The Orphan Drug Act of 1983: A Step Away From Patents but In The Right Direction

I. Introduction:

Article I Section 8 Clause 8 of the Constitution grants Congress the power "to promote the progress of science and useful arts, by securing for limited times to authors and inventors the exclusive rights to their respective writings and discoveries." In the area of drug R&D, patents have historically been Congress's reflexive tool of choice for granting this protection. However, technological advances, increasing political pressure both at home and abroad, and an interactive global environment have led many, including Congress and the FDA, to question the wisdom of traditional patent theory. One area where weaknesses have been exposed is orphan diseases (unique diseases affecting small groups of people). In this paper I will first outline the problems within the current patent approach in general. Second, I will introduce the orphan disease problem and analyze the strengths and weaknesses of the Orphan Drug Act of 1983. Finally, I will recommend a solution to encourage private enterprise R&D investment in a more socially beneficial manner by incorporating free market principles and greater FDA involvement.

II. The Current Patent System Generally:

Generally speaking the patent system serves two primary objectives.[1] The first is to motivate firms to invest heavily and complete the innovation process quickly. *Id.* This is why we provide patent holders with finite protection (20 years) but unlimited profit potential during that time period. In current practice, this approach creates a limited monopoly for the patent holder to recover manufacturing, R&D, and other fixed costs, and hopefully a profit as well.[2] The patent system seems to be accomplishing this first objective. Global spending on health research

[1] Kenneth L. Judd, *Optimal Rules for Patent Races*, Discussion Paper no. 1344, Northwestern Univ., April 2002.
[2] Tim Hubbard and James Love, *A New Trade Framework for Global Healthcare R&D* (2004), *available at* http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=340954.

has increased from $30 billion in 1990 to $105.9 Billion in 2001.[3] Furthermore, the pipeline of drugs in development is currently full by most accounts.[4] Between the years of 2002 to 2004 nearly 3,200 new drug candidates were introduced. And to cap it off, many pharmaceutical companies are flourishing. In 2002 thirteen large research based pharmaceutical companies had an aggregate profit percentage of 20.6%.[5]

The second goal of patent protection is to promote efficiency by: (1) filtering out the less efficient and less competent participants; and (2) rewarding the more efficient participants.[6] In theory this process occurs by granting profits only to those firms that "win the race." As a result, only the most effective competitors survive because the less effective are naturally selected out due to their inability to compete financially. Although competition for profits in the pharmaceutical industry is constantly "weeding out" firms that cannot compete financially, many argue that the overall goal of efficiency is not being achieved.[7]

One of the primary reasons for the inefficiency is that monopolies incentivize the monopoly holder to set prices well above marginal cost. *Id.* As a practical result, drug prices in patent enforcing countries today are excessive and therefore burden and sometimes preclude consumer purchases. *Id.* This occurs because the patent holding company controls the supply to artificially maintain higher prices. Consequently, some people in patent enforcing countries, such as the United States, cannot afford essential medicines. Government (i.e. the entire citizenry whether or not they use the drugs) is then forced to step in cover the difference through social programs such as Medicare and Medicaid.

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[3] Nicoletta Dentico and Nathan Ford, *The Courage to Change the Rules: A Proposal for an Essential Health R&D Treaty* (2005), *available at* http://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=549583.
[4] Iain M. Cockburn, *The Changing Structure Of The Pharmaceutical Industry*, Heath Affairs, Jan.-Feb. 2004, at 11.
[5] "An Information Infrastructure For The Pharmaceutical Market"; Heath Affairs, Jan.-Feb. 2004; Uwe E. Reinhardt
[6] Judd, *supra* note 1.
[7] Cockburn, *supra* note 4, at 10.

Second, patents have led to inefficient distribution of resources within individual corporations as well. Currently, only about 10% of drug sale revenues are reinvested in research and development.[8] In fact, the average large pharmaceutical company spends twice as much to market a drug as it does on R&D.[9] As the holders of a limited monopoly, for-profit companies seek to maximize their profits through vast marketing campaigns in order to recover not only the R&D costs for their patented drugs, but for their failed attempts as well. According to Tufts Institute, these costs per approved new entity average $403 million ($802 million including cost of failure and cost of capital) over an average 14 year timeline.[10]

Third, Patents have led to an over-emphasis on "me-too" drugs.[11] These "me-too" drugs are imitations of already existing drugs that offer little additional therapeutic benefit. *Id.* Between 1989 and 2000 76% of drugs approved by the FDA fell into this category.[12] One recent examples of "me-too" drug is Viagra (originally created as a treatment for hypertension).[13]

