

# Orphan Drug Act: Fostering Innovation or Abuse?

By: Grace Lee, Research Fellow

## Introduction

Luke Whitbeck, 2, was born with Gaucher disease, a rare genetic disorder.[\[1\]](#) Before using the pharmaceutical drug Cerezyme,[\[2\]](#) “Luke frequently ran high fevers, tired easily, and was skinny all over, except his belly stuck out like a bowling ball.”[\[3\]](#) Fortunately, the drug effectively helped Luke manage his symptoms. His mom reports that “Luke now spends days playing with his big brother.”[\[4\]](#) Despite the bill of good health, the Whitbecks and their insurer struggle to pay for the high cost of the drug, which amounts to \$300,000 a year[\[5\]](#)—a hefty price tag compared to common disease drugs. Similarly, many Americans are burdened with the reality of paying high prices for rare disease drug treatments, which affect 30 million people in the U.S.[\[6\]](#)

Orphan drugs, such as Cerezyme, are prescription drugs used to treat[\[7\]](#) rare diseases that affect less than 200,000 individuals.[\[8\]](#) Because rare diseases involve a small patient population, and thus a small consumer market, pharmaceutical companies need incentives to make the development of orphan drugs financially viable. Prior to 1983, the Food and Drug Administration (“FDA”) approved 10 drugs that would have qualified as an orphan drug.[\[9\]](#) In 1983, Congress passed the Orphan Drug Act (“the Act” or “ODA”) to provide various financial, commercial, and regulatory incentives to stimulate pharmaceutical companies to enter this market.[\[10\]](#) The Act successfully enabled the development of over 600 drugs and biologic products,[\[11\]](#) including Cerezyme.[\[12\]](#)

In recent years, the orphan drug market has become very lucrative,[\[13\]](#) and the number of orphan drugs introduced into the market has multiplied. In part, orphan drug spending has increased because orphan drugs continue to be extremely expensive. In 2015, the average annual price tag for an orphan drug was \$111,820 versus \$23,331 for mainstream drugs (13.8 times higher).[\[14\]](#) In 2016, the average annual cost of an orphan drug was \$140,443, whereas non-orphan drugs averaged \$27,756.[\[15\]](#) By 2020, orphan drug sales worldwide are expected to account for just over 20 percent of all brand-named drug sales.[\[16\]](#)

Given these statistics, patients, their families, and their doctors worry that they will no longer be able to afford the only available treatments for their rare diseases. The increase in cost of orphan drugs not only burdens insurers, but also government programs like Medicare and Medicaid, because use of these drugs is inelastic—purchasers of the drug have no choice but to pay for the drugs.[\[17\]](#) Further, orphan drugs have become the fastest growing health insurance expenditure, contributing to premium increases for all enrollees.[\[18\]](#)

Concerned with this issue, Kaiser Health News (“KHN”) published a [special report](#) exploring the high price of orphan drugs and found that pharmaceutical companies are potentially abusing the orphan drug incentives created by Congress.[\[19\]](#) KHN found that drug companies repurpose both mass marketed and orphan drugs, while seeking new orphan drug designations on small patient populations, to protect their drugs from competition.[\[20\]](#) This practice allows drug manufacturers to raise and maintain drug prices, contrary to the goals of the ODA to incentivize innovation and increase new drugs for rare diseases.[\[21\]](#)

Some, however, question whether there has been an actual abuse of the orphan drug laws, which has led to an increase in drug

prices. In the KHN investigation, rare disease advocates argue that drug companies may be simply finding legitimate new uses (indications) of the orphan drug, for which high prices are warranted.[\[22\]](#) FDA scholars suggest that patients may counter high prices by using the drug off-label, the practice of using prescription drugs for an unapproved indication.[\[23\]](#)

This brief further examines whether pharmaceutical companies are abusing the Orphan Drug Act. Part I examines the history and purpose behind the Orphan Drug Act and the benefits of an orphan drug designation. Part II argues that the pharmaceutical companies are abusing the Act and explains how. Part III examines how the abuse raises prices. Finally, Part IV suggests some remedies and explains current government attempts to address this problem.

## **I. Background**

### **A. Orphan Drug Act of 1983**

Congress passed the ODA, which amended the Food, Drug, and Cosmetics Act, in response to findings and concerns about drug development for rare diseases. Congress found that pharmaceutical companies and sponsors were not developing adequate drugs for rare diseases and conditions that affect a small number of individuals, such as ALS and Huntington's disease.[\[24\]](#) Pharmaceutical companies lacked interest in this market[\[25\]](#) because despite spending large amounts of money on development, the drug would not return a large profit because it only targets a small patient population.[\[26\]](#) Thus, Congress enacted the ODA to further public interest in treating people with rare diseases and provide financial incentives for pharmaceutical companies to develop drugs for rare diseases and conditions.[\[27\]](#)

Under the ODA, to receive an orphan drug designation from the FDA, the product must be: an approved new drug or biologic,[\[28\]](#) intended for the safe and effective treatment, diagnosis, or prevention of a rare disease or disorder that affects fewer than 200,000 individuals, or if the disease affects more than 200,000, the pharmaceutical company could have no reasonable expectation to recover the cost of research and development by selling the drug in the United States.[\[29\]](#) A pharmaceutical company seeking an orphan drug designation may apply for the designation at any point in time—before or after FDA approval.

## **B. The Lucrative Orphan Drug Machine: The Benefits of an Orphan Drug Designation**

Receiving an orphan drug designation can be very lucrative for pharmaceutical companies. In fact, seven of the top 10 best-selling drugs are orphan drugs.[\[30\]](#) If the FDA awards an orphan drug designation, pharmaceutical companies benefit from monopoly pricing opportunities, greater probability of receiving FDA approval, and lower costs.[\[31\]](#)

### **a. Monopoly Pricing Opportunities**

When given an orphan drug designation, pharmaceutical companies profit from monopoly pricing opportunities. Pursuant to the ODA, the FDA may award an orphan drug exclusivity for seven years,[\[32\]](#) in addition to any other available exclusivities.[\[33\]](#) Although this protection may run concurrently with patent protection, the exclusivity bars the FDA from approving other drug or biologic applications (i.e. an ANDA, NDA, or BLA) for the same use of the drug.[\[34\]](#) If awarded the exclusivity, the sponsor would have access to monopoly pricing, as a legal monopolist, allowing it to set high prices as the only seller of the drug in the market for that particular use or disease. Even

after its exclusivity or patent expires, a pharmaceutical company typically maintains its monopoly pricing, because the small number of patients with an orphan disease “reduces the economic viability for generic drugs to enter the market.”[\[35\]](#) Orphan drugs also do not have generic competitors because many orphan drugs are biologics, which “historically have had no clear path for generic approval.”[\[36\]](#) If generic drug companies do not enter the market, a sponsor may maintain orphan drug prices at its monopoly level.

