Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?

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I. INTRODUCTION

To overcome the unattractiveness of small markets, the United States government provides financial aid and incentives for drug manufacturers to create cures for rare diseases under the Orphan Drug Act ("the Act"). Recent research integrating genetic information and pharmacology holds promise for creating more effective drugs targeted at smaller populations than ever before. In the near future, it seems that a flood of new drugs targeted at small disease populations could take advantage of the government benefits under the Act. Drug applicants will include true orphan drugs along with "Trojan" applicants that seek to co-opt the benefits for drugs that should not qualify as orphans. Currently, the FDA appears ill prepared to discern between the two types of applicants and prevent abuse of the system.

In 1983, the federal government passed the Act. Congress designed the Act and subsequent modifications to provide incentives for companies to bring drugs for rare diseases to market. Traditionally, even when cures for rare diseases were discovered, the large cost associated with sponsoring a drug through clinical trials discouraged pharmaceutical companies from bringing the drugs to market. Thus, many drugs that could help rare disease populations were "orphans" without a parent company to sponsor them through clinical trials. The Act provided various financial incentives, including grants and market exclusivity, for companies to bring orphan drugs to market. The Act successfully encouraged development of previously unprofitable drugs, but also funded the development of several blockbuster drugs, which attracted criticism.

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1 B.A., Molecular and Cell Biology (emphasis in Genetics), University of California at Berkeley, 2000; J.D., Boston University School of Law, 2005. I thank the members of the Editorial Board for their insights and hard work on this note. I also thank my family and friends who have been with me through the years. Finally, special thanks to my mother for everything.


4 Thomas Maeder, The Orphan Drug Backlash, SCIENTIFIC AMERICAN, May 2003, at 83.

5 Id.

6 Id.
Beginning in October 1990, the Human Genome Project ("HGP") endeavored to bring a further understanding of human genetics to biological and medical science. With a combination of government and private actors, the HGP "catalyzed the multibillion dollar U.S. biotechnology industry and fostered the development of new medical applications." Pharmacogenomics developed through the combination of genetic knowledge with pharmacological science.

Pharmacogenomics concerns the interaction of pharmacology with an individual's specific genetic makeup. Biotechnology and pharmaceutical companies already utilize the technology to subdivide patients with the same disease into different genetic classes, changing the way drugs are delivered. One day, the technology could seriously alter the way drugs are developed and enable tailored treatments for different genetic classes within a disease population. Thus, pharmacogenomics holds the potential to increase drug efficacy via administration and development, independently.

Under the current version of the Act, pharmacogenomic technology might create an avalanche of new orphan drugs. Drug developers could genetically subdivide diseases that affect a large portion of the population into groups small enough to qualify for orphan drug status. While targeted at one specific subgroup, these pharmacogenomic orphan drugs could retain efficacy for treating other subgroups of the disease. For example, if a condition that affected millions of Americans was determined to have a genetically identifiable subgroup with a population less than 200,000, a treatment for that subgroup would qualify as an orphan drug. After developing this specific treatment, the parent company could promote it as a drug for the entire disease population. If done intentionally, this would violate the original purpose of the Act and co-opt the benefits of the Act to serve as government subsidies for a fledgling pharmacogenomic industry.

Additionally, the orphan drug approval process could be exploited via pharmacogenomic manipulation of clinical trials. Drug sponsors could screen out patient populations genetically prone to unfavorable drug reactions in an effort to improve the results of clinical trials. The Act allows "clinically superior" new orphan drugs to puncture the market exclusivity shield of old orphan drugs. Thus, pharmacogenomic technology might result in drug sponsors creating clinically superior results with a new drug that possesses no significant difference from the original drug. This would defeat the purpose of the "clinically superior" exception to the guarantee of market exclusivity.

In the abuses described above, pharmacogenomically designed drugs seem to gain benefits under the Act without necessarily fulfilling the goals of the Act. For example, some pharmacogenomic drugs might only present a more effective

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9 Office of Science, DOE, Human Genome Information: Pharmacogenomics, at http://www.ornl.gov/sci/techresources/Human_Genome/medicine/pharma.shtml (last updated July 9, 2004). A patient's genetic code often influences any potential reactions to treatment. For example, genetics largely determines an individual's allergies to certain medications and the rate at which that individual metabolizes a drug. Id.
11 See Office of Science, supra note 9 (commenting on the promise of pharmacogenomics to customize drugs even on an individual level).
alternative to other available treatments. Although possibly functioning better and with a lower occurrence of side effects, these drugs would share a redundant function with more widely prescribed drugs on the market. Imitation drugs that pass more carefully screened clinical trials do not fulfill the Act’s intent either. Congress intended that the Act provide incentives for creating treatments for rare diseases that would otherwise have no available cure. Thus, drugs that provide only a slightly (if at all) enhanced efficacy do not serve the purpose of the Act and should not receive funding.