These "me-too" drugs are a very attractive investment for a couple of reasons. First, the cost of development is much lower and the time to market much less, given that the majority of the difficult research has already been performed. More importantly, many times the drugs that attract investment under the patent scheme are "lifestyle drugs."[14] This is a problem because instead of investing already limited R&D resources into efforts to discover cures for chronic diseases, for-profit pharmaceutical companies are spending a substantial amount of their time and resources to develop drugs that are more common place and easily marketed to a larger

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[8] Hubbard and Love, *supra* note 2.
[9] Dentico and Ford, *supra* note 3.
[10] Mary Moran, *A Breakthrough in R&D for Neglected Diseases: New Ways to Get the Drugs We Need* (2005), *available at* http://medicine.plosjournals.org/perlserv/?request=get-document&doi=10.1371/journal.pmed.0020302.
[11] Dentico and Ford, *supra* note 3.
[12] Compared to only 23% that did (1% were neglected disease drugs), Cockburn, *supra* note 5, at 10.
[13] John Henkel, *Orphan Products New Hope for People with Rare Disorders* (1995), *available at* http://www.fda.gov/fdac/special/newdrug/orphan.html.
[14] Thomas W. Croghan and Patricia M. Pittman, *The Medicine Cabinet: What's In It, Why, And Can We Change The Contents?*, Health Affairs, Jan.-Feb. 2004, at 25.

percentage of the population. As evidence of this fact, 68% of new chemical entities marketed worldwide in the last 25 years were "me-too" products.[15] In the United States, 92% of medicines approved by the FDA in 2002 were "me-too" drugs. *Id.*

Finally, patents require a high level of regulation in order to protect against counterfeiting and illegal trade; a problem especially troublesome on an international scale due to the tremendous variation in patent laws from one country to the next. *Id.* Not all countries recognize patents, and only a small number actually dedicate resources to the enforcement of patents. Consequently, in many countries pharmaceutical companies do not apply for patent protection.[16] In fact, in many countries patent protection is *de facto* non-existent, and in some instances (e.g. India in the 1970's) drugs have even been officially denied *de jure* patent protection.[17] As a practical result, patent enforcing countries are left holding the bag. In the United States, markups on patented drugs average 100%, and in a number of cases as much as 800%.[18]

All of the above problems led Mark McClellan (current Administrator for the Center for Medicare and Medicaid Services and former head of the FDA) to state the following in a May 2004 interview: "I can tell you that I don't think the current situation is sustainable. Something's going to give. The question is whether prices in the United States are going to come down, and whether our focus is going to increasingly be on just paying the cost of a few additional pills--as it is in much of the rest of the world--in which case we're not going to get the same kind of innovation as I'd like to hope for."[19] He also predicted that U.S. legislators will inevitably cave to growing public pressure for lower drug costs by allowing some sort of drug importation. *Id.*

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[15] Dentico and Ford, *supra* note 3.
[16] Amir Attaran, *How Do Patents And Economic Policies Affect Access To Essential Medicines In Developing Countries?*, Health Affairs, May-Jun. 2004, at 158.
[17] John H. Burton, *TRIPS And The Global Pharmaceutical Market*, Health Affairs, May-Jun. 2004, at 147.
[18] Maria Lopez and Lori Reisner, *Is the Brand Name Drug Really Better Than the Generic?* (2001), *available at* http://www.pamf.org/health/toyourhealth/drug.html.
[19] *Interview: McClellan & Kleinke*, Health Affairs, May-Jun. 2004, at 181.

III. The Orphan Disease Problem

Unfortunately, orphan diseases are what suffer foremost when resources are not efficiently allocated. The reason is plain and simple: pursuing cures for these types of diseases is not profitable under the basic patent framework. Consequently, these diseases have historically been neglected. Due to increased public awareness spawned by various non-profit, philanthropist groups, the tide has shifted somewhat.[20] Although orphan diseases are a worldwide problem, I have chosen to focus my efforts solely on the problem as it exists in the United States today. I will address the strengths and weaknesses of the Orphan Drug Act of 1983, and then provide a recommendation for increasing efficiency and maximizing social welfare within the present system.