Furthermore, pharmaceutical companies are able to maintain their monopoly pricing despite participating in Medicaid. The federal 340B drug pricing program requires drug manufacturers to discount drugs to hospitals and clinics that serve poor communities in exchange for inclusion in Medicaid formularies, which would boost sales.[\[37\]](#) However, under the ACA, drugs with an orphan drug designation are exempt from the mandatory discounted pricing.[\[38\]](#) In fact, “a drug that has gained orphan status from one condition gains exclusion from the 340B program for all its sales.”[\[39\]](#) As a result, pharmaceutical companies benefit from monopoly pricing opportunities via FDA exclusivities, the lack of competition, and the 340B program exemption.[\[40\]](#)

#### **b. Higher FDA Approval Rates and Rise in Stocks**

Orphan drugs have a track record of being approved at much higher rates than drugs for common diseases.[\[41\]](#) The FDA typically allows sponsors to go through a shorter and less extensive approval process for orphan drugs.[\[42\]](#) In addition, publically-traded pharmaceutical companies profit from such regulatory success because their shares often rise upon receiving an orphan drug designation,[\[43\]](#) some as much as 30 percent.[\[44\]](#) Stocks often rise because investors “place positive, statistically significant, value on the orphan drug

designation.”[\[45\]](#) The orphan drug designation conveys to an investor that the sponsor is likely to receive “tangible financial benefits (both immediately and in the future)” in the form of a tax credit, waived user fees, and seven years of marketing exclusivity.[\[46\]](#)

### **c. Lower Costs**

Lastly, pharmaceutical companies with orphan drug designations benefit from lower marketing costs, lower research and development (“R&D”) costs, substantial tax-credits, and other miscellaneous cost-savings. Pharmaceutical companies have lower marketing costs because they need to reach fewer medical specialists than non-orphan drugs.[\[47\]](#) Provided that these drugs target a small population and are the only option available, “public and private programs . . . facilitate the diffusion of information about the products to patients and health professionals, thus reducing marketing costs.”[\[48\]](#)

Similarly, the cost of developing an orphan drug is much lower than developing a common-disease drug. To develop an orphan drug, a pharmaceutical company would spend about one billion dollars,[\[49\]](#) whereas the cost of bringing a common-disease drug to the market is roughly 2.8 billion dollars.[\[50\]](#) Such cost-savings mainly stems from smaller clinical trials or observational studies[\[51\]](#) and Fast Track review procedures.[\[52\]](#)

Generally, those trying to mass market a drug for common diseases must conduct two to three clinical trials to receive FDA approval,[\[53\]](#) which requires thousands of patients with the disease.[\[54\]](#) In contrast, the FDA approved two-thirds of the orphan drugs on the market with a single clinical trial,[\[55\]](#) some of which were not randomized, placebo-controlled, or double-blind.[\[56\]](#) The FDA is more flexible when evaluating drugs for rare diseases and conditions than mass market drugs[\[57\]](#) due

to the small number of patients with an orphan disease,[\[58\]](#) which can make recruiting patients difficult. For instance, a sponsor may not be able to recruit enough patients with the orphan disease at a certain point of progression.[\[59\]](#) Geographic dispersion of a small patient population makes it difficult for investigators to examine patients.[\[60\]](#) And, patients with severe physical impairments may not be able to visit a sponsor's research center, hindering participation in clinical trials.[\[61\]](#) Thus, large clinical trials may not be feasible with some orphan diseases, resulting in lower costs and less time for development.[\[62\]](#)

In addition to smaller clinical trials, further cost-savings arise from grants, exemption from fees, and tax credits. Pharmaceutical companies with orphan drugs can apply for clinical trial grants. For example, FDA's Office of Orphan Product Development administers a grant program called the Orphan Products Clinical Trials Grants Program.[\[63\]](#) On average, the office awards 15 million dollars and funds about 60 to 85 projects per fiscal year.[\[64\]](#)

Moreover, orphan drugs are not subject to prescription drug user fees,[\[65\]](#) which are fees collected by the FDA from companies that produce drugs or biologics.[\[66\]](#) In contrast, non-orphan drug sponsors may pay prescriptions user fees in excess of two million dollars for an NDA review.[\[67\]](#) Similarly, orphan drug sponsors are exempt from paying their portion of the annual market-share fee mandated by the ACA, if solely approved for orphan indications.[\[68\]](#)

Lastly, pharmaceutical companies may qualify for two different tax credits: an R&D tax credit and an orphan drug tax credit ("ODTC").[\[69\]](#) The ODTC allows sponsors of orphan drugs to write off half of its clinical trial costs.[\[70\]](#) In addition, sponsors can claim the R&D tax credit for "development costs . . . that

are qualified research expenses regardless of FDA designation or approval of the drug.”[\[71\]](#) These tax credits may give orphan drug companies significant cost-savings. For example, in 2014, the average cost of a phase III clinical trial for a non-orphan drug was \$193 million, versus \$51 million for an orphan drug.[\[72\]](#) The stark difference in numbers is due to the ODTC. Without the ODTC, the average cost of an orphan drug phase III clinical trial would have cost \$103 million.[\[73\]](#) Therefore, orphan drug companies benefit financially because they have access to grants, waived fees, and tax credits.

## **II. The Orphan Drug Abuse**

### **A. Salami Slicing The Disease**

Given these incentives, pharmaceutical companies are increasingly taking advantage of the ODA in ways that its creators never foresaw, such as engaging in salami slicing. Some drug companies would first identify a common disease, and then ascertain multiple small patient populations to “salami slice the disease into subgroups.”[\[74\]](#) The medical community often recognizes subpopulations of a disease as a subtype of the disease, as the disease becomes more precisely identified.[\[75\]](#) Rather seeking FDA approval for the treatment of the broader disease (the whole salami), sponsors will obtain approval for subtypes of the disease (the slices).[\[76\]](#) By seeking approval for a “slice,” drug companies would be able to seek FDA approval as an orphan drug rather than a mass market drug, because the same drug would treat a disease that affects less than 200,000 patients.[\[77\]](#) This process also allows drug companies to repeatedly repurpose their initially approved orphan drug by demonstrating its use in another small subtype of the disease to keep its monopoly power or reduce costs. The FDA would generally

approve the new use through the shortened approval process,[\[78\]](#) because the drug has already been tested for safety.[\[79\]](#)