Since the issue of abuse has been visited before, several plans have been proposed to curb exploitation of the Act’s benefits. While few of the ideas have been implemented, many present opportunities for the FDA to avoid potential abuse from pharmacogenomic orphan drugs. First, increased restrictions on the type of drugs given orphan designation would limit access. One such restriction involves changing the definition of “same drug” under the Act. Alternatively, measures such as a windfall profits tax or shortened marketing exclusivity term limit an orphan drug’s profits. While such financial deterrents would prove difficult to implement, the resulting burden on drug sponsors would create a disincentive for intentional exploitation of the Act’s benefits. Finally, heightened reporting requirements including pharmacogenomic data, which the FDA is exploring, could prevent potential manipulation of the clinical trial process.

II. BACKGROUND

A. THE ORPHAN DRUG ACT

In 1962, Congress changed the criteria of the FDA’s drug approval process, requiring a showing of efficacy in addition to safety for a drug to gain marketing approval. The increased complexity of the clinical trial process significantly increased the cost associated with bringing a discovered drug to market. Pharmaceutical companies focused efforts on drugs that would have large markets waiting after clinical trials. Drugs known to treat rare illnesses were rarely submitted for FDA approval because the small market awaiting these drugs made recovery of a profit almost impossible. These drugs were left as “orphans,” without a parent company to sponsor them in clinical trials. Therefore, people with rare diseases could not find a way to bring the known cures or treatments for their conditions to market.

14 Id.
15 Id. at 336.
17 Pulsinelli, supra note 13, at 303.
18 See Rohde, supra note 3, at n.39 (discussing the increasing cost of clinical trials for drug manufacturers).
19 Id. at 126.
20 See Marlene E. Haffner & John V. Kelsey, Evaluation of Orphan Products by the U.S. Food and Drug Administration, 8 INT’L J. TECH. ASSESSMENT HEALTH CARE 647, 647-48 (1992). Dr. Haffner is the Director of the Office of Orphan Products Development within the FDA.
To help solve this problem, Congress passed the Orphan Drug Act in 1982.\textsuperscript{21} The Act took effect in 1983 and was amended in 1984,\textsuperscript{22} 1985,\textsuperscript{23} and 1988.\textsuperscript{24} It created financial incentives for companies to sponsor orphan drugs through clinical trials. Drug companies reacted favorably to the incentives, but some critics believe that the benefits of the Act have been awarded to drugs that exploit the Act’s benefits and run contrary to its intent.

1. Benefits and Financial Incentives of the Act

a. Assistance in Clinical Trials

As mentioned above, the cost of bringing a drug through clinical trials can sometimes reach prohibitive levels.\textsuperscript{25} With normal drug sponsors, the FDA maintains a supremely objective, if not antagonistic, relationship during approval.\textsuperscript{26} However, orphan drug sponsors have a more collegial relationship with the FDA.\textsuperscript{27} Both parties work together to establish the necessary trials and get orphan drugs to market as soon as possible. As a result, orphan drugs make it to market much faster than non-orphan drugs.\textsuperscript{28} Because the FDA is the final arbiter of validity, its suggestions on clinical protocols help the sponsor conduct acceptable trials with a small population available for testing.

Furthermore, the decreased time spent in clinical trials can mean a longer period of profits in the market for patented orphan drugs. Drug patents, while not as protective as a grant of market exclusivity, last for twenty years.\textsuperscript{29} These patents are typically awarded long before a drug even enters clinical trials, as opposed to the market exclusivity term, which begins after trials when a drug receives market approval.\textsuperscript{30} For non-orphan drugs, clinical trials typically use up a substantial part of the twenty-year period.\textsuperscript{31} However, the time saved in clinical trials for orphan drugs can often add another year or two onto a drug’s time in the market before generic competition is allowed.\textsuperscript{32}

\textsuperscript{25} See Haffner & Kelsey, supra note 20, at 647-48.
\textsuperscript{26} Maeder, supra note 4, at 83.
\textsuperscript{27} Id.
\textsuperscript{28} Marlene E. Haffner, Orphan Products – Ten Years Later and Then Some, 49 FOOD DRUG COSM. L.J. 593, 601 (1994).
\textsuperscript{29} Id.
\textsuperscript{32} See Haffner & Kelsey, supra note 20, at 601.
b. *Tax Credit for 50% of Clinical Trial Costs*

In addition to technical assistance in developing and executing clinical trials, the Act awards a tax credit for half of human clinical trial costs incurred in bringing an orphan drug to market. This helps further reduce the expense—and risk—associated with sponsoring such products. Such a tax credit amounts to a rebate of millions of dollars for an orphan drug sponsor.