Orphan diseases in the United States are defined as diseases affecting less than 200,000 people.[21] Currently in the United States there are more than 6,000 identified orphan diseases affecting as many as 25 million Americans. *Id.* Some examples of well known orphan diseases are cystic fibrosis, hemophilia, and multiple sclerosis.[22] However, the majority of orphan diseases are obscure and unknown. In fact, approximately 47% of orphan diseases affect an estimated 25,000 or fewer people. *Id.*

Unfortunately, the patent system further exacerbates the problem because it provides a single channel (profits) through which pharmaceutical companies recoup their investment.[23] In addition, this channel has developed over time to encourage and reward development of cures on a large scale.[24] Consequently, the extreme cost of sponsoring a drug through clinical trials and the small potential market discourages pharmaceutical companies from bringing the drug to

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[20] Hubbard and Love, *supra* note 2.
[21] Orphan Drug Act of 1983, 21 U.S.C.A. § 360 (1983).
[22] Henkel, *supra* note 13.
[23] Hubbard and Love, *supra* note 2.
[24] David Loughnot, *Potential Interactions of the Oprhan Drug Act and Pharmacogenomics: A Flood of Orphan Drug Abuses?*, 31 Am. J. L. and Med. 365, 372 (2005).

market. *Id.* Many times this occurs even if an effective drug had been discovered. *Id.*

People with such diseases are reduced to a life of pain and suffering simply because they are afflicted with a disease that cannot generate a profit. *Id.* This is not the ideal situation, and it may seem inhumane, but it can be justified from a utilitarian perspective. There are only a limited amount of resources that can be dedicated to R&D. Consequently, if resources are limited, they should be allocated to diseases that affect the greatest number of people. So how do we more efficiently use available resources in order to better serve otherwise neglected people?

Due to the ineffectiveness of patents in dealing with the orphan disease problem, various alternative approaches need to be considered. When attempting to address problems legislatively, there are two general approaches. One approach draws specific legislative lines defining pre-determined criteria in an attempt to avoid problems. The problem with applying this approach to orphan diseases is that, in general, technology develops faster than the legislature deliberates and is usually difficult to predict. As a result we would continuously be chasing our tails by passing legislation to address yesterday's problems. The Alternative is to approach the problem in an ad hoc manner by delegating a significant amount of line drawing authority to an administrative body with expertise in the area. However, creates uncertainty in the market and, over time, leads to an incoherent body of law.

The Orphan Drug Act of 1983 represents a hybrid of these two approaches.[25] The act provides specific legislative lines, but also grants significant authority to the FDA. A primary example of this balance is the main provision of the act, which grants seven year market exclusivity to the orphan drug company. *Id.* This guarantees the patent holder a seven year period to market and sell the drug competition free. Unlike the traditional patent approach, the Orphan Drug Act provides the FDA with two additional discretionary tools for granting market

[25] Orphan Drug Act of 1983, 21 U.S.C.A. § 360 (1983).

exclusivity.[26] First, the company is not required to have a patent in order for the FDA to grant market exclusivity protection. *Id.* Second, the act also allows the FDA to grant an additional drug applicant simultaneous market exclusivity with the original drug. *Id.* However, specific regulations were also adopted along with the Orphan Drug Act .[27] These regulations attempt to predefine the boundaries within which the FDA may exercise its discretion. For example, in order for the FDA to grant simultaneous approval, it must be shown that the new version is safer, more effective, easier to administer, or that the original company cannot satisfy market demand.

In addition, the act provides: (1) a 50% tax credit for development costs; (2) written recommendations from the FDA aimed at speeding the drug through clinical studies and the approval process; and (3) $25 million in grants for both public and private entities to defray the cost of qualifying testing expenses. *Id.*

For the most part, results have been encouraging. In the decade prior to passage of the act only thirty-four orphan drugs received market approval.[28] In the twenty years following its passage 229 orphan drugs entered the market. The Orphan Drug Act has also allowed for smaller biotechnology based companies to be much more competitive by granting market exclusivity to certain biological compounds that otherwise would not qualify for patent protection.[29] This is important because the biotechnology is playing an increasingly greater role in modern medicine. Today, approximately 25-40 percent of big pharma sales are biotech based. *Id.* As further evidence of the act's success, the European Union, Australia, Japan and others have all followed suit and passed similar legislation.[30]

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[26] David Loughnot, *supra* note 24.
[27] 21 CFR § 316 (2004).
[28] David Loughnot, *supra* note 24, at 370.
[29] Cockburn, *supra* note 4, at 10.
[30] E.U. Parliament , *Public Policies on Orphan Drugs*, *available at* http://www.europarl.eu.int/stoa /publi/167780/chap3_en.htm.

