NOTE

TURNING ORPHANS FOR A PROFIT: THE ORPHAN DRUG ACT IS DUE FOR AN OVERHAUL

I. INTRODUCTION: A DEEPLY FLAWED SYSTEM, DESPITE WELL-INTENTIONED LEGISLATION

With a price listed at $71,306 per month, Myalept is currently one of the most expensive medications on the American drug market.[1] Myalept is used to treat patients who suffer from the rare disease congenital or acquired generalized lipodystrophy, which is characterized by a complete or partial loss of body fat.[2] The disease affects approximately one in ten million individuals in the general population,[3] yet Novelion, the biopharmaceutical company that manufactures the drug, reported a net annual revenue of $71.4 million in 2018 for Myalept alone.[4]

Hypophosphatasia ("HPP") is a rare genetic disorder that prevents the body from forming strong bones.[5] Those who suffer from HPP have

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1. Lauren Chase, *The 20 Most Expensive Prescription Drugs in the U.S.A.*, GOOD Rx (Aug. 11, 2020, 7:50 AM), https://www.goodrx.com/blog/20-most-expensive-drugs-in-the-usa; Eric Sagonowsky, *The 20 Most Expensive Pharmacy Drugs in the U.S. in 2020, from Fallen Blockbusters to New Orphan Meds*, FIERCE PHARMA (Feb. 14, 2020, 9:45 AM), https://www.fiercepharma.com/pharma/20-most-expensive-pharmacy-drugs-u-s-2020. Myalept's manufacturer increased the price by 9.9% in January 2020. Sagonowsky, *supra*. Patients typically use fourteen vials per month and each vial costs $5,093. Chase, *supra*.

2. *Myalept Replaces Missing Leptin*, MYALEPT, http://www.myalept.com/how-myalept-works (last visited Feb. 8, 2021); *Congenital Generalized Lipodystrophy*, NORD, https://rarediseases.org/rare-diseases/congenital-generalized-lipodystrophy (last visited Feb. 8, 2021).

3. *Congenital Generalized Lipodystrophy*, *supra* note 2.

4. *Novelion Therapeutics Reports Fourth Quarter and Full Year 2018 Financial Results*, GLOBENEWSWIRE (Mar. 14, 2019, 5:12 PM), https://www.globenewswire.com/news-release/2019/03/14/1754886/0/en/Novelion-Therapeutics-Reports-Fourth-Quarter-and-Full-Year-2018-Financial-Results.html. In 2017, Novelion reported net revenues of $66.3 million. *Id.*

5. *See Hypophosphatasia*, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIS. (Feb. 1, 2016), https://rarediseases.info.nih.gov/diseases/6734/hypophosphatasia. Hypophosphatasia ("HPP") develops from a mutation in the gene that encodes for alkaline phosphatase. Joseph Bennington-Castro, *What Is Hypophosphatasia? Symptoms, Causes, Diagnosis, Treatment, and*

bones that become soft or weakened, which causes skeletal deformities, fractures, and pain.[6] Severe cases can be deadly for babies.[7] In x-rays, their bones are nearly invisible.[8] Previous treatments for HPP were generally directed toward preventing its symptoms until 2015, when drug manufacturer Alexion introduced Strensiq, a medication that treated the disease itself by replacing a user's alkaline phosphatase.[9] This groundbreaking treatment, however, came at a cost: Strensiq was put on the market for approximately $285,000 per person annually.[10] Yet, this exorbitant amount was perceived to be low by some analysts who were expecting the drug to sell for an annual average price of $400,000.[11]

Myalept and Strensiq are not alone: within the deeply flawed American healthcare system, there is a disturbing trend wherein the prices for drugs that treat rare medical conditions are twenty-five times more expensive than traditional drugs,[12] resulting in a multi-billion-dollar industry.[13] Drugs like Myalept and Strensiq are life-changing for those suffering from rare diseases, but have the ability to bankrupt these same people, as well as their employers.[14]

Prevention, EVERYDAY HEALTH (Sept. 25, 2015), https://www.everydayhealth.com/hypophosphatasia/guide. Alkaline phosphatase is "an important enzyme that breaks down certain chemicals and is involved in mineralization of the bones and teeth." *Id.* HPP causes the body to produce "a non-functional form of alkaline phosphatase that cannot effectively take part in the mineralization process." *Id.*

6. *What is HPP*, SOFT BONES, https://www.softbones.org/about/what-is-hpp (last visited Feb. 8, 2021).

7. *Id.*

8. *Neonates & Infants*, HYPOPHOSPHATASIA, https://hypophosphatasia.com/hcp/patient-cohorts/neonates-infants (last visited Feb. 8, 2021).

9. *Hypophosphatasia*, MAGIC FOUND., https://www.magicfoundation.org/Growth-Disorders/Hypophosphatasia (last visited Feb. 8, 2021).

10. John Carroll, *Updated: Alexion Wins FDA Ok on Strensiq, but Startles Analysts on Price*, FIERCE BIOTECH (Oct. 23, 2013, 3:53 PM), https://www.fiercebiotech.com/regulatory/updated-alexion-wins-fda-ok-on-strensiq-but-startles-analysts-on-price.

11. *Id.*

12. AHIP, *Drug Prices for Rare Diseases Skyrocket While Big Pharma Makes Record Profits*, AHIP (Sept. 10, 2019), https://www.ahip.org/drug-prices-for-rare-diseases-skyrocket-while-big-pharma-makes-record-profits.

13. Matej Mikulic, *Top Global Orphan Drugs by Revenue in 2018*, STATISTA (Jan. 30, 2020), https://www.statista.com/statistics/319274/leading-orphan-drug-revenues.

14. *See* Katie Thomas & Reed Abelson, *The $6 Million Dollar Claim*, N.Y. TIMES (Aug. 25, 2019), https://www.nytimes.com/2019/08/25/health/drug-prices-rare-diseases.html. Dawn Patterson and her two children were prescribed Strensiq to treat their genetic condition. *Id.* Her husband's union, which covered the drug's cost for the family, faced a potential annual bill of $6 million to cover the family's healthcare costs. *Id.* The expected annual cost of $285,000 for the drug was "based on the assumption that most patients would be children or infants and would weigh an average of 50 pounds." *Id.* The actual bill for Ms. Patterson in 2018 approached $2 million. *Id.* Eventually Alexion capped the annual cost at $1.5 million for each adult covered by Express Scripts, a pharmacy benefit management ("PBM") organization, including Dawn Patterson. *Id.*

The problem is well known, with pharmaceutical companies often garnering attention for abusing their ability to raise prices of common drugs and medications with few to no consequences.[15] In 2017, United States President Donald Trump agreed that drug prices are too high and declared that the pharmaceutical industry "is getting away with murder."[16] Yet, despite the constant public shaming by the media, these manufacturers continue to take advantage of a system originally designed to fund the research and development of treatments for rare diseases.[17]

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15. *See* Shamard Charles, *No End in Sight to Rising Drug Prices, Study Finds*, NBC NEWS (May 31, 2019, 11:00 AM), https://www.nbcnews.com/health/health-care/no-end-sight-rising-drug-prices-study-finds-n1012181 (discussing a research study that found a large increase in prices for commonly produced drugs); Garrett Johnson & Wayne T. Brough, *Big Pharma Is Abusing Patients, and It's Hurting Americans*, CNN BUS. (Sept. 13, 2019, 7:53 AM), https://www.cnn.com/2019/09/12/perspectives/drug-patents-abuse/index.html (detailing how "Big Pharma" spends hundreds of millions on lobbying and donations to keep drug prices high at the expense of Americans who wish to require affordable treatment). At a hearing before the Senate Finance Committee, top executives of several pharmaceutical companies admitted that while they control the prices of commonly used prescription drugs, they could not commit to lowering the price of those same drugs. *Drug Pricing in America: A Prescription for Change, Part II: Hearing Before the S. Comm. on Fin.*, 116th Cong. 19-21, 27, 29 (2019).

16. Katie Thomas, *The Fight Trump Faces over Drug Prices*, N.Y. TIMES (Jan. 23, 2017), https://www.nytimes.com/2017/01/23/health/the-fight-trump-faces-over-drug-prices.html. In 2020, President Trump issued four executive orders to make "medications affordable and accessible for all Americans." *Congress Didn't Act on Prescription Drug Prices. So President Trump Did.*, WHITE HOUSE (July 27, 2020), https://www.whitehouse.gov/articles/congress-didnt-act-on-prescription-drug-prices-so-president-trump-did. One of the orders bans rebates on prescription drugs paid by pharmaceutical companies to PBMs for people who have prescription drug coverage through Medicare. Exec. Order No. 13,939, 85 Fed. Reg. 45,759 (July 24, 2020). Generally, when a pharmaceutical company sets the price a person pays for a drug, known as the list price, the company may offer a rebate to the PBM, such as Express Scripts or CVS. Katie Thomas, *Meet the Rebate, the New Villain of High Drug Prices*, N.Y. TIMES (July 27, 2018), https://www.nytimes.com/2018/07/27/health/rebates-high-drug-prices-trump.html. Health insurance companies use PBMs to manage different benefits, including the development of formularies, or lists of medications that an insurance company will cover. *Id.* Thus, a pharmaceutical company is incentivized to provide these rebates to PBMs, as it is then likely the PBMs will include that company's drug on a health insurance company's formulary. *See id.* Experts criticized President Trump's July 24, 2020 order, however, noting that the rebates provided to the PBMs are usually shared with health insurance companies and go toward lowering insurance premiums for seniors. Victoria Knight, *Trump Again Claims He's Bringing Down Drug Prices, but Details of How Are Skimpy*, KHN (Aug. 26, 2020), https://khn.org/news/president-trump-once-again-claims-hes-bringing-down-drug-prices-but-details-of-how-are-skimpy. Thus, without the discount, premiums are likely to increase for certain patient-consumers. *Id.* Additionally, Executive Order 13,939 provides that prior to banning the rebates, "the Secretary of Health and Human Services shall confirm . . . that the action" does not, *inter alia*, increase Medicare beneficiary premiums. Exec. Order No. 13,939, 85 Fed. Reg. at 45,759.