\[\text{26 U.S.C. § 45C (2000) (excluding from the tax credit any expenses which are funded via grant).}\]

\[\text{See Wesley A. Cann, Jr., Symposium: Corporate and Legal Implications of Re-Pricing Medicines in Developing Nations: Article: On the Relationship Between Intellectual Property Rights and the Need of Less-Developed Countries for Access to Pharmaceuticals: Creating a Legal Duty to Supply under a Theory of Progressive Global Constitutionalism, 25 U. PA. J. INT'L ECON. L. 755, 791 (2004) (stating that it currently costs over $800 million to bring a new drug to market. While that figure includes costs unassociated with clinical trials, the cost of clinical trials is a substantial portion of drug development, and a 50% credit would still amount to millions of dollars).}\]

\[\text{21 U.S.C. § 360ee(a) (2000).}\]

\[\text{Frequently Asked Questions Regarding the OOPD Grant Program, at http://www.fda.gov/orphan/grants/faq.htm (last visited Nov. 26, 2004).}\]


\[\text{See Robert A. Bohrer & John T. Prince, A Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act, 12 HARV. J.L. & TECH. 365, 371-72 (1999) (finding that while the "market protection is narrow," it can be "essentially as effective as patent protection").}\]

\[\text{Maeader, supra note 4, at 83. Two other exceptions exist to the market exclusivity provision. The first is if the sponsor company cannot supply enough of the drug to satisfy market demand. See U.S.C § 360cc(b)(1) (1994). The second is when the sponsor company agrees to approval of another application. See U.S.C § 360cc(b)(2) (1994).}\]
However, companies soon saw the provision as an incentive even with patentable drugs. Marketing exclusivity is guaranteed for seven years following market approval, while a patent is good for twenty years after discovery of a drug. While twenty years is obviously longer than seven, drug development and clinical trials can use up a substantial portion of that period before the drug ever reaches the market. Thus, the guaranteed period of seven years exclusivity is an attractive option to a parent company seeking to recoup investment in research and development.

2. The Act’s Success and Problems

a. Success of the Act

In the opinion of many, the Act was considered a tremendous success. In the decade before the Act’s passage, only thirty-four “orphan drugs” received market approval. In the twenty years following its passage, 229 such drugs entered the market. Many groups suffering from rare diseases have received treatments developed by both large corporations and small firms. Furthermore, several foreign countries have passed measures almost identical to the Act in hopes to spur orphan drug development domestically.

b. Problems with the Act

Despite the Act’s successes, many critics believe that some pharmaceutical and biotechnology companies have already exploited its benefits. Critics often point to Epogen as an example of drug manufacturers co-opting the Act’s benefits in inappropriate situations. In the 1980s, Amgen was a small biotechnology company in southern California. Amgen submitted a promising new drug, epoetin alpha, to the FDA for orphan designation in 1986. The application said the drug was intended to treat anemia associated with end-stage renal disease. The FDA awarded Epogen orphan drug status in 1986 and Amgen brought it to market as an orphan drug in 1989. Soon thereafter, doctors realized the drug had tremendous potential in helping patients suffering from anemia not necessarily caused by end-stage renal failure. Suddenly, Epogen was a blockbuster drug, bringing Amgen

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41 Pulsinelli, supra note 13, at 311 (explaining that the market exclusivity provision “was originally intended to compensate for a lack of patent protection”).
43 STRONGIN, supra note 29, at 5.
44 Id.
45 Id.
46 Id.
47 Id.
48 Id.
49 Id. at 83.
50 Id. at 81.
52 Id.
53 Id.; see also Amgen, History of Epogen, at http://www.epogen.com/professional/about/epogen_history.jsp (last visited Oct. 15, 2004).
54 Pulsinelli, supra note 13, at 321.
over one billion dollars in revenue each year. Some critics say Amgen knew of the broad applications of Epogen and that Amgen narrowly targeted end-stage renal failure patients only to secure the Act's benefits and reduce the initial investment required for the drug. This method of subdividing a larger disease into smaller subgroups is called "salami slicing" and is acknowledged as one of the problems associated with the Act.

c. Off-Label Prescriptions Create Potential for Abuse

Blockbuster orphan drugs such as Epogen rely upon the practice of off-label drug prescription and usage. The FDA generally approves a drug only when clinical trials prove that it is safe and effective for its intended use. The particular use the FDA approves becomes the drug's "indication" and must be displayed on the drug's label. However, the medical community generally accepts a doctor's right to prescribe medicine off-label. Therefore, doctors often prescribe drugs for uses other than the approved indication. As in the example above, Epogen was originally approved only for treating anemia associated with end-stage renal disease. Doctors quickly recognized the usefulness of the drug and prescribed it for patients with other forms of anemia. A recent Knight Ridder analysis "found that the off-label use for some drugs is as high as 90 percent of all its prescriptions sold."

d. Reactions to Perceived Abuse

As mentioned earlier, several orphan drugs, such as Epogen and HGH, went on to become blockbuster drugs. These drugs were applicable to enormous disease populations, but still qualified for orphan drugs designation. Many observers feel that blockbuster drugs that were advanced with the aid of the Act abuse the privileges awarded to orphan drugs. Therefore, several changes to the Act have been proposed in Congress in hopes of preventing these perceived abuses. Proponents of amending the Act to exclude blockbuster drugs cite the original intent of the Act and a possible erosion of public support for the Act as motivating factors for such amendments.