This practice is commonly seen in the oncology space because researchers now stratify cancer based on genome, rather than its effect on an organ or tissue.[\[80\]](#) When classified based on genome, a cancer drug, which may be an orphan drug, is used to treat that specific mutated genome or characteristic of cancer, rather than a specific organ or tissue.[\[81\]](#) However, a sponsor will seek orphan status based on a cancer's effect on the organ or tissue when seeking FDA review,[\[82\]](#) rather than seeking approval to treat the mutated genome or characteristic as a mass market drug. As a result, a sponsor can file for multiple orphan statuses as long as the disease involves the specific mutated genome or characteristic with less than 200,000 patients, even though the drug benefits more than 200,000 individuals.[\[83\]](#)

For example, Avastin (generic name: bevacizumab) blocks the development of new blood cells by inhibiting the vascular endothelial growth factor A (VEGF-A).[\[84\]](#) Given that this characteristic is found in a number of other cancers,[\[85\]](#) Genentech, Avastin's sponsor, has multiple orphan drug approvals in different cancers such as renal cell carcinoma,[\[86\]](#) ovarian cancer,[\[87\]](#) malignant glioma,[\[88\]](#) primary peritoneal carcinoma,[\[89\]](#) and fallopian tube carcinoma.[\[90\]](#) For a drug approved in 2004, Genentech has exclusivity over the drug until 2021.[\[91\]](#) Similarly, Imbruvica (generic name: Ibrutinib) targets the upregulation of the B-Cell receptor.[\[92\]](#) Given that a key characteristic in B-cell non-Hodgkins Lymphoma ("NHL") is an upregulation of the B-cell receptor, Pharmacyclics, Imbruvica's sponsor, has orphan drug approvals for seven different NHLs.[\[93\]](#) The company has exclusivity over the drug until 2024, despite being first approved in 2012.[\[94\]](#) Thus, both sponsors appear to have salami sliced the market into submarkets, thereby obtaining exclusivity longer than the standard seven years.

The practice of salami slicing is troublesome because it runs contrary to Congress's intention of the ODA. As previously mentioned, the ODA was enacted to spur innovation in the orphan drug markets. By salami slicing, drug companies are not creating new drugs. Rather, they are merely dividing a possible large disease population into artificial submarkets to maintain exclusivity over a drug. Moreover, the practice of "seeking initial FDA approval for a small population means that a potentially larger population is not receiving treatment."[\[95\]](#) Even if the drug is eventually approved for a larger population or another slice of the population, one may be wary of the drug's safety because safety was only clinically proven in the initially sliced population, not the population at large or other subpopulations.[\[96\]](#)

## **B. Repurposing a Mass Market Drug**

Alternatively, other pharmaceutical companies are manipulating the system by repurposing already approved mass market drugs developed for common diseases as an orphan drug. The drug companies would market and sell these drugs to treat orphan diseases by conducting additional testing on an orphan population.[\[97\]](#) This practice is unsettling because many drugs that now have orphan status are not entirely new—these are not "true orphan[s]."[\[98\]](#) Rather, these drugs, some with familiar brand names, are later approved as orphans after getting their NDA approved. According to KHN's investigation, a third of the orphan approvals are repurposed mass market drugs or drugs that received multiple orphan approvals.[\[99\]](#)

For example, "Botox, stocked in most dermatologists' offices, started out as a drug to treat painful muscle spasms of the eye and now has three orphan drug approvals. [It is] also approved

as a mass market drug to treat a variety of ailments, including chronic migraines and wrinkles.”[\[100\]](#) Similarly, Herceptin (generic name: trastuzumab) was approved in 1998 to treat breast cancer with the HER2 mutation, a non-orphan disease.[\[101\]](#) In 2010, Genentech, Herceptin’s sponsor, recycled the mass market drug and received orphan drug status to treat metastatic gastric or gastroesophageal junction adenocarcinoma with the HER2 mutation.[\[102\]](#) Genentech also has an orphan drug designation to treat patients with pancreatic cancer with the HER2 mutation.[\[103\]](#)

### **C. Hybrid Repurposing**

Lastly, another popular method of repurposing a mass market drug is for a sponsor to test an approved drug for an adult disease on kids,[\[104\]](#) as the drug nears the end of its exclusivity. A common disease affecting children may qualify as a rare disease, because juvenile patient populations are small enough for an otherwise common disease to be classified as an orphan disease.[\[105\]](#) In fact, “50% of rare disease patients are children.”[\[106\]](#) By treating the pediatric population as a subpopulation, the FDA not only awards drugmakers an orphan drug exclusivity, but also the pediatric exclusivity, which provides an additional exclusivity of six months and runs after all other patents and exclusivities expire.[\[107\]](#) Drug manufacturers are able to exploit such a method because “there is a loophole that allows manufacturers to skip pediatric testing requirements when developing a mass-market drug for treating rare diseases in children.”[\[108\]](#)

For example, FDA approved Humira to treat millions of individuals with rheumatoid arthritis.[\[109\]](#) Three years later, AbbVie, the maker of Humira, asked the FDA to designate Humira

as an orphan drug to treat juvenile rheumatoid arthritis, which affects only 30 to 50 thousand individuals.[\[110\]](#) FDA approved this pediatric use,[\[111\]](#) providing Humira with an extended exclusivity period.

Some, however, question whether pharmaceutical companies truly are abusing the law, because repurposing drugs results in scientific breakthroughs and patients benefit for new uses. In fact, repurposing drugs for new indications is an effective strategy for researching new medicines, because it allows sponsors to build upon previous R&D and speed through FDA review.[\[112\]](#) The KHN investigation suggests that drug companies are not breaking the law; rather, they are taking advantage of a law that its creators did not intend or foresee.[\[113\]](#) However, this argument is, in part, flawed. Although repurposing drugs result in new drug uses, there is no additional benefit to the patient when a drug company merely slices a patient population to protect its exclusivity over the drug. Instead, the practice unjustifiably awards FDA exclusivities without generating innovation, going against the purpose of the ODA to create new drugs for rare diseases.

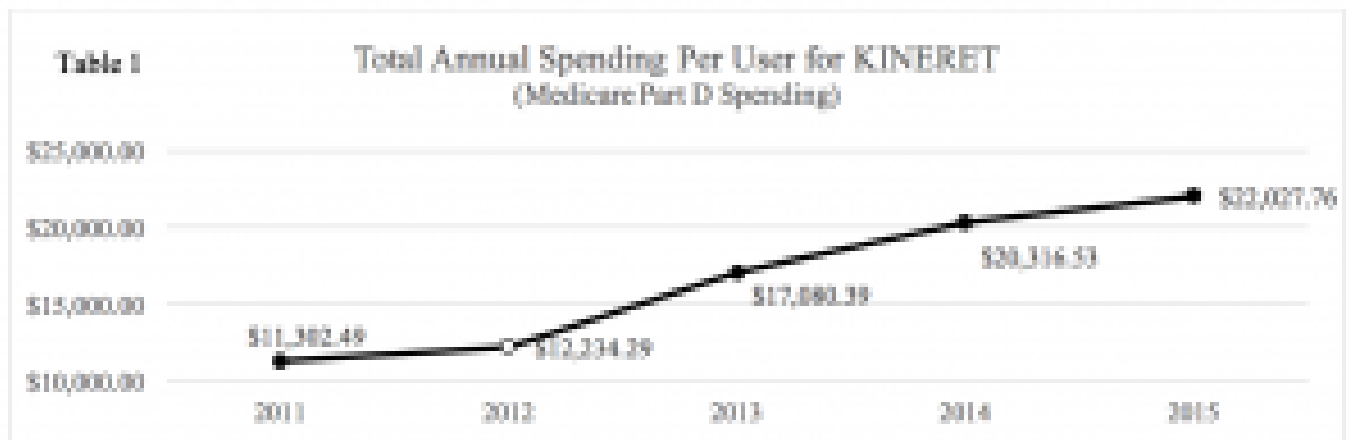
### **III. The ODA Abuse Drives Up Drug Prices**