17. *See infra* Part II; Brittany De Lea, *These Drugmakers Are Hiking Prices in 2019*, FOX BUS. (Jan. 2, 2019), https://www.foxbusiness.com/healthcare/these-drugmakers-are-hiking-prices-in-2019.

Prior to 1983, pharmaceutical manufacturers were reluctant to spend money on the production of drugs for these niche markets.[18] In the 1960s, several drugs were linked to severely injurious side effects, prompting Congress to pass amendments in order to ensure the safety of drugs being marketed to Americans.[19] These amendments, however, required pharmaceutical companies to undergo stringent drug testing by way of clinical trials and a lengthy approval process with the Federal Food and Drug Administration ("FDA"), ultimately making it more difficult to obtain approval.[20] Companies halted the development of rare disease medications due to the expenses needed to satisfy the new requirements, coupled with the small markets associated with these drugs.[21]

As a result of lobbying efforts by patient advocates and other support groups, like special committees and task forces,[22] in 1983, Congress passed the Orphan Drug Act ("ODA" or "the Act"), giving these companies lucrative incentives to develop and research remedies for these rare diseases.[23] Under the ODA, drug manufacturers or sponsors can request the Secretary of Health and Human Services ("HHS") to designate a drug as one used to treat a rare disease or condition, thus granting it status as an "orphan drug."[24] The United States government defines conditions that affect fewer than 200,000 Americans as "rare" diseases.[25] To date, over 7,000 rare diseases have

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18. Diana Kwon, *How Orphan Drugs Became a Highly Profitable Industry*, SCIENTIST (Apr. 30, 2018), https://www.the-scientist.com/features/how-orphan-drugs-became-a-highly-profitable-industry-64278.

19. *Kefauver-Harris Amendments Revolutionized Drug Development*, FOOD & DRUG ADMIN. (Sept. 10, 2012), https://www.fda.gov/consumers/consumer-updates/kefauver-harris-amendments-revolutionized-drug-development.

20. Jeff Rum, *Drug Pricing, a Complex Issue Affecting the Rare Disease Community*, NAT'L GAUCHER FOUND. (Aug. 28, 2018), https://www.gaucherdisease.org/blog/drug-pricing-a-complex-issue-affecting-the-rare-disease-community.

21. *Id.*

22. *Id.*

23. *See id.*; Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. §§ 360aa-ee); OFF. OF INSPECTOR GEN., DEP'T OF HEALTH & HUM. SERVS., OEI-09-00-00380, ORPHAN DRUG ACT IMPLEMENTATION & IMPACT 4, 7 (2001).

24. 21 U.S.C. § 360aa; 21 C.F.R. §§ 316.1(a)(1)(ii), 316.24(b) (2020).

25. 21 U.S.C. § 360bb(a)(2)(A); *see also FAQ About Rare Diseases*, NAT'L CTR. FOR ADVANCING TRANSLATIONAL SCIS. (Nov. 30, 2017), https://rarediseases.info.nih.gov/diseases/pages/31/faqs-about-rare-diseases. The definition of a rare disease or condition also includes any disease or condition which "affects more than 200,000 in the United States and for which 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 the sales in the United States of such drug." 21 U.S.C. § 360bb(a)(2)(B). While this Note focuses on the issues that stem from orphan drugs that treat patient populations of less than 200,000 Americans, it is worthwhile to note that on November 17, 2020, members of the House passed a bill designed to

been identified in the United States, making these conditions not so rare.[26] Instead, these diseases affect a total of approximately twenty-five to thirty million people in the United States alone, meaning that between twenty-five to thirty million Americans need access to affordable treatments.[27]

Due to the ambiguous language of the ODA and its enforcing regulation, the FDA's Code of Federal Regulations Part 316, pharmaceutical companies have manipulated the Act, exploiting the benefits to turn a profit for themselves[28] without providing the benefit to the public that the statute was intended to remedy.[29] These benefits

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close a loophole created by 21 U.S.C. § 360bb(a)(2)(B). *See* Fairness in Orphan Drug Exclusivity Act, H.R. 4712, 116th Cong. (2020); *see also H.R. 4712 (116th): Fairness in Orphan Drug Exclusivity Act*, GOVTRACK, https://www.govtrack.us/congress/bills/116/hr4712 (last visited Feb. 8, 2021). Under the law as it currently stands, a company only needs to demonstrate the drug is not economically viable for the first approval; to extend market exclusivity, the drug developer can "piggyback" on the older drug's orphan status without having to show unprofitability again. Angus Liu, *Newly Passed House Bill Could Close Orphan Drug Loophole that Evergreens Exclusivity*, FIERCE PHARMA (Nov. 19, 2020, 12:11 PM), https://www.fiercepharma.com/pharma/house-passes-bill-could-close-orphan-drug-loophole-evergreening-exclusivity. The new bill requires drug companies to show "there is no reasonable expectation" that the research and development costs will be recovered from sales of the drug in the United States in the first twelve years it is marketed. H.R. 4712 § 2.

26. *See FAQ About Rare Diseases*, *supra* note 25.

27. *Id.*

28. 21 U.S.C. §§ 360aa-ee; 21 C.F.R. §§ 316.1–316.52 (2020); Troy Brennan, *Manipulating the Orphan Drug Act*, CVS HEALTH PAYOR SOLUTIONS (Feb. 21, 2017), https://payorsolutions.cvshealth.com/insights/manipulating-orphan-drug-act; *see also* Sarah Jane Tribble & Sydney Lupkin, *Drugs for Rare Diseases Have Become Uncommonly Rich Monopolies*, NPR (Jan. 17, 2017, 4:59 AM), https://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies (detailing a Kaiser Health News investigation that showed many drugs designated as "orphans" were originally approved for mass-marketing or were designated as "orphans" for more than one rare disease, which entitled the drug maker to the same statutory incentives and exclusivities multiple times).

29. Sarah Jane Tribble & Sydney Lupkin, *Sky-High Prices for Orphan Drugs Slam American Families and Insurers*, KHN (Jan. 17, 2017), https://khn.org/news/sky-high-prices-for-orphan-drugs-slam-american-families-and-insurers. Luke Whitbeck was two years old when he began taking Cerezyme, a $300,000 per year orphan drug to treat Gaucher disease, a genetic condition that affects only about 6,000 people in the United States. *Id.* His mother, Meg Whitbeck, described the daunting uncertainty of the possibility that the family may need to pay for Luke's medication, stating "we're not going to not treat Luke, but we're also never going to be able to pay these bills." *Id.*; *see also* Howard LeWine, *Millions of Adults Skip Medications Due to Their High Cost*, HARV. HEALTH PUB. (June 15, 2020, 12:00 AM), https://www.health.harvard.edu/blog/millions-skip-medications-due-to-their-high-cost-201501307673 (discussing a news report from the National Center for Health Statistics, which found that about eight percent of adult Americans do not take their medicines as prescribed because they cannot afford them); Micaela Marini Higgs, *The High Price of Insulin Is Literally Killing People*, VICE (Apr. 5, 2017, 8:00 AM), https://www.vice.com/en_us/article/ezwwze/the-high-price-of-insulin-is-literally-killing-people (reporting one case wherein a diabetic man died because he was fifty dollars short of reaching his $750 GoFundMe goal to pay for a month's supply of insulin).

include seven years of market exclusivity and tax credits for qualified clinical trials.[30] In many cases, these orphan-designated drugs are not remotely isolated treatments for rare diseases.[31] Rather, data shows that the FDA approves the orphans for multiple uses and pharmaceutical companies mass-market them to a large population.[32]

The United States District Court for the District of Columbia previously found that so long as a drug satisfied the two requirements set forth in the ODA, the drug would be granted orphan drug designation and exclusivity.[33] The drug would still be entitled to that designation and exclusivity even if there was a non-orphan drug already on the market to treat the same disease, and the would-be orphan drug did not demonstrate clinical superiority to the already-approved, non-orphan drug.[34] Despite both the FDA and Congress attempting to close this loophole in the ODA,[35] a subsequent case, *Eagle Pharmaceuticals, Inc. v. Azar*,[36] has made clear that any drug that was designated as an orphan prior to 2017 is not subject to the clinical superiority requirements.[37] This makes it likely that drugs similarly situated to the one at issue in *Eagle Pharms., Inc.*, or those drugs that were approved for marketing but denied orphan drug exclusivity because the FDA found they were not clinically superior to an already-approved product prior to the enactment of the FDA Reauthorization Act of 2017 ("FDARA"), will now be granted seven years of exclusivity.[38]

The even larger problem with the ODA as it currently stands is that orphan drug exclusivity is applied only to the approved indication or use

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30. 21 U.S.C. §§ 360cc(a), ee; 26 U.S.C. § 45C.

31. *See* Tribble & Lupkin, *supra* note 28.

32. *Id.*

33. Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217, 220 (D.D.C. 2014). The two requirements are: (1) designation by the FDA as an "orphan drug" for use in treating a rare disease or condition, and (2) receipt of FDA approval to be marketed to the public. *Id.*

34. *Id.* at 230.