B. PHARMACOGENOMICS

As mentioned in the previous discussion regarding the Act, drugs were historically targeted at large disease populations. Since development of drugs is

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55 See Maeder, supra note 4, at 82 (explaining that Epogen and Procrit, an almost identical drug, shared the market and generated over five billion dollars revenue annually for their respective manufacturers).
56 Id. at 87.
57 Pulsinelli, supra note 13, at 321-22.
59 Id.
60 Id.
62 See generally Pulsinelli, supra note 13; Maeder, supra note 4. Both authors acknowledge the contention from critics that highly profitable drugs abuse the privileges awarded under the Act.
63 Pulsinelli, supra note 13, at 324-35.
costly, large markets have been required to make the endeavor profitable. Pharmaceutical companies and biotechnology companies alike sought products that would have a consistent effect on every recipient. Customization of drugs to individual patients was initially crude, with manufacturers or doctors altering the dosage or delivery method in response to patient requirements. All levels of customization were based on physical signs or symptoms such as physical size, gender, or adverse reactions to treatment. The emergence and growth of biotechnology (aided by the Act) would help change the basis of drug customization.

Pharmacogenomics deals with the integration of genetic information and technology into the field of pharmacology. This hybrid field arose due to tremendous advances in genetic technology aided by the Human Genome Project and other bioinformatics projects that have rendered genetic information more easily accessible and usable. Patients’ positive or adverse reactions to drugs are dictated in large part by genetic predisposition. Using this information and new technology, pharmacogenomics aims to create more effective treatments. The potential of pharmacogenomics includes seriously reducing the occurrence of adverse reactions to drugs and actually developing drugs based on the genetic code of the recipient.

Currently, pharmacogenomics is investigating methods to predict how patients will respond to drugs. Accessing information in a patient’s genetic code allows doctors to prescribe a more effective dosage of the drug and possibly avoid adverse drug reactions depending on patient allergies and metabolism. St. Jude Children’s Research Hospital in Memphis, Tennessee, has already developed such a test. The genetic screen employed tests patients for mutations in the thiopurine S-methyltransferase ("TPMT") gene.

65 Rohde, supra note 3, at n.39.
66 See Lars Noah, The Coming Pharmacogenomics Revolution: Tailoring Drugs to Fit Patients’ Genetic Profiles, 43 JURIMETRICS J. 1, 5 (2002) ("[P]hysicians frequently must try different medications at different dosages until they find the one that seems to work best in a particular patient.").
67 See id. at 5-7 (describing a “trial and error” method employed by physicians which allows them to determine the correct drug and dosage for an individual patient based on outward signals such as adverse reactions).
68 See Maeder, supra note 4, at 87 (pointing out that five of the ten best-selling biotech drugs in the world in 2001 were originally approved as orphan drugs and another three were approved for orphan indications).
70 See Sandra Soo-Jin Lee et al., The Meanings of “Race” in the New Genomics: Implications for Health Disparities Research, 1 YALE J. HEALTH POL’Y L. & ETHICS 33, 36 (2001) (observing that many believe the sequenced human genome and related technology will help create the field of pharmacogenomics).
71 See Evans & Relling, supra note 10, at 464-65 (mentioning many polymorphisms in genes which affect the metabolism and transportation of drugs); but see Kathryn A. Phillips et al., Potential Role of Pharmacogenomics in Reducing Adverse Drug Reactions, 286 JAMA 2270, 2275 (2001) ("The link between [adverse drug reactions] and genetic variability is complex, and our findings do not imply a causal relationship or that [adverse drug reaction] incidence would necessarily be reduced if drug selection and dosing were based on genetic variability.")
73 Id.
TPMT regulates how the liver breaks down certain drugs, including 6-mercaptopurine, a chemical that's a lifesaver for victims of acute lymphoblastic leukemia, a deadly form of cancer that afflicts approximately 2,400 American children and adolescents each year. Between 10 and 15 percent of children metabolize the drug either too quickly or too slowly. The former don't gain a benefit from a standard dose, while the latter can accumulate lethal levels of the drug.

This genetic screen informs doctors of the recipient's metabolic rate and allows them to administer the proper dosage of the drug and thereby reduce the frequency of adverse reactions.

In addition to employing existing medicine in a more effective manner, pharmacogenomics is concerned with utilizing genetic information to help create new drugs. For example, SmithKline Beecham introduced a vaccine for preventing Lyme disease called LYMErix. Unfortunately, a class action suit against the company claimed that a genetically identifiable subgroup composing up to thirty percent of recipients are predisposed to develop "an incurable autoimmune disorder called treatment-resistant Lyme arthritis from the vaccine." Theoretically, a genetic screen such as the one described in the previous paragraph could avoid the adverse drug reactions, but would still leave up to thirty percent of the population with no available treatment. Pharmacogenomics could potentially help design drugs based on the recipients' genetic codes. Thus, in the LYMErix example, SmithKline Beecham could potentially use genetic information from the subgroup to aid development of a safe version of LYMErix. Hypothetically, companies could eventually alter drugs based on all of the relevant factors present in one individual (e.g., genetic code, weight, diet, other medication, etc.) to obtain the maximum efficacy with minimal dosages and side effects.