#### **A. Method of Raising and Maintaining High Prices**

Drug companies abusing the ODA are raising the cost of prescription drugs because their practice allows them to maintain high prices.[\[114\]](#) When pharmaceutical companies salami slice diseases and repurpose older drugs as treatments for orphan diseases, they may maintain their exclusivity over the drug repeatedly. Given that the FDA will not approve a generic drug when a competing brand name has a valid exclusivity, drug manufacturers can keep generic competition out of each market

with an orphan population/disease.[\[115\]](#) By preventing generic competitors from entering the market via the use of renewed exclusivities,[\[116\]](#) abusers of the ODA can maintain monopoly prices or raise prices.

For example, Kineret (generic name: anakinra) was approved in 2001 to treat rheumatoid arthritis, a mass-market disease[\[117\]](#) by “block[ing] the biologic activity of IL-1 alpha and beta.”[\[118\]](#) In December 2012, the FDA approved Kineret as an orphan drug for the treatment of cryopyrin-associated periodic syndromes,[\[119\]](#) because those patients have a secretion of IL-1 beta.[\[120\]](#) Under Medicare Part D, the total annual spending per user for Kineret rose from \$12,234 in 2012 to \$17,080 in 2013.[\[121\]](#) This is a 40% increase, the highest price increase recorded between 2011 and 2015.[\[122\]](#) Given that the drug’s patent was set to expire in December 2013,[\[123\]](#) it appears as if Kineret’s sponsor specifically filed for orphan exclusivity to keep competitors out of the market, as there was no generic version of the drug,[\[124\]](#) and raise the prices of an existing drug.



Unfortunately, “Congress did not include any safety valves [in the ODA] that would allow the FDA to limit market exclusivity in case a sponsor was able to excessively profit off an orphan drug.”[\[125\]](#) Neither the Federal Trade Commission nor the

Department of Justice has the authority to regulate prices under the antitrust laws.[\[126\]](#) Without any safety check in place, drug companies will continue to unreasonably profit from this abuse against the purpose of the ODA, particularly impacting those with insurance plans that do not cover orphan drugs and must pay out-of-pocket.[\[127\]](#)

## **B. Off-Label Practice as a Possible Solution**

Some FDA scholars claim that the high prices that arise out of the orphan drug abuse could be alleviated through physicians prescribing drugs off-label, the practice of prescribing an FDA approved drug for an unapproved indication.[\[128\]](#) In theory, a physician may counter high prices by prescribing a patient with an orphan disease a cheaper off-label drug that is an equivalent of the orphan drug. Instead of the pricey orphan drug, the physician could prescribe a generic drug, a copy-cat version of a brand-name drug,[\[129\]](#) or a version of the orphan drug marketed for a different indication. Prescribing off-label could lower prices because an alternate version of the orphan drug may have generics in the market that generated competition, resulting in lower prices, and generics are typically priced cheaper than those with patent protection or FDA exclusivity.[\[130\]](#)

Unfortunately, a physician may run into several hurdles that render off-labeling practices impractical. First, many of these orphan drugs do not have a generic competitor in the market, allowing drug companies to maintain its monopoly prices.[\[131\]](#) Furthermore, an off-label usage may not be covered by insurance, due to potential claims that it is an experimental treatment.[\[132\]](#) If the treatment is not covered, requesting coverage is a difficult process,[\[133\]](#) making the treatment very expensive and cumbersome.

Next, physicians themselves may not know about an off-label usage—especially if the physician is confined to a specialized practice of medicine in which the drug’s approved use is not within the physician’s specialization,[\[134\]](#) and if drugs companies do not share information on an off-label usage.[\[135\]](#) As a result, if a physician does not know that an approved drug could be used for other populations or uses, and the drug company does not divulge such information, the physician cannot engage in off-labeling practices.[\[136\]](#)

Additionally, drug companies may package dosages in a way that makes taking other dosages impossible. For example, Xifaxan (rifaximin) is an orphan drug that may be used to treat Hepatic encephalopathy (HE), an orphan disease, and E.coli-induced traveler’s diarrhea, a non-orphan condition.[\[137\]](#) The traveler’s diarrhea requires 200mg, whereas HE requires 550mg.[\[138\]](#) So, substituting a HE dosage with the traveler’s diarrhea off-label is difficult. Even if a patient were to substitute a drug with a lower dosage, patients often find it impractical to take several pills if their dosage requirement is higher than or a non-multiple of the non-orphan drug. While compounding pharmacies, specialty pharmacies that create pharmaceutical products for the specific needs of a patient,[\[139\]](#) can reformulate the non-orphan drug for the patient, the cost of the compounded drug will likely rise significantly, potentially negating the savings of using an off-label drug. Thus, although a viable solution, engaging in off-label practices to combat high drug prices is often difficult and impractical to put into practice.

#### **IV. Reform Efforts**

In conclusion, when pharmaceutical companies abuse the ODA by slicing patient populations or repurposing mass market drugs to

seek an orphan drug designation repeatedly, drug prices escalate. Many policy makers and academics have suggested various direct and indirect reforms to restrain pharmaceutical companies from taking advantage of the law. Some suggest that the FDA should “require multiple orphan designations on the same drug product to run simultaneously or permit a manufacturer to only receive a single market-exclusivity period for a product’s first orphan drug indication.”[\[140\]](#) Others suggest that the FDA should revoke a drug company’s orphan drug exclusivity “if an orphan drug proved to have commercial potential or exceeded the 200,000-patient threshold.”[\[141\]](#) However, none have survived Congressional scrutiny.[\[142\]](#)

In March 2017, three senators, Orrin Hatch, Chuck Grassley, and Tom Cotton sent a letter to the Government Accountability Office (GAO), raising the possibility that regulatory or legislative changes might be needed “to preserve the intent of this vital law’ that gives drugmakers lucrative incentives to develop drugs for rare diseases.”[\[143\]](#) In response, the GAO agreed to open an investigation, which will most likely take about 9 months to investigate. It will be interesting to see whether the GAO can substantiate the claims of the orphan drug abuse.