35. 21 C.F.R. § 316.25 (2020). After the *Depomed, Inc.* complaint was filed, the FDA amended 21 C.F.R. § 316.25 to provide that a clinical superiority hypothesis is required for orphan drug designation where the drug is "the same drug as an already approved drug." *Depomed*, 66 F. Supp. 3d at 236 n.12; 21 C.F.R. § 316.25(a)(3). In 2017, Congress passed the FDA Reauthorization Act of 2017 ("FDARA"), which provides that if a sponsor seeks orphan drug exclusivity for a drug that is the same as an already-approved or licensed drug "for the same rare disease or condition as the already-approved drug, the Secretary shall require such sponsor, as a condition of such exclusive approval or licensure, to demonstrate that such drug is clinically superior to any already-approved or licensed drug that is the same drug." FDA Reorganization Act of 2017, Pub. L. No. 115-52, 131 Stat. 1005, 1049 (2017); 21 U.S.C. § 360cc(c).

36. No. 16-790, 2018 WL 3838265, at *1 (D.D.C. June 8, 2018), *aff'd* 952 F.3d 323, 323 (D.C. Cir. 2020).

37. *See Eagle Pharms., Inc.*, 2018 WL 3838265, at *3.

38. *See Eagle Pharms., Inc.*, 952 F.3d at 329, 331, 341.

of a designated drug.[39] Thus, the same drug can be designated and approved as an orphan drug for more than one rare disease and in some cases, multiple rare diseases.[40] For each additional designation and approval, the pharmaceutical manufacturer is entitled to a fresh batch of incentives.[41] This also permits an orphan drug manufacturer to obtain sequential periods of exclusivity for separate components of the same disease.[42]

The ODA and its enforcing regulations should be amended to ensure that Congress's original intent is recognized.[43] Specifically, both the Act and the regulations should be amended to prohibit the granting of orphan designation to a drug already approved and marketed, even if the new version is clinically superior to the already-approved drug.[44] Congress and the FDA must act to restrict serial exclusivity by ending drug manufacturers' ability to stack incentives.[45] Finally, the language of the ODA should be amended to permit the FDA to revoke orphan drug designation, and thus revoke market exclusivity, in specific circumstances.[46] Market exclusivity categorically decreases competition and increases prices.[47] If Congress and the FDA tighten restrictions on when and how long a drug may be designated as an orphan drug, and thus enjoy exclusivity under the ODA, competition will increase, prices will decrease, and consumers—millions of sick Americans—will benefit.[48]

This Note will begin by looking at the historical background of drugs generally and the FDA approval process.[49] Part II will also discuss the ODA's passage and detail the benefits currently enjoyed by drug

39. 21 C.F.R. § 316.31(b).

40. Tribble & Lupkin, *supra* note 28.

41. *See id.*

42. *See* 21 C.F.R. § 316.31(b); *see also infra* Part III.B (discussing how drugs like Keytruda receive multiple periods of exclusivity for different, but related, indications).

43. *See* 21 U.S.C. § 360aa-ee; 21 C.F.R. pt. 316.

44. *See infra* Part IV.A (foreshadowing the solution set forth by this Note).

45. *See infra* Part IV.A.

46. *See infra* Part IV.C.

47. *See* Avik Roy, *The Competition Prescription: A Market-Based Plan for Affordable Drugs*, FREOPP (May 16, 2017), https://freopp.org/a-market-based-plan-for-affordable-prescription-drugs-931e31024e08; Kelsey Waddill, *Orphan Drug Act Raises Prescription Drug Spending, Needs Reworking*, HEALTHPAYER INTELLIGENCE (Sept. 13, 2019), https://healthpayerintelligence.com/news/orphan-drug-act-raises-prescription-drug-spending-needs-reworking (discussing a report produced by the American's Health Insurance Plans, which points out that designated orphan drugs also serve common diseases, not just rare diseases, thereby increasing the size of the drugs' markets and eliminating the need to charge exorbitant prices).

48. *See* Roy, *supra* note 47.

49. *See infra* Part II.

companies in the United States under the Act.[50] Part III will discuss the legal issues created by the ODA's incentives and detail the manipulation of the provided benefits, as well as United States federal courts' and Congress's responses to some of these abuses.[51] Part IV sets forth the argument that as a result of the extensive abuse of the Act, the statute should be amended to eliminate any ambiguity and close certain loopholes that currently exist.[52] First, Part IV argues that the ODA should be amended to provide that even if a drug is clinically superior to an already-approved, non-orphan drug, its application for orphan drug designation will be automatically denied, therefore prohibiting the drug to benefit from any market exclusivity.[53] Next, Part IV purports that the Act's criteria should be revised to make it more difficult for a drug to be designated as an orphan by excluding any drug that was previously approved as an orphan drug.[54] Finally, Part IV argues that the ODA should be amended to permit the FDA to revoke market exclusivity should sales of the orphan drug reach a certain threshold or should the number of patients taking the drug exceed 200,000 Americans.[55]

II. THE STORY BEHIND THE ODA

According to the United States government, the terms "orphan drugs" and "orphan designation" refer to a special status given to drugs that treat rare diseases and conditions upon the request of a sponsor, that in most cases is the drug manufacturer itself.[56] These drugs are considered "orphans" because they generally lack sponsors to develop

50. *See infra* Part II.B.
51. *See infra* Part III.
52. *See infra* Part IV.
53. *See infra* Part IV.A.
54. *See infra* Part IV.A.
55. *See infra* Part IV.B–C.
56. *See generally Designating an Orphan Product: Drugs and Biological Products*, FOOD & DRUG ADMIN. (Apr. 6, 2020), https://www.fda.gov/industry/developing-products-rare-diseases-conditions/designating-orphan-product-drugs-and-biological-products (explaining the special status given to drugs that are deemed orphan drugs in the United States today). Harry Shirkey, M.D., was the first to write the term "orphan" in the context of therapeutic drugs in a 1968 editorial comment entitled "Therapeutic Orphans." Frank J. Sasinowski & Andrew J. Hull, *A Brief History of the Name 'Orphan Drugs,'* MEDCITY NEWS (Feb. 22, 2015, 9:32 AM), https://medcitynews.com/2015/02/brief-history-name-orphan-drugs. In his editorial, Dr. Shirkey, a pediatrician in Birmingham, Alabama, discussed the inequality in the development of pediatric drugs. *Id.* He argued that "[b]y an odd and unfortunate twist of fate, infants and children [were] becoming 'therapeutic or pharmaceutical orphans.'" *Id.* Following Dr. Shirkey's publication, others, including Dr. Marion J. Finkel, began to apply "orphan" to other types of diseases that were similarly abandoned. *See id.* Dr. Finkel served as the FDA's first Director of Orphan Products Development in 1982. *Id.* Dr. Finkel started the trend of using the term "orphan" to describe drugs and therapies that treated rare diseases. *Id.*

them, due, in large part, to their costly research and limited profit potential.[57] This Part will discuss the early origins of orphan drugs, and Congress's response to a growing awareness that few medical treatments were being developed for rare diseases.[58]

A. The Ebbs and Flows of Drug Development in the Nineteenth and Twentieth Centuries

In the nineteenth century, pharmacy science was an experimental process.[59] In 1848, Congress passed its first major attempt at drug regulation: The Drug Importation Act of 1848.[60] Throughout the rest of the century, the United States made strides in protecting the public from adulterated foods, including the appointment of chemists to positions within the federal government.[61]

The FDA was established by Congress on June 30, 1906, by way of the passage of the Federal Food and Drugs Act.[62] This Act, to be administered by the FDA, banned manufacturers from selling mislabeled and adulterated products and from misleading consumers with false claims.[63] It was mainly passed in response to Upton Sinclair's *The*

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57. *FDA at Rare Disease Day/February 28, 2011*, FOOD & DRUG ADMIN. (Nov. 3, 2017), https://www.fda.gov/industry/developing-products-rare-diseases-conditions/fda-rare-disease-day-february-28-2011. Drug companies themselves proffer the argument that ever-increasing prices for orphan drugs are justified due to the high cost of research and development of these drugs. Shawn Radcliff, *Why Are Drug Prices for Rare Diseases on the Rise?*, HEALTHLINE (Apr. 5, 2019), https://www.healthline.com/health-news/critics-orphan-drug-law-ripe-for-abuse; *see also infra* text accompanying notes 271-79.

58. *See infra* Part II.A–C; NAT'L ORG. FOR RARE DISORDERS, TRENDS IN ORPHAN DRUG COSTS AND EXPENDITURES DO NOT SUPPORT REVISIONS IN THE ORPHAN DRUG ACT: BACKGROUND AND HISTORY 1 (2017), https://rarediseases.org/wp-content/uploads/2018/05/NORD-IMS-Report_FNL.pdf.

59. *See Drugs and Their Manufacture in the Nineteenth Century*, CTR. FOR THE HIST. OF MED., https://collections.countway.harvard.edu/onview/exhibits/show/apothecary-jars/nineteenth-century-drugs (last visited Feb. 8, 2021).

60. *Milestones in U.S. Food and Drug Law History*, FOOD & DRUG ADMIN. (Jan. 31, 2018), https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/milestones-us-food-and-drug-law-history; Wesley J. Heath, *America's First Drug Regulation Regime: The Rise and Fall of the Import Drug Act of 1848*, 59 FOOD & DRUG L.J. 169, 170 (2004). The Import Drug Act required the inspection of any imported drugs by government agents in order to prevent adulterated drugs from entering the United States. *Milestones in U.S. Food and Drug Law History*, *supra*. After issues with its implementation and enforcement, the Import Drug Act was mostly repealed in 1922. Heath, *supra*, at 176-78, 198.

61. *See Milestones in U.S. Food and Drug Law History*, *supra* note 60.

62. *Id.*; John P. Swann, *FDA's Origin*, FOOD & DRUG ADMIN. (Feb. 1, 2018), https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/fdas-origin. At the time, the FDA was still known as the Bureau of Chemistry—the predecessor of the FDA. *Milestones in the U.S. Food and Drug Law History*, *supra* note 60.