III. LEGAL ISSUES

The potential interactions of pharmacogenomics and the Act raise both new and old concerns. New concerns revolve around the interpretation of the Act with respect to pharmacogenomic drugs and the ability of pharmacogenomics to alter the landscape of orphan drug approval. Old concerns include many critics' complaints that the drug industry abuses the benefits of the Act.

A. PHARMACOGENOMIC INTERACTIONS WITH THE ACT

1. Methods of Developing New Drugs Funded by the Act

a. High-Tech "Salami Slicing"

Pharmacogenomic technology could allow drug developers to obtain the benefits of the Act while developing drugs targeted at large populations. The blueprint for such a course of action has already been revealed by the numerous
blockbuster drugs that entered the market as orphan drugs.\textsuperscript{78} In the past, this salami slicing has been based on distinctions regarding medical classifications. Pharmacogenomics might allow drug sponsors to nudge salami slicing from the arena of medical judgment towards the arena of scientific fact. This would present new issues for the FDA to handle.

Common diseases which affect a large number of people often have different variations, even if the variations only include disease sufferers with different allergies or rates of drug metabolism. Under the Act, a rare disease is “any disease or condition which . . . affects less [sic] than 200,000 persons in the United States.”\textsuperscript{79} Therefore, treatments for medically differentiable subgroups of a disease should qualify as orphan drugs provided the population is fewer than 200,000 individuals.

In some cases, a single drug may help treat many different diseases. For example, epoetin alfa increases red blood cell count, which helps combat anemia associated with end-stage renal failure and several other unrelated conditions.\textsuperscript{80} Thus, although drugs that restore red blood cells have a large market,\textsuperscript{81} two drugs treating anemia have been awarded orphan designation because they were targeted at anemia coincident with end-stage renal disease.\textsuperscript{82} Pharmacogenomics could possibly take this salami slicing to a new level. Congenital diseases, for example, may arise from a variety of different mutations that occur in single or multiple metabolic pathways.\textsuperscript{83} Each genetic variation could possibly be considered a disease unto itself for orphan drug designation purposes.\textsuperscript{84} The key factor in determining what drugs will receive the orphan designation will be the FDA’s interpretation of the term “medically plausible.”

In response to public anger regarding several highly successful orphan drugs developed via the salami slicing method, the FDA declared that all disease subsets must be “medically plausible.”\textsuperscript{85} The exact meaning of “medically plausible” is unclear, and the use of the term has been likened to “a medical decision, with a dollop of policy thrown in.”\textsuperscript{86} Congress has explained, “FDA declines to provide examples of medical plausibility [of a disease subgroup] or to further develop the definition of this term. Application of the concept is a matter of judgment based on the specific facts of each case.”\textsuperscript{87} While this kind of case-by-case discretion will provide the most flexibility while examining orphan drug applications, it is not necessarily the most desirable manner in which to control access to the Act’s benefits. Companies that might develop orphan drugs would likely prefer a more

\textsuperscript{78} Epogen, Procrit, and HGH (human growth hormone) are all examples of blockbuster drugs whose parent companies utilized (whether intentionally or not) the “salami slicing” methodology. See generally Maeder, \textit{supra} note 4.


\textsuperscript{80} Maeder, \textit{supra} note 4, at 81-82 (“Epogen proved useful for other . . . purposes: restoring red blood cells in people suffering from bone marrow suppression as a result of taking AIDS drugs or cancer chemotherapy, and reducing the need for transfusions in surgery patients.”)

\textsuperscript{81} \textit{Id.} at 84 (showing that annual worldwide sales of epoetin alfa reached $5.88 billion in 2001).

\textsuperscript{82} \textit{Id.} at 81. Epogen and Procrit are the epoetin alfa products of Amgen and Ortho Biotech, respectively.

\textsuperscript{83} See Evans & Relling, \textit{supra} note 10, at 465 (discussing mutations in “pathways” and “networks” of genes that lead to different conditions).

\textsuperscript{84} If each genetic variation affected a different step in the pathway, it seems that a strong argument could be made that each mutation gives rise to a medically plausible subset of the disease.

\textsuperscript{85} Pulsinelli, \textit{supra} note 13, at 322.

\textsuperscript{86} \textit{Id.}

transparent manner of application review that does not leave final discretion with an unclear group of arbiters.

Drug sponsors’ preferences for simple guidelines were most clearly evident when the Act was first passed. At the time, the FDA neglected to give a transparent definition of diseases that would qualify as an orphan. The original version of the Act defined a “rare disease or condition” as “any disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.”