Despite these actions, a key question remains: how can the ODA be amended to create access to necessary medication while fostering innovation? While efforts are being made, including FDA’s announcement to implement new controls to curb the orphan drug abuse,[\[144\]](#) House Republicans’ proposal to eliminate the tax credits that contribute to the orphan drug industry[\[145\]](#) may further stifle innovation in the orphan drug markets, as such savings are an important incentive that fuels sponsors to enter the market. Clearly, the goal of preserving and promoting the intent of the ODA to foster innovation still has a long way to go.

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[1] Sarah Tribble & Sydney Lupkin, *High Prices for Orphan Drugs Strain Families and Insurers*, NPR (Jan. 17, 2017), <http://www.npr.org/sections/health-shots/2017/01/17/509507035/high-prices-for-orphan-drugs-strain-families-and-insurers>; see also *Gaucher Disease*, Genetics Home Reference, <https://ghr.nlm.nih.gov/condition/gaucher-disease> (last visited May 17, 2017).

[2] Cerezyme, <https://www.cerezyme.com> (last visited May 17, 2017); Search Orphan Drug Designations and Approvals, <https://www.accessdata.fda.gov/scripts/opdlisting/ood/detailedIndex.cfm?cfgridkey=62491> (last visited May 17, 2017).

[3] Tribble & Lupkin, *supra* note 1.

[4] *Id.*

[5] *Id.* Note, Cerezyme is a long-term enzyme replacement therapy treatment. *Gaucher Disease*, Sanofi Genzyme, [https://www.cerezyme.com/patients/gaucher\\_disease.aspx](https://www.cerezyme.com/patients/gaucher_disease.aspx) (last visited Nov. 6, 2017).

[6] *Orphan Drug 101 Infographics*, ISR Reports, <https://www.isrreports.com/free-resources/5408> (last visited May 17, 2017).

[8] 21 U.S.C. § 360bb(a)(2)(A) (2016).

[9] Michael Daniel et al., *The Orphan Drug Act: Restoring the Mission to Rare Diseases*, 39 Am. J. of Clinical Oncology 210, 210 (2015).

[10] See Part I(B).

[11] *Developing Products for Rare Diseases & Conditions*, FDA, <https://www.fda.gov/forindustry/developingproductsforrare diseases/conditions/default.htm> (last visited Sept. 26, 2017).

[12] Cerezyme was approved in 1994. *Search Orphan Drug Designations and Approvals*, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/ood/detailedIndex.cfm?cfgridkey=62491> (last visited Oct. 12, 2017).

[13] *Orphan Drug 101 Infographics*, ISR Reports, <https://www.isrreports.com/free-resources/5408> (last visited May 17, 2017).

[14] Tribble & Lupkin, *supra* note 1 (citing *Orphan Drug Report 2015*, EvaluatePharma, Oct. 2017, at 9, available at <http://info.evaluategroup.com/rs/607-YGS-364/images/EP0D15.pdf>).

[15] *Orphan Drug Report 2017*, EvaluatePharma, Feb. 2017, at 9, available at <http://info.evaluategroup.com/rs/607-YGS-364/images/EP0D17.pdf>.

[16] Tribble & Lupkin, *supra* note 1.

[17] *Id.*

[18] *Id.*

[19] See Sarah Tribble & Sydney Lupkin, *The Orphan Drug Machine: Drugmakers Manipulate Orphan Drug Rules to Create Prized Monopolies*, Kaiser Health News (Jan. 17, 2017), <http://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies>.

[20] *Id.*

[21] Orphan Drug Act of 1983, Public L. No. 97-414, §§

1(b)(5)–(6), 96 Stat. 2049.

[22] Tribble & Lupkin, *supra* note 19.

[23] *Understanding the Unapproved Use of Approved Drugs “Off Label,”* FDA, <https://www.fda.gov/forpatients/other/offlabel/default.htm> (last visited Sept. 8, 2017).

[24] Orphan Drug Act of 1983, Public L. No. 97-414, § 1(b)(1), 96 Stat. 2049.

[25] Orphan Drug Act of 1983, Public L. No. 97-414, § 1(b)(2), 96 Stat. 2049.

[26] Orphan Drug Act of 1983, Public L. No. 97-414, § 1(b)(4), 96 Stat. 2049.

[27] Orphan Drug Act of 1983, Public L. No. 97-414, §§ 1(b)(5)–(6), 96 Stat. 2049.

[28] 21 U.S.C. § 360bb(a)(1) (2016).

[29] 21 U.S.C. § 360bb(a)(2) (2016); 21 C.F.R. § 316.20(8) (2016).

[30] Tribble & Lupkin, *supra* note 19.

[31] To see how orphan drugs economically compare to non-orphan drugs see Kiran N. Meekings et al., *Orphan Drugs Development: An Economic Viable Strategy for Biopharma R&D*, 17 *Drug Discovery Today* 660 (2012), available at <http://csmres.co.uk/cs.public.upd/article-downloads/Meekings-Reuters-paper.pdf>.

[32] 21 U.S.C. § 360cc(a) (2016).

[33] For example, the FDA may award a New Chemical Entity

Exclusivity (21 CFR § 314.108 (2016)) or a Pediatric Exclusivity (Best Pharmaceuticals for Children Act of 2002, 21 U.S.C. §301; Food and Modernization Act of 1997, Public L. No. 105-115, § 505(A), 111 Stat. 2296 (1997)), which has the additional benefit of not running concurrently with other exclusivities.

[34] *Patents and Exclusivity*, FDA/CDER SBIA Chronicles (May 19, 2015),  
<https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf>.

[35] Steven Simoens, *Pricing and Reimbursement of Orphan Drugs: The Need for More Transparency*, Orphanet J. of Rare Diseases, (2011), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3132155/>; note, this particularly true in the biopharmaceutical space because it is difficult to bring biosimilars to the market.

[36] *Id.*; Comm. on Accelerating Rare Diseases Research & Orphan Product Dev. & Bd. on Health Sciences Policy, *Rare Diseases and Orphan Products: Accelerating Research & Development* 181 (Marilyn Field & Thomas Boat eds., 2010).

[37] Fiona Morton & Lysle Boller, *Enabling Competition in Pharmaceutical Markets*, (Hutchins Center Working Paper No. 30 , 2017),  
[https://www.brookings.edu/wp-content/uploads/2017/05/wp30\\_scottmorton\\_competitioninpharma1.pdf](https://www.brookings.edu/wp-content/uploads/2017/05/wp30_scottmorton_competitioninpharma1.pdf). The Government Accountability Office estimates that 40% of hospitals are eligible for the 340B pricing program. Shelby Livingston, *340B Hospitals Laud Bill that Seeks to Close Orphan Drug ‘Loophole,’* Modern Healthcare (Sept. 28, 2016),  
<http://www.modernhealthcare.com/article/20160928/NEWS/160929885>.