63. *Part I: The 1906 Food and Drugs Act and Its Enforcement*, FOOD & DRUG ADMIN. (Apr. 24, 2019), https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/part-i-1906-food-and-

Jungle, which exposed the appalling conditions that workers in the meat-packing industry experienced.[64] In addition to food safety, the FDA is also tasked with regulating medications.[65] Under Harvey W. Wiley's tenure as commissioner of the FDA during the early 1900s, the focus remained on ensuring food safety, which Wiley believed posed a greater problem than potentially dangerous drugs.[66]

Because of the numerous shortcomings of the 1906 Act, advocates and the FDA itself pushed for a new bill in the 1930s.[67] But it was not until the new "sulfa wonder drug," Elixir Sulfanilamide, killed over one hundred people, including many children, that Congress took action.[68] On June 25, 1938, President Franklin D. Roosevelt signed the Food, Drug and Cosmetic Act into law.[69] While the new law provided for stricter labeling requirements and pre-market approval for all drugs, it, too, had shortcomings.[70] Under the 1938 Act, so long as a drug manufacturer followed guidelines used to determine that drugs were safe for human consumption, the manufacturer was permitted to sell its products in the U.S. marketplace.[71] However, during this time, there was no requirement that drug manufacturers prove that their drugs actually worked.[72] In fact, manufacturers could begin to sell a drug if the FDA

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drugs-act-and-its-enforcement.

64. *See Upton Sinclair's The Jungle: Muckraking the Meat-Packing Industry*, CONST. RTS. FOUND., Fall 2008, https://www.crf-usa.org/bill-of-rights-in-action/bria-24-1-b-upton-sinclairs-the-jungle-muckraking-the-meat-packing-industry.html (noting that Sinclair's description of diseased, rotten, and contaminated meat shocked the public and, coupled with unjust practices within the meat-packing industry, led to increased public scrutiny and federal legislation).

65. *Part I: The 1906 Food and Drugs Act and Its Enforcement*, *supra* note 63.

66. *Id.*; *Milestones in the U.S. Food and Drug Law History*, *supra* note 60.

67. *See Part II: 1938, Food, Drug, Cosmetic Act*, FOOD & DRUG ADMIN. (Nov. 27, 2018), https://www.fda.gov/about-fda/fdas-evolving-regulatory-powers/part-ii-1938-food-drug-cosmetic-act. Numerous products demonstrated the failures of the 1906 Act. *Id.* These products included "Banbar, a worthless 'cure' for diabetes that the old law protected," and "the Wilhide Exhaler, which falsely promised to cure tuberculosis and other pulmonary diseases." *Id.*

68. *Id.* The untested medication constituted a "highly toxic chemical analogue of antifreeze." *Id.*

69. *Id.* The Constitution does not explicitly give the federal government any power to regulate drugs and thus, Congress asserted its power to regulate interstate commerce to enact the law. *History of Federal Regulation: 1902-Present*, FDAREVIEW.ORG https://www.fdareview.org/issues/history-of-federal-regulation-1902-present (last visited Feb. 8, 2021).

70. *Part II: 1938, Food, Drug, Cosmetic Act*, *supra* note 67; *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 19; *see* Shawn Kennedy, *FDA Kefauver-Harris Amendment (1962)*, IMARC (Feb. 20, 2015), https://www.imarcresearch.com/blog/bid/361199/FDA-Kefauver-Harris-Amendment-1962 (foreshadowing future amendments to the federal law as a result of the deficiencies in the current law).

71. Kennedy, *supra* note 70.

72. *Id.*

did not act within sixty days to prevent its marketing.[73] The FDA lacked the authority to enforce some of the statutory provisions of the Act.[74]

Over this period of time, the pharmaceutical industry began developing numerous lifesaving prescription drugs.[75] Insulin was used commercially by those afflicted with diabetes in most western countries by the end of 1923.[76] Commonly used drugs, like penicillin, were also developed in the 1920s.[77] In the post-World War II era, the pharmaceutical industry took off.[78] Different antibiotics were developed to treat bacterial infections and illnesses.[79] In the 1950s, Americans referred to new drugs as "magic bullets" because of how quickly and effectively they cured illnesses.[80] The industry had transformed from federally operated laboratories and non-profit research centers to private, for-profit manufacturers who took the lead in new drug discovery and development.[81]

This led to one of the darkest episodes in worldwide pharmaceutical research history.[82] In the 1950s, the drug thalidomide was first marketed in Germany as a mild, over-the-counter sleeping pill—safe even for pregnant women.[83] It was marketed in forty-six countries and sales

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73. *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 19.

74. *Id.*

75. Jeremy A. Greene & Scott H. Podolsky, *Reform, Regulation, and Pharmaceuticals—The Kefauver-Harris Amendments at 50*, 367 NEW ENG. J. MED. 1481, 1481 (2012).

76. Michael Bliss, *The History of Insulin*, DIABETES CARE, Dec. 1993, at 4, 6. Sir Frederick Banting and his assistant, Dr. Charles Best, discovered a synthetic form of insulin in Canada. *Frederick G. Banting*, NOBEL PRIZE, https://www.nobelprize.org/prizes/medicine/1923/banting/biographical (last visited Feb. 8, 2021). Banting later shared the Nobel Peace Prize in Physiology or Medicine in 1923 with J.J.R. Macleod, who gave Banting facility space in which to conduct experimental work in the field. *Id.*

77. *3 Drug Discoveries in the 1920s that Changed the World*, RONDAXE (Sept. 12, 2020), https://www.rondaxe.com/3-drug-discoveries-in-the-1920s-that-changed-the-world. Penicillin was considered a "miracle drug." Alina Bradford, *Penicillin: Discovery, Benefits and Resistance*, LIVE SCI. (May 30, 2019), https://www.livescience.com/65598-penicillin.html. In 1928, Alexander Fleming discovered penicillin in Europe while he was investigating staphylococcus, a common type of bacteria that may cause infections in patients with weakened immune systems. *Alexander Fleming*, SCI. HIST. INS., https://www.sciencehistory.org/historical-profile/alexander-fleming (Dec. 5, 2017). The scientific community did not take notice of penicillin until a decade later, and Fleming ultimately received the Nobel Prize in Physiology or Medicine for the discovery in 1945. *Id.*

78. *History of Federal Regulation: 1902-Present*, *supra* note 69.

79. *Id.*

80. *Id.*

81. David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD & DRUG L.J. 125, 126 (2000).

82. *See Thalidomide*, SCI. MUSEUM (Dec. 11, 2019), http://broughttolife.sciencemuseum.org.uk/broughttolife/themes/controversies/thalidomide.

83. Bara Fintel et al., *The Thalidomide Tragedy: Lessons for Drug Safety and Regulation*, HELIX (July 28, 2009), https://helix.northwestern.edu/article/thalidomide-tragedy-lessons-drug-safety-and-regulation.

nearly matched those of aspirin.[84] By 1960, an Australian obstetrician, Dr. William McBride, recommended the drug to his pregnant patients to alleviate morning sickness, and in the process, he set a worldwide trend.[85]

By 1961, thalidomide was reported as the likely cause for a large increase in the number of disabled babies born in Europe.[86] The strong sedative properties caused so-called "monster-forming" children, where limbs, and sometimes eyes, ears, and internal organs, failed to develop properly.[87] By the end of the year, the drug was withdrawn from the market.[88] By March 1962, the drug was banned in most countries where it had been previously sold.[89]

In July of 1962, United States President John F. Kennedy and the American press praised Frances Kelsey, the FDA inspector who refused to approve thalidomide for use in the United States.[90] Kelsey believed that the drug's approval application was underdeveloped; there was a lack of data indicating whether the drug could cross the placenta and be ingested by an unborn, developing baby, and there were no results available from American clinical trials.[91] The thalidomide tragedy, coupled with Kelsey's refusal to grant the drug's application, spurred changes within the FDA's approval process in the form of the Kefauver-Harris Amendments.[92]

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84. *Id.* The drug was not marketed in the United States. *Id.*; *see infra* text accompanying notes 90-92.

85. Fintel et al., *supra* note 83.

86. Frederick Dove, *What's Happened to Thalidomide Babies?*, BBC NEWS (Nov. 3, 2011), https://www.bbc.com/news/magazine-15536544.

87. *Id.*

88. *Id.*

89. Fintel et al., *supra* note 83.

90. *Id.* At this time, news traveled to the United States that thousands of children in Europe had been born with "shortened, missing or flipper-like arms and legs" because of thalidomide. *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 19. Unknown to the FDA, thalidomide manufacturer William S. Merrill Company distributed the drug to 1,200 physicians in the United States, including those who treated pregnant women. *Id.* In response, the FDA launched a nationwide campaign to recover the drugs and President Kennedy issued warnings to the American people. *Id.* In total, there were seventeen births of deformed infants tied to thalidomide in the United States. *Id.*

91. Fintel et al., *supra* note 83. Approximately 20,000 Americans were given the drug in two clinical trials spanning the 1950s and 1960s. Katie Thomas, *The Story of Thalidomide in the U.S., Told Through Documents*, N.Y. TIMES, https://www.nytimes.com/2020/03/23/health/thalidomide-fda-documents.html (Mar. 24, 2020).

92. Fintel et al., *supra* note 83.

1. Far-Reaching Legislation: Kefauver-Harris Amendments

By October 1962, the Drug Amendments of 1962,[93] commonly known as the Kefauver-Harris Amendments, were passed unanimously by both houses of Congress and signed by President Kennedy.[94] The legislation was originally introduced by Senator Carey Estes Kefauver in 1959, who believed patients were paying too much for their treatment and were being misled by false advertising claims.[95] He advocated for government control over drug safety labels and contents, and marketing and distribution processes, as well as control over drug pricing and competition.[96]

Senator Kefauver led Senate hearings that discussed the ways in which the Federal Food, Drug and Cosmetic Act could be strengthened and eventually introduced legislation aimed at controlling the labeling, marketing, and competition of drugs.[97] The proposed legislation included a "scheme of compulsory patent sharing" where "each pharmaceutical company would, after three years, be required to share its new patents with competitors, while collecting an annual royalty fee" of around eight percent.[98]

Once the devastation of thalidomide became clear, Senator Kefauver reintroduced his legislation, which was co-sponsored by Senator Oren Harris,[99] to include provisions that were designed to prevent another tragedy.[100] The bill was also revised to remove the pricing and patent-sharing provisions.[101] Soon thereafter, the Kefauver-Harris Amendments became law.[102]

The Amendments, *inter alia*, established a new process for drug manufacturers to follow before receiving market approval and expanded the FDA's authority.[103] Manufacturers must prove that their drugs are effective before they go on the market and must report any serious side

93. Pub. L. No. 87-781, 76 Stat. 780 (1962).

94. *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 19.

