hw.html> ,

<http://www.aapsj.org/view.asp?art=aapsj0903034#Business%20Importance%20of%20Patents>

^{xvii} Role of Patents in Pharmaceutical Innovation:

<http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL3075601102005.pdf>

^{xviii} <http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL3075601102005.pdf>

^{xix} <http://www.law.umaryland.edu/marshall/crsreports/crsdocuments/RL3075601102005.pdf>

^{xx} Why Drugs Are Prices So High?

http://www1.umn.edu/umnnews/Feature_Stories/A_hard_pill_to_swallow_why_U.S._drug_prices_are_so_high.html

^{xxi} Trends in capitalized preclinical, clinical and total cost per approved new drug:

<http://www.cptech.org/ip/health/econ/dimasi2003.pdf>

References:

<http://www.earth.columbia.edu/cgsd/documents/lehman.pdf>

<http://www.ddmag.com/article-Improving-the-Odds-100609.aspx>