Drug sponsors were reluctant to invest the time and money required to demonstrate commercial infeasibility of the drugs and were hesitant to share cost and expected revenue information with the FDA. As a result of this uncertain definition of “rare disease or condition,” drug companies were reluctant to submit applications for approval. In 1984, Congress decided to change the definition of “rare disease or condition” to refer to any disease or condition which affects fewer than 200,000 people. This new definition provided much more simplicity and predictability for drug sponsors, and drug companies increased the number of applications for orphan drug status.

b. New Drugs to Treat the Untreated

In other cases, a cure to a common disease might be unavailable to a small percentage of that population. The LYMERix example above shows a situation in which people affected by a common disease might create the opportunity for an orphan drug treatment. To determine the size of such a subgroup, drug developers would turn to pharmacogenomic technologies. A genetic screen would allow doctors to measure what percentage of people is likely to have an adverse reaction to the conventional treatment.

Furthermore, other pharmacogenomic technologies might even help develop drugs to treat the subgroup. If this genetically identifiable subgroup numbers fewer than 200,000 individuals, a cure directed towards helping its members would possibly qualify for orphan drug designation regardless of whether the treatment also worked for the rest of the disease population. Such treatments would need to be analyzed under the FDA’s “medically plausible” subgroup definition mentioned above.

2. Clinical Superiority – Not Necessarily Better

Pharmacogenomics could also impact the application of the definition of “same drug” under the Act. From the beginning of the Act, “the FDA’s . . . policy [was] to
not consider requests for [the same] orphan drug designation made after that drug has received full FDA marketing approval for that particular disease.”¹⁹⁵ Therefore, the marketing exclusivity guarantee prevented drugs that were viewed as the same from receiving orphan drug designation. Before the popularity of biotechnology, drugs typically consisted of simple chemical structures with a known active site that determined the effect and effectiveness of the drug.¹⁹⁶ For simpler drugs, the active site determined whether two drugs were different.⁹⁷

However, due to the complexity of the biochemical structure of most orphan drugs, the distinction between “same” and “different” became more uncertain.⁹⁸ As a result, the FDA decided to abandon molecular analyses for the purposes of determining “same” and “different” under the Act.⁹⁹ Citing the clarity of application and beneficial results for patients, the FDA decided to equate “different” with “clinically superior.”¹⁰⁰ The exception for clinically superior drugs is broad: “FDA will not interpret the Orphan Drug Act to block approval of any drug proved to be clinically superior to a drug with currently effective exclusive marketing rights.”¹⁰¹ Furthermore, FDA will grant approval for drugs demonstrating superiority in clinical trials with a “substantial portion” of the population indicated for the original drug.¹⁰²

Pharmacogenomics could have interesting implications for the emphasis placed on “clinical superiority.” One exception to the FDA’s grant of market exclusivity under the Act is when a second drug is proven to be “clinically superior.” A lower occurrence of side effects or increased efficacy during clinical trials can serve as a basis for determining a new drug to be clinically superior to another drug.¹⁰³ As discussed earlier, pharmacogenomics can help identify patients who are susceptible to adverse drug reactions.¹⁰⁴ With such technology, a drug sponsor could create significantly better clinical results without altering a drug at all. Using data gathered during the first clinical trials and subsequent data gathered from market usage, companies could identify genetic subgroups of the population who present a higher likelihood of negative or neutral drug reactions.¹⁰⁵ Then a company could use that information to design a new clinical trial excluding patients who are likely to produce the unwanted results. Thus, the data obtained from this new clinical trial would likely appear more favorable or impressive than the original trial even if both trials used the exact same drug. While obtaining such information for use in creating a new clinical trial could prove difficult, the FDA should prepare for the possibility.

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¹⁹⁶ See Bohrer & Prince, supra note 39, at 384 (asserting that “before the development of recombinant proteins by the biotechnology industry . . . smaller, simpler structures provided the basis for most drugs”).
¹⁹⁷ Id.
¹⁹⁸ See id. at 387-98 (examining some earlier litigation arising from conflicts over the definition of “same” and “different” under the Act).
¹⁹⁹ Id. at 392; see also Orphan Drug Regulations, 57 Fed. Reg. at 62,077 (rejecting the proposal that FDA adopt an “active moiety” standard of “sameness” for macromolecules under the Act).
¹⁺⁰ Bohrer & Prince, supra note 39, at 392.
¹⁺¹ Orphan Drug Regulations, 57 Fed. Reg. at 62,078.
¹⁺² FDA Orphan Drug General Provision, 21 C.F.R. §316.3(b)(3) (1999).
¹⁺³ Bohrer & Prince, supra note 39, at 392.
¹⁺⁴ See supra Part II(B).
¹⁺⁵ See Noah, supra note 66, at 12 (describing pharmaceutical companies as seeking out possible subgroups that will respond most favorably and with least side effects to a tested treatment).
B. CHANGING THE ACT TO REMEDY OR PREVENT PROBLEMS

The potential interactions of pharmacogenomics with the Act are numerous and some open the door to possible exploitation of the Act’s benefits. As described above, some pharmacogenomic drugs could utilize old methods of co-opting the Act’s benefits (e.g., salami slicing), while some new methods also exist (e.g., modified clinical trials). Critics of the Act proposed several changes to try and deal with perceived or feared abuse. Those past suggestions could possibly help curb abuse from pharmacogenomics, although novel solutions might work also.