[38] 42 U.S.C. § 256b(e) (2010); Michael McCaughan, *Health Policy Brief: Pricing Orphan Drugs*, Health Affairs, (July 21, 2017),

[http://healthaffairs.org/healthpolicybriefs/brief\\_pdfs/healthpolicybrief\\_168.pdf](http://healthaffairs.org/healthpolicybriefs/brief_pdfs/healthpolicybrief_168.pdf).

[39] Morton & Boller, *supra* note 37; See also *Pharm. Research & Mfrs. of Am. v. United States Dept. of Health & Human Servs., et al.*, 138 F.Supp3d 31 (D. D.C. 2015).

[40] To provide some context, the program saved covered entities 3.8 billion dollars in 2013. See Medicare Payment Advisory Commission, *Report to the Congress: Overview of the 340B Pricing Program*, MedPac, May 2015, available at: <http://www.medpac.gov/docs/default-source/reports/may-2015-report-to-the-congress-overview-of-the-340b-drug-pricing-program.pdf?sfvrsn=0>.

[41] Tribble & Lupkin, *supra* note 19.

[42] *Id.* See also Part II c.

[43] *Id.*

[44] *Id.*

[45] Kathleen Miller, *Do Investors Value the FDA Orphan Drug Designation?*, Orphanet J. of Rare Diseases, June 2017, available at:

<https://ojrd.biomedcentral.com/articles/10.1186/s13023-017-0665-6>.

[46] *Id.*

[47] Simoens, *supra* note 35.

[48] Enrique Seoane-Vazquez et al., *Incentives for Orphan Drug Research and Development in the United States*, Orphanet J. Rare Diseases (2008), <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2631478/#B23>.

[49] Tribble & Lupkin, *supra* note 1.

[50] Joseph A. DiMasi, Henry G. Grabowski, & Ronald W. Hansen, *Innovation in the pharmaceutical industry: New estimates of R&D costs*, 47 J. of Health Econ. 20, 20–21 (2016).

[51] Matthew Herder, *What is the Purpose of the Orphan Drug Act?*, PLOS (Jan. 3, 2017), <https://doi.org/10.1371/journal.pmed.1002191> (citing Meekings et al., *supra* note 31).

[52] Sinéad Murphy et al., *Unintended Effects of Orphan Product Designation for Rare Neurological Diseases*, *Annals of Neurology*, Oct 2012, available at <https://dx.doi.org/10.1002%2Fana.23672>. Orphan Drugs are typically given a Fast Track review because they are treatments for serious or life-threatening diseases. *Id.* See also FDCA § 506; USC §356.

[53] Tribble & Lupkin, *supra* note 19.

[54] *Step 3 Clinical Research*, FDA, <https://www.fda.gov/forpatients/approvals/> (last visited Oct. 3, 2017). To conduct clinical trials, the FDA generally requires three phases. *Id.* The first phase involves conducting two separate studies on two distinct populations—healthy volunteers and unhealthy volunteers. This trial involves 20–100 individuals to determine the safety and dosage of the drug. *Id.* The second clinical trial requires testing the drug on several hundred test subjects. *Id.* This trial is used to gain preliminary data on the effectiveness of the drug for the particular indication as well as any side effects. *Id.* Lastly, the third clinical trial, also known as the pivotal trial, is administered to thousands of test subjects (300 to 3,000). *Id.* The purpose of the pivotal trial is to gather information on the drug's efficacy, while monitoring for any adverse reactions to evaluate the overall benefit-risk relationship of the drug. *Id.* Note, sometimes the

FDA may require an additional phase—phase IV—on several thousand volunteers who have the disease/condition, if needed. *Id.*

[55] Tribble & Lupkin, *supra* note 19; Margaret Hamburg, *Why FDA Supports a Flexible Approach to Drug Development*, FDA Blog, <https://blogs.fda.gov/fdavoice/index.php/2014/02/why-fda-supports-a-flexible-approach-to-drug-development/> (last visited May 17, 2017).

[56] Erika Augustine et al., *Clinical Trials in Rare Diseases: Challenges and Opportunities*, J. Child Neurology, Sept. 2013, at 4, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3964003/pdf/nihms-569668.pdf>.

[57] Tribble & Lupkin, *supra* note 19; Margaret Hamburg, *supra* note 55.

[58] Murphy et al., *supra* note 52.

[59] Augustine et al., *supra* note 56, at 5–6.

[60] *Id.*

[61] *Id.*

[62] In 2015, the FDA took on average 12.9 years to approve a non-orphan drug, whereas the FDA took on average 10.1 years to approve an orphan drug. *Orphan Drug Report 2015*, EvaluatePharma, Oct. 2015, at 18, available at <http://info.evaluategroup.com/rs/607-YGS-364/images/EP0D15.pdf>.

[63] *Information on the Orphan Products Clinical Trials Grants Program*, FDA, <https://www.fda.gov/ForIndustry/DevelopingProductsforRareDiseasesConditions/WhomtoContactaboutOrphanProductDevelopment/ucm134580.htm> (last visited May 17, 2017).

[64] *Id.* Each grant may last from three to four years. *Id.*

[65] *Id.*

[66] *Prescription Drug User Fee Act*, FDA, <https://www.fda.gov/forindustry/userfees/prescriptiondruguserfee> (last visited May 17, 2017).

[67] McCaughan, *supra* note 38.

[68] *Id.*

[69] 21 U.S.C. § 45C (2015).

[70] Michael Daniel et al., *supra* note 9, at 210. “The tax credit can also be carried forward for 20 years, so companies can use the credit when they begin making profits, and it may be partly transferred if they merge or are sold to a company with a tax liability.” Miller, *supra* note 45.

[71] Alexander Korniaikov et al., *The Orphan Drug and Research Tax Credits: The “Substantially All” Rule*, *The Tax Advisor* (Oct. 1, 2014), <https://www.thetaxadviser.com/issues/2014/oct/korniaikov-oct14.html>.

[72] *Orphan Drug Report 2015*, EvaluatePharma, Oct. 2015, at 17, *available at* <http://info.evaluategroup.com/rs/607-YGS-364/images/EP0D15.pdf>.

[73] *Id.*

[74] *Id.* at 212; Tribble & Lupkin, *supra* note 19 (quotations omitted).

[75] Ryan Marling, *Salami-Slicing, Precision Medicine and The Orphan Drug Act*, Christiansen Institute (Feb. 23, 2017),

<https://www.christenseninstitute.org/blog/salami-slicing-precision-medicine-orphan-drug-act>.