95. *Id.* Senator Kefauver sat on the Senate Subcommittee for Antitrust and Monopoly. *Id.* He was a democratic lawmaker from Tennessee who became a national figure in the early 1950s after his involvement in the Senate's Special Committee to Investigate Organized Crime. *Estes Kefauver: A Featured Biography*, U.S. SENATE, https://www.senate.gov/artandhistory/history/common/generic/Featured_Bio_KefauverEstes.htm (last visited Feb. 8, 2021).

96. *History of Federal Regulation: 1902–Present*, *supra* note 69.

97. *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 19.

98. *History of Federal Regulation: 1902–Present*, *supra* note 69.

99. *Harris, Oren*, HIST., ART & ARCHIVES, https://history.house.gov/People/Listing/H/HARRIS,-Oren-(H000249) (last visited Feb. 8, 2021). Representative ("Rep.") Harris was a democratic lawmaker from Arkansas. *Id.*

100. *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 19.

101. *History of Federal Regulation: 1902–Present*, *supra* note 69.

102. *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 19.

103. *See id.*

effects.[104] Manufacturers must also produce "adequate and well-controlled clinical studies conducted by qualified experts" as evidence of a drug's effectiveness.[105] Further, the Amendments required the FDA to approve a new drug application within 180 days.[106] It also provided the FDA with the power to control prescription drug advertising, including a requirement that all advertisements contain accurate information about side effects.[107] The FDA grew, increasing its staff from 1,000 employees in 1951 to nearly 6,500 two decades later, aiding in its ability to enforce the new standards.[108] Opponents criticized the Amendments as "an excessive expansion of government power."[109] Significantly, although the Amendments established new standards for drug safety and efficacy, cost control measures were not addressed.[110]

2. Neglected Patients: A Lack of Products to Treat Rare Diseases

From 1967 up until the passage of the ODA in 1983, the FDA approved only thirty-four drugs developed specifically to treat rare diseases.[111] The stringent standards of the Kefauver-Harris amendments made it more difficult for drug manufacturers to obtain approval for drugs, due in part to the exorbitant costs of research and development.[112] Over time, it was made clear that the "task of proving efficacy is much

104. *Id.*

105. *See id.*; *see also* Reid Wilkening, *The Price of Pills: A Brief History of the Kefauver-Harris Amendment*, PHAROS, Autumn 2019, at 17, 21. The randomized controlled trial remains a significant tool for FDA investigations into pharmaceutical companies. *Id.* However, the efficacy requirements increased the time necessary to develop new compounds, an unintended consequence of the standards. *Id.*

106. *Kefauver-Harris Amendments Revolutionized Drug Development*, *supra* note 19. Approval from the FDA was required before the drug could be marketed in the United States. *Id.*

107. *Id.*

108. *History of Federal Regulation: 1902–Present*, *supra* note 69.

109. *What Are the Kefauver-Harris Amendments?*, INFOED GRANTS & CONTS. (Oct. 15, 2012), https://infoedglobal.com/2012/10/15/what-are-the-kefauver-harris-amendments. Other critics argued that the regulations delayed beneficial new medicines from reaching patients. Arthur Daemmrich, *Invisible Monuments and the Costs of Pharmaceutical Regulation: Twenty-Five Years of Drug Lag Debate*, 45 PHARMACY HIST. 3, 3 (2003). Additionally, between the early 1970s and the mid-1990s, there was evidence that Europeans accessed significant therapies before Americans. *Id.* Further, economists criticized the legislation and the FDA for valuing the prevention of marketing dangerous drugs over Americans' access to life-saving medicines. *Id.* Economist Milton Friedman and some of his colleagues found the legislation akin to a tax on drug sales that had virtually no effect on the safety of the drugs. *Id.* According to them, "[T]his tax was spent on 'invisible monuments' instead of on visible public health measures." *Id.*

110. Jay Hancock, *Talk About Déjà Vu: Senators Set to Re-Enact Drug Price Hearing of 60 Years Ago*, KHN (Feb. 22, 2019), https://khn.org/news/talk-about-deja-vu-senators-set-to-re-enact-drug-price-hearing-of-60-years-ago.

111. NAT'L ORG. FOR RARE DISORDERS, *supra* note 58, at 1.

112. Rum, *supra* note 20.

more difficult, expensive, and time-consuming than the task of proving safety."[113]

The goal of the FDA's review process is to ensure that the drugs that are approved are safe and effective for consumption.[114] First, a drug sponsor must demonstrate the results from preclinical testing of laboratory animals and explain its methodology to test the drug on humans to the FDA.[115] The FDA then decides whether it is "reasonably safe" for the company to move forward with human testing.[116] Next, the FDA and a local institutional review board ("IRB") review the application.[117]

As a first step, the IRB must approve the clinical trial protocols.[118] Phase I testing involves studies conducted with healthy volunteers in order to determine the side effects of the drug.[119] Once it is determined that Phase I was safe and acceptable, Phase II studies will commence.[120] Phase II emphasizes effectiveness and the goal is to "obtain preliminary data on whether the drug works in people who have a certain disease or condition."[121] If Phase II reveals the drug is effective, Phase III begins, and the studies become more extensive and involve a larger number of test subjects—from several hundred to three thousand people.[122] The researchers then examine different populations, dosages, and

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113. *History of Federal Regulation: 1902–Present*, *supra* note 69.

114. *See The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, FOOD & DRUG ADMIN. (Nov. 24, 2017), https://www.fda.gov/drugs/drug-information-consumers/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective.

115. *Id.* A sponsor can be a company, research institution, or other organization that takes responsibility for the development of a drug. *Id.*

116. *Id.*

117. *Id.* The institutional review board ("IRB") is a group of individuals whose purpose is to protect the rights and welfare of human subjects that participate in research studies. *Institutional Review Boards Frequently Asked Questions*, FOOD & DRUG ADMIN. (Apr. 18, 2019), https://www.fda.gov/regulatory-information/search-fda-guidance-documents/institutional-review-boards-frequently-asked-questions; *What Is the Institutional Review Board (IRB)?*, OR. ST. U., https://research.oregonstate.edu/irb/frequently-asked-questions/what-institutional-review-board-irb (last visited Feb. 8, 2021). Under FDA regulations, an IRB reviews and monitors any research activities. *Institutional Review Boards Frequently Asked Questions*, *supra*. Each IRB must register with the FDA before approving studies if the study involves FDA regulations. *Id.*; *see also* 21 C.F.R. § 56.106 (2020). An IRB consists of a panel of individuals with varying backgrounds, including non-scientists and members unaffiliated with the institution conducting the study. *What is the Institutional Review Board (IRB)?*, *supra*.

118. *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, *supra* note 114. Clinical trial protocols describe "the type of people who may participate in the clinical trial, the schedule of tests and procedures, the medications and dosages to be studied, the length of the study, the study's objectives, and other details." *Id.*

119. *Id.*

120. *Id.*

121. *Id.*

122. *Id.*

combinations with other drugs and produce a comprehensive study.[123] Then, the drug sponsor applies for FDA approval.[124]

Prior to 1983, pharmaceutical companies focused solely on researching and developing drugs that could be mass marketed to large patient populations, thus recouping their investment and turning a profit, as the costs of obtaining approval were the same regardless of the projected consumer market population.[125] Drugs to treat asthma, hypertension, and other common diseases were developed.[126] Drug companies disregarded the market made up of rare diseases and conditions.[127] The pharmaceutical industry as a whole was "concerned less with research for the sake of research, or overall social welfare, and was concerned more with making profits through rational business decisions."[128]

B. The Passage of the ODA

By the 1970s, patients in dire need of treatment began calling for reform,[129] and in 1979, the FDA and the National Institute of Health ("NIH") created a task force.[130] Chaired by Marion J. Finkel, then Associate Director for New Drug Evaluation at the FDA Bureau of Drugs,[131] the committee recognized that these rare diseases, and the people afflicted by them, were underserved.[132] The committee considered possible incentives that would encourage pharmaceutical manufacturers to produce these needed drugs and therapies.[133] Because it was such a widespread and diverse problem, the committee's report ultimately called for Congress to address this issue.[134]

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123. *Id.*

124. *Id.*

125. Rohde, *supra* note 81, at 125-26; *see also History of Federal Regulation: 1902–Present*, *supra* note 69.

126. Rohde, *supra* note 81, at 126.

127. *Id.*

128. *Id.*

129. John Swann, *The Story Behind the Orphan Drug Act*, FOOD & DRUG ADMIN. (Feb. 23, 2018), https://www.fda.gov/industry/orphan-products-development-events/story-behind-orphan-drug-act. By the early 1980s, some twenty to twenty-five million patients suffered from approximately 5,000 rare diseases. *Id.*

130. *Id.*; NAT'L ORG. FOR RARE DISORDERS, *supra* note 58, at 1.

131. Koichi Mikami, *Orphans in the Market: The History of Orphan Drug Policy*, 32 SOC. HIST. MED. 609, 613 (2019).

132. NAT'L ORG. FOR RARE DISORDERS, *supra* note 58, at 1.

133. Mikami, *supra* note 131, at 613.

134. *See id.*; *see also* INTERAGENCY TASK FORCE, SIGNIFICANT DRUGS OF LIMITED COMMERCIAL VALUE 1-2 (1979).