Notwithstanding its success, the Orphan Drug Act is not without weaknesses. The first is the "Off-Label" problem. This refers to a generally accepted practice where doctors prescribe medicines for uses not specifically indicated on the label. As a result, drug companies label a drug as targeting a specific orphan disease when in reality it can be used for various other non-orphan diseases. This allows the company to take advantage of the benefits of the Orphan Drug Act for what could potentially be a blockbuster drug.[31] An example of this is Allergan's product Botox. Briefly mentioned earlier, Botox was originally created as a cure for the orphan disease Blepharospasm. In stead, it is currently used cosmetically as a high priced "wrinkle eraser." In 2005 Botox was Allergan's highest selling product (estimated $800-840 million in total sales).[32]

Another weakness deals with the law's inability to adapt to technological advances. A primary example of this is the pharmacogenomics problem. Pharmacogenomics is the science of utilizing genetic variations to facilitate drug development and to create optimal patient treatments. In essence, drugs can be specifically tailored according to certain genetic characteristics. [33] Amongst other things, this would increase the effectiveness of any given drug by decreasing genetic based side-effects as well as non-responsiveness. *Id.*

Pharmacogenomics raises complex issues both practically and legally as well. One complexity arises from what is termed "Salami Slicing." This is the practice of tailoring a drug to one specific mutation of a disease. The problem arises when we attempt to apply the definition of "rare disease or condition" as found in the Orphan Drug Act to the "Salami Slicing" situation. According to the Orphan Drug Act rare diseases are, "any disease that affects less than 200,000 persons in the United States." If we apply this definition literally, each specific

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[31] David Loughnot, *supra* note 24, at 370.
[32] Allergan, Inc., 2005 Fourth Quarter Operating Results (2006).
[33] Editorial, *From Bench to Bedside and Back Again*, Can. Med. Assoc. J., June 8, 2004, *available at* http://www.cmaj.ca/cgi/content/full/170/12/1765.

mutation of a disease would theoretically qualify as an orphan disease. As a result, many diseases not in need of orphan drug treatment would thus qualify.

However, denying orphan status to genetic mutations of a disease may not be the correct answer either. Even if the foundational drug exists, developing genetically altered forms that target specific genetic mutations is a costly process. *Id.* Moreover, these genetic mutations in many cases only affect small subsets of the population as well. Thus, without government subsidization, little financial incentive would exist for companies to develop such drugs.

Pharmacogenomics also creates the possible opportunity for firms in pursuit of market exclusivity to select study participants with a specific genetic predisposition. This could aid companies in deceptively speeding a drug through clinical trials as well as obtaining significantly superior test results that would allow them to qualify under the "clinically superior" exception to the seven year market exclusivity grant.[34]

IV. My Recommendation

It is important to recognize that attempting to incentivize private industry to invest in what is essentially an unprofitable venture (i.e.orphan diseases) is a very difficult proposition. Therefore, it is important to take a practical, realist approach to the problem. Otherwise we risk attempting to fix what may not be broken, because we are blinded by an unachievable perfect world ideal. This is my primary fear when considering radical sweeping proposals such as the Free Market Drug Act recently proposed by Congressman Dennis Kucinich in 2004.[35] Nonetheless, there still is much room for improvement. Consequently, my recommendation is for continued FDA involvement along with minor alterations to the current Orphan Drug Act aimed at utilizing free market principles to further encourage both public and private enterprise participation with the ultimate primary objective being the efficient use of our limited resources.

[34] *Berlex Laboratories, Inc. v. Food and Drug Admin.*, 942 F.Supp. (19 D.D.C.1996).
[35] H.R. 5155, 108th Cong. (2004).

1. Remain Conscious of Synergistic Relationships

Most of the current experience and capability in drug development exists in large multi-national pharmaceutical companies.[36] However, much of the recent success as well as future potential lies in the biotechnology and public sectors. Id. at 829. Furthermore, due to their smaller scale operations biotech companies are more capable of sustaining profitability than traditional big pharma in the orphan drug discovery arena. *Id.* at 830. In addition, because their operations are relatively small in scale their revenues do not need to be as large in order to be profitable. *Id.* Meanwhile large multi-national corporations with expansive R&D facilities cannot afford the opportunity cost of foregoing research on large blockbuster drugs for orphan diseases. What is more, smaller biotech companies simply do not have the resources to absorb the costs of pursuing a drug throughout the entire approval process.