[76] *Id.*

[77] Michael Daniel et al., *supra* note 9, at 212.

[78] See part II.

[79] Tribble & Lupkin, *supra* note 19; 21 C.F.R. § 314.127 (2015).

[80] Michael Daniel et al., *supra* note 9, at 211; D. Heim et al., *Cancer Beyond Organ and Tissue Specificity: Next-generation-sequencing Gene Mutation Data Reveal Complex Genetic Similarities Across Cancer*, *Int'l J. of Cancer* 2362, 2362 (2014).

[81] D. Heim et al., *supra* note 77, at 2362.

[82] *Id.*

[83] *Id.*

[84] *Avastin*, RxList, <https://www.rxlist.com/avastin-drug.htm> (last visited Oct. 19, 2017).

[85] *Bevacizumab (Avastin)*, Cancer Research UK, <http://www.cancerresearchuk.org/about-cancer/cancer-in-general/treatment/cancer-drugs/drugs/bevacizumab> (last visited Oct. 19, 2017).

[86] *Search Orphan Drug Designations and Approvals*, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=172903> (last visited Oct. 19, 2017).

[87] *Search Orphan Drug Designations and Approvals*, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedI>

ndex.cfm?cfgridkey=216405 (last visited Oct. 19, 2017).

[88] *Search Orphan Drug Designations and Approvals*, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/ood/detailedIndex.cfm?cfgridkey=222906> (last visited Oct. 19, 2017).

[89] *Search Orphan Drug Designations and Approvals*, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/ood/detailedIndex.cfm?cfgridkey=317810> (last visited Oct. 19, 2017).

[90] *Search Orphan Drug Designations and Approvals*, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/ood/detailedIndex.cfm?cfgridkey=318010> (last visited Oct. 19, 2017).

[91] Tribble & Lupkin, *supra* note 19. Note, this drug was first approved for mass market in 2004. *Id.*

[92] Matthew Davids & Jennifer Brown, *Ibrutinib: A First in Class Covalent Inhibitor of Burton's Tyrosine Kinase*, 10 *Future Oncology* 957, 957 (2014), available at <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4632638/pdf/nihms617965.pdf>.

[93] Imbruvica is used to treat B-cell lymphomas such as chronic lymphocytic leukemia, chronic lymphocytic leukemia, small lymphocytic lymphoma, mantle cell lymphoma, marginal zone lymphoma, nodal splenic marginal zone lymphoma, and Waldenstrom's macroglobulinemia. *Types of Non-Hodgkins Lymphomas*, Am. Cancer Society, <https://www.cancer.org/cancer/non-hodgkin-lymphoma/about/types-of-non-hodgkin-lymphoma.html> (last visited Oct. 19, 2017).

[94] Tribble & Lupkin, *supra* note 19.

[95] Michael Daniel et al., *supra* note 9, at 211. Put differently, a drug company may “strategically position[] drugs for the treatment of rare diseases that might otherwise have

been tested and approved for a nonorphan indication. Subsequent to approval, off-label use for common conditions is widespread.” Stacey Lauderdale, *The Unintended Consequences of the Orphan Drug Act*, Vizient (Aug. 22, 2017), <http://newsroom.vizientinc.com/vizient-blog/pharmacy/unintended-consequences-orphan-drug-act>.

[96] “[T]here is no need to conduct phase I and phase IIa clinical trials.” T. I. Oprea & J. Mestres, *Drug Repurposing: Far Beyond New Targets for Old Drugs*, 14 *The Am. Ass’n of Pharm. Scientists J.* 759, 760 (2012), available at [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3475856/pdf/12248\\_2012\\_Article\\_9390.pdf](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3475856/pdf/12248_2012_Article_9390.pdf).

[97] Tribble & Lupkin, *supra* note 19.

[98] *Id.*

[99] *Id.*

[100] *Id.*

[101] *Highlights of Prescribing Information*, FDA, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2017/103792s5337lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/103792s5337lbl.pdf) (last visited, Oct. 13, 2017); Search Orphan Drugs and Designation, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=292409> (last visited, Oct. 13, 2017); Michael Daniel et al., *supra* note 9, at 211.

[102] *Id.*

[103] *Search Orphan Drug Designations and Approvals*, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=292409> (last visited Oct. 19, 2017).

[104] Tribble & Lupkin, *supra* note 19.

[\[105\]](#) Scott Gottlieb, *FDA is Advancing the Goals of the Orphan Drug Act*, FDA Blog (Sept. 12, 2017), <https://blogs.fda.gov/fdavoice/index.php/tag/best-pharmaceuticals-for-children-act/>.

[\[106\]](#) Beth Snyder Bulik, *Big Pharma Grapples With Idiosyncrasies of Orphan Drug Marketing*, FiercePharma (June 3, 2015), <http://www.fiercepharma.com/sales-and-marketing/big-pharma-grapples-idiosyncrasies-of-orphan-drug-marketing>.

[\[107\]](#) Pediatric Exclusivity (Best Pharmaceuticals for Children Act of 2002, 21 U.S.C. §301; Food and Modernization Act of 1997, Public L. No. 105-115, § 505(A), 111 Stat. 2296 (1997)); *Patents and Exclusivity*, FDA/CDER SBIA Chronicles (May 19, 2015), <https://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf>.

[\[108\]](#) Sarah Jane Tribble, *FDA Moves to Rein in Drugmakers' Abuse of Orphan Drug Law*, NPR (Sept. 13, 2017), <http://www.npr.org/sections/health-shots/2017/09/13/550700062/fda-moves-to-rein-in-drugmakers-abuse-of-orphan-drug-law>.

[\[109\]](#) Tribble & Lupkin, *supra* note 19.

[\[110\]](#) *Id.*

[\[111\]](#) *Id.*

[\[112\]](#) Daniel Grau & George Sebedzijia, *Innovative Strategies for Drug Repurposing*, Drug Discovery & Dev. (Sept. 6, 2007), <https://www.dddmag.com/article/2007/09/innovative-strategies-drug-repurposing>.

[\[113\]](#) Tribble & Lupkin, *supra* note 19.

[\[114\]](#) *Id.*

[\[115\]](#) *Id.*

[\[116\]](#) Note, this practice may be used in combination with other exclusivities and patents to prevent competitors into the market.

[\[117\]](#) Tribble & Lupkin, *supra* note 19; *Highlights of Prescribing Information*, FDA, [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2016/103950s5175lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103950s5175lbl.pdf) (last visited Oct. 23, 2017).

[\[118\]](#) LABEL: KINERET- anakinra injection, solution, U.S. Library of Medicine, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d9d74915-6606-4570-9c52-c4001d3177de> (last visited Oct. 24, 2017).