One case in particular caught the attention of Representative ("Rep.") Elizabeth Holtzman.[135] A researcher at Mount Sinai Hospital named Melvin H. Van Weort developed an effective treatment for myoclonus, a rare neurological disease.[136] However, after approaching agencies like the FDA and the NIH, Dr. Van Weort could not find adequate funding to produce the chemical compound needed for the treatment.[137] One of Dr. Van Weort's patients, Sharon Dobkin, contacted Rep. Holtzman and convinced her that legislative action was needed.[138] Based on the task force's recommendations, Rep. Holtzman introduced a bill that would provide administrative and economic assistance, including extensions on the patent lives of certain drugs and the release of direct federal grants, to pharmaceutical companies for the research and development of drugs used to treat rare diseases.[139] To Rep. Holtzman, the primary solution was a separate office to coordinate research and development activities at the NIH, alleviating the advisory board at the FDA who handled it at the time.[140] While Holtzman realized "that no single piece of legislation [would] be able to solve all the issues," she contended that her "bill [would] provide an administrative framework."[141]

At a June 1980 hearing held by the Subcommittee on Health and the Environment, Rep. Holtzman identified Sharon Dobkin to members of the Subcommittee, noting "[t]he basic problem is clear."[142] "Certain drugs and chemical compounds," she continued, "already identified, are not being produced simply because they are unprofitable."[143] Although these drugs have a "limited commercial value," they have an "incalculable value to the afflicted patients and their families."[144] Rep.

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135. ELIZABETH HOLTZMAN & CYNTHIA L. COOPER, WHO SAID IT WOULD BE EASY?: ONE WOMAN'S LIFE IN THE POLITICAL ARENA 106-07 (1996); *see also* Mikami, *supra* note 131, at 616. Rep. Holtzman was a Democratic congresswoman from New York. *Holtzman, Elizabeth*, HIST., ART & ARCHIVES, https://history.house.gov/People/Detail/15213?ret=True (last visited Feb. 8, 2021). She was "a self-proclaimed political outsider" who earned national prominence as an active member of the Judiciary Committee during President Nixon's impeachment inquiry and as a cofounder of the Congressional Caucus on Women's Issues. *Id.*

136. Mikami, *supra* note 131, at 616.

137. *Id.*

138. *Id.*

139. *Id.*

140. *Volume II: Drug Regulation Reform–Oversight: Hearing on How Can We Best Use Our Limited Resources and at the Same Time Insure Safe and Effective Drugs to Diseases Which Infrequently Occur Before the Subcomm. on Health and the Env't of the Comm. on Interstate and Foreign Com.*, 96th Cong. 4 (1980) (statement of Rep. Elizabeth Holtzman).

141. *Id.*

142. *Id.* at 3.

143. *Id.*

144. *Id.*

Holtzman's bill, however, did not pass in the House of Representatives and soon thereafter, she lost her Congressional seat.[145] Rep. Ted Weiss, another democratic lawmaker from New York, resubmitted her bill in 1981.[146] Later that year, Rep. Henry Waxman submitted his own version of the bill.[147] Finally, in January 1983, Waxman's bill became law when President Ronald Reagan signed the ODA with the purpose of encouraging the development of drugs for rare diseases.[148]

C. The Law as It Stands Today

As originally enacted and as it stands today, the ODA provides a pharmaceutical company with several incentives if and when the FDA grants orphan designation to one of the company's drugs.[149] First, the sponsors of an approved orphan product are provided with seven years of market exclusivity with certain exceptions.[150] Second, the drug company is provided with a tax credit for a percentage of the cost of conducting human clinical trials.[151] Third, the company is given federal research grants to defray the costs of testing expenses, developing medical devices, and medical foods for rare diseases and conditions.[152]

Under 21 U.S.C. § 355, any drug seeking approval from the FDA for marketing and distribution in interstate commerce must prove the drug's safety and effectiveness by way of extensive and costly human clinical trials.[153] An orphan drug, however, is entitled to a streamlined approval process while it is still being developed, and under the ODA, clinical trials involving human testing are not required.[154] Instead, the

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145. Mikami, *supra* note 131, at 617.

146. *Id.*

147. *Id.* at 609, 617.

148. *Id.* at 617; OFF. OF INSPECTOR GEN., DEP'T OF HEALTH & HUM. SERVS., ORPHAN DRUG ACT IMPLEMENTATION & IMPACT 1 (2001).

149. *See* 21 U.S.C. §§ 360aa-ee (1988); 21 U.S.C. §§ 360aa-ee (2018).

150. 21 U.S.C. § 360cc(a) (1988); 21 U.S.C. § 360cc(a) (2018). During this time, the FDA may not approve any other application for the same drug to treat the same rare disease until seven years have passed. 21 U.S.C. § 360cc(a) (2018). Because FDA approval is mandatory for any drug to be marketed, this effectively provides the first manufacturer that receives approval of such a drug the exclusive ability to market the drug for seven years, thereby setting any price it chooses. *See id.* The regulations define the term "same drug" to mean, *inter alia*, "a drug that contains the same active moiety as a previously approved drug and is intended for the same use of the previously approved drug." 21 C.F.R. § 316.3(b)(14) (2020).

151. 21 U.S.C. § 360dd (1988); 21 U.S.C. § 360dd (2018).

152. 21 U.S.C. § 360ee (1988); 21 U.S.C. § 360ee (2018).

153. 21 U.S.C. § 355(a)-(b); *see also supra* text accompanying notes 114-24; *Drug Approval Process*, FOOD & DRUG ADMIN., https://www.fda.gov/media/82381/download (last visited Feb. 8, 2021).

154. OFF. OF ORPHAN PRODS. DEV. (OOPD), RECOMMENDED TIPS FOR CREATING AN ORPHAN DRUG DESIGNATION APPLICATION 14-15 (2018), https://www.fda.gov/media/111762/download.

application must show that the drug "promise[s] to treat, diagnose or prevent" the rare disease or condition.[155] The data used to support this scientific rationale "may include clinical study data, in vivo animal data, and in vitro data."[156] If there is no clinical data or animal studies, the FDA will even consider an explanation of "what the data means and how it relates to the disease" when reviewing the application.[157]

The Act also provides for exceptions to the market exclusivity provision.[158] The FDA will approve the same drug to be marketed if: (1) the sponsor of the first drug "cannot ensure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated"; or (2) the sponsor provides the FDA, in writing, the consent to approve other applications before the seven-year period is complete.[159] Additionally, an orphan drug is still entitled to market exclusivity, even if the same drug is already on the market, if the sponsor of the orphan drug proves the orphan drug is superior to the existing drug.[160] These incentives worked—there are currently 5,788 orphan drug designations listed on the FDA's website.[161]

III. DRUG MANUFACTURERS HAVE TAKEN GROSS ADVANTAGE OF THE ODA

The ODA was not intended to create enormous profit margins for drug manufacturers at the expense of those suffering from the rare diseases of which such medications were designed to treat.[162] In 2016,

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Animal studies or other clearly explained data may be considered in lieu of clinical data. *Id.*

155. *Id.* at 9.

156. *Id.* at 12. "In vivo" is Latin for "within the living" and it refers to testing on a whole living organism. Jamie Eske, *What Is the Difference Between In Vivo and In Vitro?*, MED. NEWS TODAY (Aug. 31, 2020), https://www.medicalnewstoday.com/articles/in-vivo-vs-in-vitro. "In vitro" is Latin for "in glass." *Id.* In vitro data results from laboratory testing and usually involves studying microorganisms, human cells, or animal cells in culture. *Id.*

157. OFF. OF ORPHAN PRODS. DEV. (OOPD), *supra* note 154, at 15.

158. *See* 21 U.S.C. § 360cc(b).

159. *Id.*

160. § 360cc(c).

161. *See Search Orphan Drug Designations & Approvals*, FOOD & DRUG ADMIN., https://www.accessdata.fda.gov/scripts/opdlisting/oopd/listResult.cfm (last visited Feb. 8, 2021) (showing the FDA search engine that contains every orphan drug designation that was approved as of October 12, 2020).

162. *See supra* Part II; *see also* Mikami, *supra* note 131, at 611, 629. Mikami characterizes the Orphan Drug Act as a market-based policy wherein the U.S. government sought to create market incentives to encourage pharmaceutical companies to invest in producing new drugs, while avoiding interference in the pharmaceutical market more generally. *Id.* However, the author also argues that this approach has not been used as intended because pharmaceutical companies are using the billions of dollars in profits from one orphan drug to finance products for other rare diseases and

the average annual cost for orphan drugs was $140,443, compared with $27,756 for mainstream drugs.[163] This Part will examine the two major issues caused by the ODA.[164] First, the ODA grants orphan drug designation, along with the incentives that designation provides, to drugs that are clinically superior, even if that drug is the "same drug" as one already existing on the market.[165] Second, the ODA allows drug manufacturers to receive orphan status for the same drug to treat numerous diseases, thereby stacking the incentives the ODA provides.[166]

Supporters of the Act, like the National Organization for Rare Disorders, seem to ignore its downfalls, citing the number of orphan drugs as evidence of the advancement in treatments and care for patients with rare diseases.[167] While it cannot be denied that the ODA stimulated innovation for treatments, including gene therapies and cancer treatments, it is also true that many companies have taken advantage of it—gross advantage, many would argue.[168]

A study done by researchers at Johns Hopkins University estimated that sales revenue from orphan drugs will rise at more than double the rate of the overall prescription drug market in 2020, with orphan drugs raking in a whopping $176 billion in sales.[169] According to EvaluatePharma, seven of the top ten drug companies are global industry players because of sales derived from their orphan drug products.[170] A report produced by America's Health Insurance Plans ("AHIP") found that from 1998 to 2017, the average annual cost for orphan drugs increased twenty-six-fold, while the cost for specialty and traditional drugs only doubled.[171] In fact, orphan drugs are being approved and

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conditions, with no economic benefits to the patients. *Id.* at 629.