1. Methods to Control Abuse with Hindsight

Suggestions to help curb abuse of the Act’s benefits have resulted in many proposals to punish perceived abuse through removal of the Act’s benefits or imposition of increased profit taxes. Each of these proposals include a specific “trigger event,” which would serve as a signal that the benefits of the Act are no longer necessary or that profit taxes should be implemented to prevent abuse.

a. Termination of Exclusivity

The strongest financial incentive for abuse is the seven-year guarantee of market exclusivity. Even though tax incentives and grants for research clearly provide additional motivation for companies to pursue approval for an orphan drug, the profits generated from even one additional year of market exclusivity can dwarf those other incentives. Therefore, many lawmakers interested in limiting the potential profits realized under the Act have proposed alterations to the exclusivity term. Several such proposals have included a conditional shortening of the term based upon the occurrence of a “trigger event.”

The proposed amendments in 1992 conditioned exclusivity on the total revenue derived from an orphan drug. After an introductory two-year period, orphan drugs would continue to enjoy market exclusivity provided total revenue from the drug never exceeded $200 million. When revenue did exceed $200 million, exclusivity would be revoked. This “trigger event” would include all revenue derived from a particular drug, including off-label usage. Thus, drug sponsors trying to take advantage of a larger market via off-label uses would likely lose market exclusivity if successful.

Amendments proposed in 1990, 1991, 1992, and 1994 included a different “trigger event.” Under these proposals, marketing exclusivity would be terminated once the rare disease population became larger than 200,000 individuals. This would have affected AIDS treatments, such as AZT and pentamidine, for which the population grew well past 200,000 after FDA already awarded orphan

106 Pulsinelli, supra note 13, at 332-36
107 Id. at 333-36.
108 Id. at 310 (“[Market exclusivity] is the most significant incentive . . .”); see also Maeder, supra note 4, at 83 (“The seven-year market exclusivity clause has been key to the effectiveness of the [Act].”).
109 Pulsinelli, supra note 13, at 332-36.
110 Id. at 334.
111 Id.
112 Id.
113 Id.
114 Id. at 334-35.
However, these proposals would not include off-label usage. Therefore, market exclusivity would be revoked only if the population for a drug’s initial indication exceeded 200,000 persons. Since pharmacogenomic drugs could target small patient populations and rely on off-label usage, such a trigger event would not likely affect the benefits awarded to pharmacogenomic drugs. Furthermore, such restrictions might hinder the continued development of orphan drugs due to uncertainty regarding the financial future of the drug. For example, sponsors will have a disincentive to create cures for diseases affecting close to 200,000 individuals if the market exclusivity guarantee will be terminated should that population suddenly increase.

The effects of patent law present an important factor when contemplating changes to market exclusivity. If the drugs created through pharmacogenomics are patentable, then the market exclusivity provision of the Act becomes less valuable when compared to the other provisions. Unfortunately, no further attention will be given to the possible impact of patent law because the science and legal issues reach beyond the scope of this paper. However, any potential impact is limited to discussions involving market exclusivity and does not affect the subsequent proposals.

b. Windfall Profit Taxes

Since the massive profits received from a blockbuster drug are often the source of antipathy towards perceived abuses of the Act, one suggested remedy called for a windfall profit tax on all revenue above a certain level. The proposals in Congress have typically utilized the cost of developing the drug in question as a basis for determining the revenue level at which the tax would begin. Beyond the threshold level, all profits would be taxed at a high rate to prevent companies from realizing the perceived windfall.

Unfortunately, this proposal presents too many problems. First, the administration of such a system would be costly, since each drug would have a unique level at which the tax would begin. Additionally, drug companies might find this system undesirable because companies typically work hard to keep costs of drug development confidential. Next, the true cost of a drug is difficult to determine because drugs that eventually go to market must absorb costs of failed drugs. Finally, a profits tax will increase a manufacturer’s incentive to increase prices and pass the cost on to the consumer.

c. Stricter Regulation of Off-Label Prescriptions

The FDA could attempt to regulate the prescription of orphan drugs for off-label uses. Since most perceived abuses of the Act result from off-label prescriptions, this

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115 Id. at 323.
116 See id. (mentioning that the proposals call for monitoring the size of the disease population rather than total prescriptions or sales).
117 Pulsinelli, supra note 13, at 335.
119 Id.
120 Pulsinelli, supra note 13, at 336.
would have the added benefit of targeting the class of drugs most likely to offend the original intent of the Act. However, constitutional and general health care concerns would likely deter the FDA from pursuing this strategy. The FDA regulates drug manufacturers, not doctors, and even the regulation of manufacturers is subject to limits regarding off-label advertising. Furthermore, it is widely believed that the practice of off-label prescribing actually enhances the quality of health care given to patients. Thus, it appears unlikely that the FDA would successfully attempt to pursue this path of regulation.