[\[119\]](#) *Search Orphan Drug Designations and Approvals*, FDA, <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=312110> (last visited Oct. 21, 2017).

[\[120\]](#) LABEL: KINERET- anakinra injection, solution, U.S. Library of Medicine, <https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=d9d74915-6606-4570-9c52-c4001d3177de> (last visited Oct. 24, 2017).

[\[121\]](#) *2015 Medicare Spending Data*, CMS, <https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Information-on-Prescription-Drugs/2015MedicareData.html> (last visited Oct. 21, 2017).

[\[122\]](#) See Table 1. Note, Kineret's sponsor did not report any shortages to affect prices, according to FDA's database. *FDA Drug Shortages*, FDA, [https://www.accessdata.fda.gov/scripts/drugshortages/dsp\\_SearchResults.cfm](https://www.accessdata.fda.gov/scripts/drugshortages/dsp_SearchResults.cfm) (last visited Oct. 23, 2017).

[\[123\]](#) *Patent Terms Extended under 35 USC §156*, USPTO,

<https://www.uspto.gov/patent/laws-and-regulations/patent-term-extension/patent-terms-extended-under-35-usc-156> (last visited Oct. 24, 2017).

[124] See *Orange Book: Approved Drug Products with Therapeutic Equivalent Evaluations*, FDA, [https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm/search\\_product.cfm](https://www.accessdata.fda.gov/scripts/cder/ob/default.cfm/search_product.cfm) (last visited Oct. 24, 2017).

[125] Sumin Kim, *The Orphan Drug Act: How the FDA Unlawfully Usurped Market Exclusivity*, 11 Northwestern J. of Tech. & Intellectual Prop. 541, 543 (2013).

[126] Amanda Hamilton, *What Can the FTC Do about Orphan Drug Prices?*, 31 Antitrust Health Care Chronicle, Aug. 2017, at 19, available at [https://www.americanbar.org/content/dam/aba/publications/antitrust\\_law/at301000\\_newsletter\\_201708.authcheckdam.pdf](https://www.americanbar.org/content/dam/aba/publications/antitrust_law/at301000_newsletter_201708.authcheckdam.pdf).

[127] *Id.*; *What should You Know About Orphan Drugs an Obamacare Health Insurance*, eHealth, <https://resources.ehealthinsurance.com/about-insurance/know-orphan-drugs-obamacare-health-insurance> (last visited May 17, 2017) [hereinafter eHealth].

[128] *Understanding Unapproved Use of Approved Drugs “Off-Label,”* FDA, <https://www.fda.gov/forpatients/other/offlabel/default.htm> (last visited Oct. 18, 2017).

[129] Charles Ornstein & Katie Thomas, *Generic Drug Prices Are Falling, but Are Consumers Benefiting?*, N.Y. Times (Aug. 8, 2017), <https://www.nytimes.com/2017/08/08/health/generic-drugs-prices-falling.html>.

[\[130\]](#) *Generic Drug Facts*, FDA, <https://www.fda.gov/drugs/resourcesforyou/consumers/buyingusingmedicinesafely/understandinggenericdrugs/ucm167991.htm> (last visited Sept. 20, 2017).

[\[131\]](#) See Part II.

[\[132\]](#) Vernon Sumwalt, *"Off Label" Use of Medical Products and Services*, LexisNexis Legal Newsroom Workers Compensation Law (June 9, 2011), <https://www.lexisnexus.com/legalnewsroom/workers-compensation/b/workers-compensation-law-blog/archive/2011/06/09/off-label-uses-of-medical-products-and-services.aspx?Redirected=true>. See also Geeta Anand, *As Costs Rise, New Medicines Face Pushback*, The Wall St. J. (Sept. 18, 2007), <https://www.wsj.com/articles/SB119007210553130427>.

[\[133\]](#) *CMA Report: Medicare Coverage for Off-Label Drug Use*, Center for Medicare Advocacy (Sept. 2010), <http://www.medicareadvocacy.org/cma-report-medicare-coverage-for-off-label-drug-use>.

[\[134\]](#) Note, this problem will not occur if the off-label usage and the approved use is both within the same specialty, such as oncology.

[\[135\]](#) Drug companies typically holds information on off-label usage, given that they know most about their drugs. Thomas Nechyba, *Microeconomics: An Intuitive Approach* 496 (2d. ed. 2016).

[\[137\]](#) *Highlights of Prescribing Information*, FDA (Feb. 12, 2014), [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2014/021361s013lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/021361s013lbl.pdf).

[\[138\]](#) *Id.*

[\[139\]](#) *Human Drug Compounding*, FDA, <https://www.fda.gov/drugs/guidancecomplianceregulatoryinformation/pharmacycompounding/default.htm> (last visited Sep. 29, 2017).

[\[140\]](#) Henry Waxman et al., *Getting to the Root of High Prescription Drug Prices: Drivers and Potential Solutions*, The Commonwealth Fund (July 2017), [http://www.commonwealthfund.org/~media/files/publications/fund-report/2017/jul/waxman\\_high\\_drug\\_prices\\_drivers\\_solutions\\_report.pdf](http://www.commonwealthfund.org/~media/files/publications/fund-report/2017/jul/waxman_high_drug_prices_drivers_solutions_report.pdf).

[\[141\]](#) *Id.*; Kim, *supra* note 125, at 547.

[\[142\]](#) Congress declined to amend the Orphan Drug Act in fear that such restriction would hinder innovation. Kim, *supra* note 125, at 546. The FDA declined to change its definition of a rare disease, preferring a bright line rule. *Id.* at 546–47. The FDA also declined to restrict market exclusivity also fearing that such restriction would hinder innovation. *Id.* at 547. In fact, one could assume that Congress fears that there is not enough incentive under the current law for new orphan drugs because a prior version of the enacted 21st Century Cures Act provided a provision to provide an additional incentive—providing an additional six months of exclusivity for drugs with a second orphan indication. 21st Century Cures Act of 2016, H.R. 6, 114th Cong. § 2151 (2015), available at [www.congress.gov/bills/114th-congress/house-bill/6](http://www.congress.gov/bills/114th-congress/house-bill/6).

[\[143\]](#) Sarah Jane Tribble, *GAO to Launch Investigation of FDA's Orphan Drug Program*, Kaiser Health News (Mar. 21, 2017), <http://khn.org/news/gao-to-launch-investigation-of-fdas-orphan-drug-program>.

[\[144\]](#) Tribble, *supra* note 108.

[\[145\]](#) Sarah Jane Tribble, *House Republican Aim to Yank Tax Credits for Orphan Drugs*, Kaiser Health News (Nov. 2, 2017), <https://khn.org/news/house-republicans-aim-to-yank-tax-credits-for-orphan-drugs/>.