163. EVALUATEPHARMA, ORPHAN DRUG REPORT 2017, at 4 (2017), http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf.

164. *See infra* Part III.A–B.

165. *See infra* Part III.A; 21 C.F.R. § 316.3(b)(14) (2020).

166. *See infra* Part III.B.

167. *See* NAT'L ORG. FOR RARE DISORDERS, *supra* note 58, at 3. The high number of orphan drug approvals reflects a commitment by the FDA to encourage development of orphan drugs and the success of the Orphan Drug Act ("ODA") generally. Diane Dorman, *Don't Let the Maker of a Buprenorphine Drug Abuse the Orphan Drug Act*, STAT (May 28, 2019), https://www.statnews.com/2019/05/28/buprenorphine-drug-abusing-orphan-drug-act. However, the loopholes within the Act, which are frequently exploited by drug manufacturers, threaten the integrity of the ODA. *See id.*

168. Dorman, *supra* note 167; *see infra* Part III.A–B.

169. Michael G. Daniel et al., *The Orphan Drug Act: Restoring the Mission to Rare Diseases*, 39 AM. J. CLINICAL ONCOLOGY 210, 211 (2016).

170. EVALUATEPHARMA, *supra* note 163.

171. AHIP, THE RISE OF ORPHAN DRUGS 5 (2019), https://www.ahip.org/wp-content/uploads/IB_OrphanDrugs-1004.pdf.

entering the market at higher rates than ever before.[172] Among newly launched drugs, the AHIP report found that the share of orphan drugs increased more than four-fold, from ten percent to forty-four percent over the same twenty-year period.[173]

One of the most egregious abuses by drug manufacturers related to drug pricing involves Turing Pharmaceuticals and its CEO, Martin Shkreli.[174] In 2015, Shkreli's company acquired the rights to and raised the price of Daraprim, an old orphan drug mainly used to treat HIV/AIDS, from an affordable $13.50 to an outrageous $750 per tablet.[175] One can even find Shkreli's face in a Google Images search for the term "worst people."[176] But the situation involving Shkreli also raised the question: How was he able to get away with pricing the drug at such a high cost?[177]

A. The ODA's Barrier to Competition

As originally enacted, the ODA's plain language unintentionally provided a loophole allowing a drug manufacturer to receive market exclusivity for its drug—even if the same drug was already on the market.[178]

In *Depomed, Inc. v. U.S. Department of Health & Human Services*,[179] pharmaceutical company, Depomed, Inc. ("Plaintiff"), manufactured Gralise, a drug to treat the rare condition post-herpetic neuralgia ("PHN").[180] Under the ODA, Plaintiff submitted an application to the FDA, requesting orphan designation for Gralise.[181] Gralise then met the statutory criteria that entitled it to market exclusivity under the ODA in that: (1) the FDA designated Gralise as an orphan drug, and (2) the FDA approved Gralise to be marketed to the public.[182]

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172. *Id.* at 1.

173. *Id.* at 4.

174. *See* Issie Lapowsky, *Why Does the Web Hate Martin Shkreli? Let Us Count the Ways*, WIRED (Aug. 4, 2017, 7:02 PM), http://www.wired.com/story/martin-shkreli-guilty-securities-fraud.

175. *Id.*; Sarah Massey, *Martin Shkreli: A Timeline of Events that Shook Up the Pharmaceutical Industry*, XTALKS (Jan. 13, 2016), https://xtalks.com/martin-shkreli-timeline.

176. Lapowsky, *supra* note 174.

177. *See* Meg Tirrell, *Martin Shkreli's Legacy: Putting a 'Fine Point' on the Drug Pricing Debate*, CNBC (Mar. 9, 2018, 6:47 PM), https://www.cnbc.com/2018/03/09/martin-shkrelis-legacy-shaping-the-drug-pricing-debate.html.

178. *See* 21 U.S.C. § 360cc (1988); Depomed, Inc. v. U.S. Dep't of Health & Hum. Servs., 66 F. Supp. 3d 217, 220 (D.D.C. 2014).

179. 66 F. Supp. 3d 217.

180. *Id.* at 220.

181. *Id.* at 224.

182. *Id.* at 220.

The FDA, however, declined to recognize the exclusivity period for Gralise.[183] Prior to Plaintiff's application under the ODA for Gralise, the FDA approved another drug, Neurontin, for use in treating PHN.[184] Neurontin was produced by pharmaceutical company Pfizer.[185] However, Pfizer never sought or obtained orphan drug designation for Neurontin for use in treating PHN.[186] By the time Plaintiff submitted Gralise as an orphan product in 2006, Neurontin and generic versions of Neurontin were on the market for several years.[187]

The FDA argued that Neurontin and Gralise were the "same drug" under the regulations because both drugs' active ingredient is gabapentin.[188] Thus, the FDA proffered that Plaintiff must prove that Gralise is clinically superior to Neurontin in order for Gralise to receive marketing exclusivity under the ODA.[189]

The District Court for the District of Columbia disagreed with the FDA, however, and granted Plaintiff's motion for summary judgment.[190] The court ordered the FDA to recognize orphan drug marketing exclusivity to Plaintiff for Gralise without requiring Plaintiff to show Gralise was clinically superior to the already-approved drugs on the market.[191] The court agreed with Plaintiff's argument: the FDA's refusal to recognize exclusivity was contrary to the text of the ODA.[192] At the time, the ODA itself did not state that Plaintiff was required to show its drug was clinically superior.[193] Instead, Gralise met the two statutory requirements to receive the incentives provided by the ODA.[194]

The FDA argued that the text of the ODA at the time of the litigation was ambiguous since the statute did not speak to "whether exclusivity must be recognized when a drug is designated as an orphan drug and approved for marketing but is the same drug as one that has already been approved for the same disease or condition."[195] As a result,

183. *Id.* at 226.
184. *Id.* at 223.
185. *Id.* at 223-24.
186. *Id.*
187. *Id.* at 224.
188. *Id.* at 225. "Same drug" is defined as a "drug that contains the same active moiety as a previously approved drug and is intended for the same use as the previously approved drug." 21 C.F.R. § 316.3(b)(14) (2020).
189. *Depomed, Inc.*, 66 F. Supp. 3d at 217, 225.
190. *Id.* at 237.
191. *Id.*
192. *Id.* at 233.
193. *Id.* at 221.
194. *Id.* at 231.
195. *Id.* at 228.

the court should defer to the agency's decision to deny exclusivity, the FDA proffered.[196]

In evaluating the case, the court applied the two-step framework established in *Chevron, USA, Inc. v. National Resource Defense Council*,[197] and found the ODA unambiguously requires market exclusivity when the FDA designates an orphan drug as such and has approved that drug for marketing.[198] Specifically, the court found the ODA "employs the familiar and readily diagrammable formula, 'if x and y, then z.'"[199] As such, so long as Plaintiff met the two statutory requirements and did not fall under the two plainly stated exceptions, Plaintiff's drug was entitled to market exclusivity.[200]

The FDA also set forth compelling, policy-oriented arguments in its favor.[201] Specifically, the FDA maintained that: (1) requiring exclusivity for Gralise could allow Plaintiff "to cut off any new gabapentin entrants into the marketplace, which has been wide open for a decade, without providing any benefit in the treatment of PHN"; and (2) "similarly-situated drug manufacturers could conceivably obtain successive periods of exclusivity for the same drug, provided that they obtained seriatim designations and approvals."[202]

The court was unmoved by these arguments.[203] First, the court found that nothing in the statute suggests that Congress intended to incentivize only one sponsor to produce a certain drug.[204] The court went so far as to suggest that "general market forces" serve as a possible reason the legislature permitted this.[205] Further, the court proffered, manufacturers before Plaintiff had the opportunity to seek exclusivity

196. *Id.* at 228-29.

197. 467 U.S. 837 (1984). A court is first required to determine "whether Congress has directly spoken to the precise question at issue." *Id.* at 842. "If the intent of Congress is clear," the Supreme Court held, "that is the end of the matter; for the court, as well as the agency, must give effect to the unambiguously expressed intent of Congress." *Id.* at 842-43. If the court in its analysis finds, however, that the statute is silent or ambiguous on the specific issue, step two requires the court to defer to any agency interpretation that is based on a permissible construction of the statute. *Id.* at 843-44. The agency's interpretations will be considered permissible by the court, "unless they are arbitrary or capricious in substance, or manifestly contrary to the statute." *Id.* at 844.

198. *Depomed, Inc.*, 66 F. Supp. 3d at 229.

199. *Id.* at 230.

200. *Id.*

201. *Id.* at 233.

202. *Id.* at 234.

203. *See id.* The court acknowledged these arguments as relevant to the first step in the *Chevron* analysis based on "the longstanding rule that a statute should not be construed to produce an absurd result." *Id.* The court reasoned that, under precedent, "[t]he plain meaning of legislation should be conclusive, *except* in the rare cases [in which] the literal application of a statute will produce a result demonstrably at odds with the intentions of its drafters." *Id.*

204. *Id.* at 235.