2. Preventing Abuse by Limiting Access to the Act’s Benefits

Rather than implementing “trigger event” penalties for orphan drugs, the FDA could increase scrutiny on orphan drug applications, attempting to close the loopholes that lead to perceived abuses. The benefits of this route are twofold: (1) it affords greater simplicity than post-hoc determinations of profit or size of a certain disease population; and (2) it keeps the benefits of the Act consistent, thus providing the same incentives for drug companies to fund research in the future. The Act’s definitions of “same” and “different” and “medically plausible” provide two options for limiting access to the Act’s benefits.

a. Clarifying “Same” and “Different”

Drugs that are the “same” as current orphan drugs and carry the same designation will not be awarded orphan drug status. As mentioned earlier, the definition of “same” under the Act currently refers to two drugs with nearly identical efficacy in clinical trials. With this definition, a drug that is structurally identical could be viewed as different under the Act if the clinical trial results are better. Since pharmacogenomics could help this result to occur, it might be useful for the FDA to incorporate some new definition for “same” under the Act. Since “clinically superior” is correlated with “different,” the definition of “clinically superior” could provide a useful starting point. If the FDA required that clinical superiority be demonstrated with the same genetic demographics as the previous studies, such abuses might be avoided.

The FDA recently took steps to request pharmacogenomic data from drug sponsors. While this policy still requires revision and expansion, such information will help the FDA understand the nature of the pharmacogenomic drugs it deals with in the future. Whether drug companies will voluntarily share pharmacogenomic data (which may be viewed as sensitive information) with the FDA remains to be seen.

b. Clarifying “Medically Plausible”

Only drugs targeting “medically plausible” subgroups of diseases can receive designation as orphan drugs. However, the FDA and Congress have expressly declined to clarify the definition of “medically plausible.” Defining “medically plausible...”

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122 See Washington Legal Found. v. Henney, 202 F.3d 331, 336 (D.C. Cir. 2000) (holding the FDA may not prevent drug manufacturers from educating doctors about off-label uses of their products).
124 FDA, supra note 16.
plausible” in a specific manner might help prevent abuse via salami slicing. Unfortunately, the possible definitions and subsequent ramifications have not yet been explored publicly. It appears reasonable that the term must remain malleable in response to the malleable nature of drug development. Perhaps the increased precision that pharmacogenomics brings to pharmacology might eventually help provide the FDA with the ability to define “medically plausible.”

IV. CONCLUSION

Just as it aided the biotechnology industry, the Orphan Drug Act will likely provide assistance to a fledgling pharmacogenomics industry. However, the FDA and Congress must be wary of the interactions between this new technology and the Act. Current regulations, developed before the advent of this new field, may not be well adapted to handling pharmacogenomic drug applications. Pharmacogenomic research presents opportunities to make the Act an even greater success while simultaneously opening up potential avenues for abuse by sponsor companies. Salami slicing and screened clinical tests present just two manipulation techniques that the FDA may have to confront in orphan drug applications. The FDA should attempt to anticipate these problems and take sufficient steps to prevent them.

Potential solutions would address potential problems between pharmacogenomics and the Act while also addressing existing criticisms of the Act. The only interactions between pharmacogenomics and the Act which people will likely find objectionable are blockbuster drugs receiving the Act’s benefits. Pharmacogenomics presents a new avenue for this potential abuse, but the problem has existed for much of the Act’s life. Many solutions have been presented which condition the continued supply of benefits under the Act upon the economic necessity of the orphan drug. These remedies include revocation of market exclusivity and windfall profit taxes, neither of which address one of the largest benefits of the Act, namely, the aid of the FDA in getting the drug through clinical trials as quickly as possible.

While these proposed solutions could provide incentives to prevent abuse of all types, they also lower the incentives of sponsor companies to bring orphan drugs to market. The better solution would be to keep the incentives where they are and to eliminate blockbuster drugs from the approval process. Unfortunately, pharmacogenomics will present new difficulties in limiting abuse in the application process.

Other options include altering the regulations within the Act to take into account the technological advances of pharmacogenomics. Terms such as “same” and “medically plausible” contain vagueness that pharmacogenomics can exploit. Identifying clearer definitions with these terms and all regulations would help close loopholes that let offending drugs through. If such steps are implemented successfully, the Act may very well continue to operate as it has for the past two decades without further revision.

126 See Maeder, supra note 4, at 84-85 (describing the numerous orphan drugs created by biotechnology companies and the growth of that industry incident with the success of several orphan drugs).