As a result, relationships have developed that allow big pharma to focus on large scale projects and late stage development while biotech/not-for-profit companies focus on early stage discovery. *Id.* These synergistic relationships have developed as a result of the free market interaction that has occurred in the industry's present environment. Consequently, my first recommendation is to remain especially mindful of possible side-effects on these healthy cooperative dynamics that have evolved as we attempt to fix other problems.

2. Adjustments to the Orphan Drug Act of 1983

As stated previously, the Orphan Drug Act (especially the market exclusivity option) has proven largely successful. However, some weaknesses, as described above, have been exposed. Two main adjustments could significantly address these weaknesses. The first weakness is the act's inability to evolve with technological advances. The second is its lack of guidance in dealing with the aforementioned "off-label" and "pharmacogenomics" problems. Proposed

[36] Moran, *supra* note 10.

solutions to these problems can generally be lumped into two groups. The first group attempts to regulate abuse of the act with hindsight. Windfall profit taxes and post hoc restrictions that attempt to control abuses (e.g. improper "off-label" prescriptions) are examples. The second group attempts to limit access to the act's benefits. These proposals usually focus on redefining terms within the act in order to exclude possible abuses from the scope of the act.

My proposal regarding the Orphan Drug Act is more in line with the latter group. I propose we first amend the act to address the current loopholes that exist. Every term such as "clinically superior" and "medically plausible" should be reconsidered with the "off-label" and "pharmacogenomics" problems specifically in mind. Furthermore, in situations of abuse, as determined by the FDA, benefits of the act should be taken away according to predetermined criteria established and implemented by the FDA. Finally, in contemplation of unforeseen problems, the act should also include a clause that requires re-approval by the appropriate congressional sub-committee with the FDA acting in an advisory role every 2 years.

3. Restructuring the FDA's Role

In order for this approach to work properly, and increase overall efficiency, the structure of the FDA would have to be altered slightly. The FDA has become extremely large and powerful (approx. 10,700 employees as of 2004).[37] Along with that power, the FDA has also become increasingly sensitive to political pressure.[38] This power and political sensitivity is especially pronounced when it comes to new drugs entering the market. The following quote from former FDA commissioner Alexander Schmidt in 1974 is evidence of this phenomena:

> "In all of the FDA's history, I am unable to find a single instance where a Congressional committee investigated the failure of FDA to approve a new drug. But, the times when hearings have been held to criticize our approval of new drugs have been so frequent that we aren't able to count them...The message to FDA staff could not be clearer. Whenever a controversy over a new

[37] Interview: McClellan and Kleinke, *supra* note 20, at 185.
[38] Daniel P. Carpenter, *The Political Economy of FDA Drug Review: Processing, Politics, And Lessons For Policy*, Health Affairs, Jan.-Feb. 2004, at 52.

> drug is resolved by its approval, the Agency and the individuals involved likely will be investigated. Whenever such a drug is disapproved, no inquiry will be made."

Although the pressure to slow down the approval process has been countered in recent years by patient advocacy groups, the same fundamental problem still remains: The FDA is subject to Congressional oversight and to advocacy and press influences. *Id.* at 56.

Consequently, I subscribe to the proposal of privatizing the drug review process by allowing the FDA to subcontract certain responsibilities to private enterprises. This will help disseminate responsibility and control, as well as diminish the size of the FDA. *Id.* at 61. In this model the FDA essentially becomes a certifier of private review companies. *Id.* This is beneficial for three reasons. First, it decreases the amount of direct political pressure to which the FDA would be exposed by distancing them from the day-to-day operations. Second, it reduces bureaucracy and increases efficiency by allowing private industry to compete for FDA contracts. Finally, it puts the staffing problem, currently the most pervasive influence on drug approval times, into the hands of private industry as opposed to an already overloaded administrative body. *Id.* at 58.

IV. Conclusion

Privatization of the FDA's approval process, minor alterations to the Orphan Drug Act, and recognition of existing synergistic relationships are the keys to improving the current orphan disease situation. However, these recommendations are not meant to serve as an end-all-say-all resolution. Instead they are meant to represent the three principles that I believe are key to continual progress: (1) greater reliance on the free market in order to lessen the bureaucratic load; (2) effective and competent legislation that is updated to meet present demands; and (3) recognition of past success from a practical perspective. Although we may never completely resolve the orphan disease problem, if we adhere to these principles I believe we stand the greatest chance of success.