205. *Id.*

and failed to do so.[206] Thus, according to the court, Plaintiff should be rewarded with market exclusivity for manipulating a statute, designed to produce therapies for rare diseases, because Plaintiff filed an application for such reward first, even though the same drug had been on the market for years.[207]

Second, the court noted that this scenario would not arise if the FDA had fashioned regulations to prevent such abuse.[208] In fact, the court stated that "this result would only occur *if the FDA permitted it to happen*."[209] The court suggested that the FDA could change its regulatory scheme and require applicants like Plaintiff to demonstrate clinical superiority prior to orphan designation.[210]

The FDA, despite withdrawing its appeal,[211] doubled down on its clinical superiority requirement, issuing a notice in the Federal Register, stating:

> In consideration of any uncertainty created by the court's decision in *Depomed*, the Agency is issuing this statement. It is the Agency's position that, given the limited terms of the court's decision to G[ralise], FDA intends to continue to apply its existing regulations in part 316 to orphan-drug exclusivity matters. FDA interprets section 527 of the [Food, Drug and Cosmetic] Act and its regulations (both the older regulations that still apply to original requests for designation made on or before August 12, 2013, as well as the current regulations) to require the sponsor of a designated drug that is the "same" as a previously approved drug to demonstrate that its drug is "clinically superior" to that drug upon approval in order for the subsequently approved drug to be eligible for orphan-drug exclusivity.[212]

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206. *Id.*

207. *See id.*

208. *Id.*

209. *Id.*

210. *Id.*

211. Michelle L. Butler, *FDA Withdraws Appeals in the Depomed Case*, HYMAN, PHELPS & MCNAMARA PC (Nov. 11, 2014), http://www.fdalawblog.net/2014/11/fda-withdraws-its-appeal-in-the-depomed-case. The motion to dismiss the appeal was unopposed and was granted on November 7, 2014. *Id.*

212. Policy on Orphan-Drug Exclusivity; Clarification, 79 Fed. Reg. 76,888, 76,888 (Dec. 17, 2014). The regulations also state that "[u]nless FDA previously approved the same drug for the same use or indication, FDA will not approve another sponsor's marketing application for the same drug for the same use or indication before the expiration of 7 years from the date of" the approval of an orphan designated drug. 21 C.F.R. § 316.31(a) (2020). In other words, an orphan drug will not receive orphan drug exclusivity unless it is shown to be clinically superior to the prior version. *Eagle Pharms., Inc. v. Azar*, No. 16-790, 2018 WL 3838265, at *2, *3 (D.D.C. June 8, 2018), *aff'd* 952 F.3d 323 (D.C. Cir. 2020); *Braeburn Inc. v. U.S. FDA*, 389 F. Supp. 3d 1, 9 (D.D.C. 2019). The purpose is to undercut "evergreening," or a company's ability to "[o]btain infinite, successive 7-year periods of exclusivity for the same drug for the same use when the previously approved drug had

Quickly thereafter, Congress passed the FDARA, which amended the ODA to reflect the FDA's regulatory practice of requiring a demonstration of clinical superiority.[213] Currently under the ODA and its enforcing regulations, clinical superiority is tested at the designation stage and the exclusivity stage.[214] At the designation stage, the sponsor of a drug that is the same as an already-approved drug "may seek and obtain orphan-drug designation for the subsequent drug for the same rare disease or condition if it can present a plausible hypothesis that its drug may be clinically superior to the first drug."[215] Then, once a drug is approved for marketing, the FDA requires the manufacturer to demonstrate "that the drug is clinically superior to the previously approved drug."[216] Once it does so, the FDA will recognize the exclusivity period for that drug.[217]

A subsequent case, *Eagle Pharmaceuticals, Inc. v. Azar*,[218] made clear that despite the legislative changes made, FDARA and the requirements of clinical superiority do not apply to drugs designated as orphans and approved for marketing prior to 2017.[219] Drug manufacturer Eagle Pharmaceuticals, Inc. ("Plaintiff") produced Bendeka, its drug to treat two forms of cancer, and requested orphan designation for Bendeka.[220] The FDA designated Bendeka as an orphan product and approved it for marketing, but denied Plaintiff's request for market exclusivity on the basis that Plaintiff failed to show Bendeka was clinically superior to an already-approved drug to treat the same disease.[221] Plaintiff challenged the FDA's decision, arguing that under *Depomed*, it did not have to prove clinical superiority, and even if it did, it met the requirement.[222]

The United States District of Columbia Circuit Court of Appeals agreed with the district court and the *Depomed* court, finding that the

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such exclusivity." Orphan Drug Regulations, 78 Fed. Reg. 35,117, 35,127 (June 12, 2013).

213. FDA Reauthorization Act of 2017, Pub. L. No. 115-52, 131 Stat. 1005, 1049 (2017).

214. *Id.*

215. 21 C.F.R. § 316.20(a).

216. 21 C.F.R. § 316.34(c). A drug is "clinically superior," and thus the drug is not considered the "same drug" as the one already on the market, when the drug is "shown to provide a significant therapeutic advantage over and above that provided" by an already-approved drug in one of three ways. 21 C.F.R. § 316.3(b)(3). This can be proven with a showing that: (1) the new drug has a greater effectiveness as assessed by effect on a clinically meaningful endpoint in adequate and well-controlled trials; (2) the new drug is safer in a substantial portion of the target population; or (3) the sponsor can demonstrate the drug makes a major contribution to patient care. *Id.*

217. 21 C.F.R. § 316.3(b)(3).

218. 952 F.3d 323 (D.C. Cir. 2020).

219. *Id.* at 326, 329, 342.

220. *Id.* at 328-29.

221. *Id.*

222. *Id.* at 329.

ODA, prior to the FDARA, was unambiguous.[223] At the time the decision was handed down, the FDARA was in effect, and the ODA stipulated that clinical superiority was required.[224] The district court found that Congress may have amended the statute because it believed *Depomed* was wrongly decided, but was concerned that other district courts might follow course.[225] Or, the court offered in the alternative, Congress may have believed that *Depomed* was rightly decided, and chose to reform the statute in line with the FDA's policy prescriptions.[226] The court stated it would not engage in any such speculation, however.[227] Congress expressly instructed that "[n]othing in the amendments . . . shall affect any determination under the prior orphan-drug exclusivity provision."[228] Thus, the court found the 2017 amendment was irrelevant in its determination of the case.[229] In summary, any drug that met the two statutory requirements prior to the 2017 FDARA does not have to show it is clinically superior to any already-approved drug in order to enjoy seven years of market exclusivity and thus, these decisions bar any competition the drug manufacturers may have faced if decided differently.[230]

B. The ODA's Endless Exclusivity

The previous section of this Part addressed the issues stemming from circumstances where the same drug, produced by different manufacturers, is designated as an orphan drug to treat the *same* rare disease or condition.[231] This Section explains the issues that arise when the same drug, produced by the same manufacturer, is approved to treat *different* rare diseases or conditions.[232]

The ODA provides that the Secretary of the Department of HHS shall, by regulation, promulgate procedures for the implementation of orphan drug designation and market exclusivity.[233] Under the regulations, the FDA is entitled to refuse to grant a request for orphan

223. *Id.* at 326, 329, 342.
224. *See id.* at 326 n.3.
225. Eagle Pharms., Inc. v. Azar, No. 16-790, 2018 WL 3838265, at *10 (D.D.C. June 8, 2018).
226. *Id.*
227. *Id.*
228. *Id.*
229. *Id.*
230. *See id.*
231. *See supra* Part III.A.
232. *See infra* Part III.B.
233. 21 U.S.C. §§ 360bb(d), cc(d) (2018).

drug designation for one of following four reasons[234]: (1) if the "drug is not intended for a rare disease or condition";[235] (2) "if there is insufficient information about the drug, or the disease or condition for which it is intended, to establish a medically plausible basis for expecting the drug to be effective in the prevention, diagnosis, or treatment of that disease or condition";[236] (3) if the drug is the same drug as an already-approved drug for the same rare disease or condition and the sponsor has not shown the new drug is clinically superior to the already-approved drug;[237] or (4) "if the request for designation contains an untrue statement of material fact or omits material information or if the request is otherwise ineligible under this part."[238]

Under the regulations, the "FDA may approve a sponsor's marketing application for a designated orphan drug for use in the rare disease or condition for which the drug was designated, or for select indication(s) or use(s) within the rare disease or condition for which the drug was designated."[239] The regulations further state that the orphan drug exclusivity protects "only the approved indication or use of a designated drug."[240] Thus, the FDA "may later approve the drug for additional indication(s) or use(s) within the rare disease or condition not protected by the exclusive approval" and the FDA will recognize subsequent exclusivity periods for "these new (not previously approved)

234. *See* 21 C.F.R. § 316.25(a) (2020).

235. § 316.25(a)(1). A drug is not intended for a rare disease or condition if:

> (i) There is insufficient evidence to support the estimate that the drug is intended for treatment of a disease or condition in fewer than 200,000 people in the United States, or that the drug is intended for use in prevention or in diagnosis in fewer than 200,000 people annually in the United States; or (ii) Where the drug is intended for prevention, diagnosis, or treatment of a disease or condition affecting 200,000 or more people in the United States, the sponsor has failed to demonstrate that there is no reasonable expectation that development and production costs will be recovered from sales of the drug for such disease or condition in the United States. A sponsor's failure to comply with § 316.21 [which lays out the requirements a sponsor shall meet in order for the FDA to determine whether a drug qualifies for orphan drug designation] shall constitute a failure to make the demonstration required in this paragraph.

Id.

236. § 316.25(a)(2).

237. § 316.25(a)(3).

238. § 316.25(b).

239. § 316.31(a). "An 'indication' for a drug refers to the use of that drug for treating a particular disease." Omudhome Ogbru, *Indications for Drugs (Uses), Approved vs. Non-Approved*, MEDICINENET, https://www.medicinenet.com/indications_for_drugs__approved_vs_non-approved/views.htm (last visited Feb. 8, 2021). For example, insulin is indicated for the treatment of diabetes, but many drugs have more than one indication, meaning there is more than one disease for which the drug is used. *Id.*

240. § 316.31(b).

indication(s) or use(s) from the date of approval of the drug for such new indication(s) or use(s)."[241]

Taken together, these regulations permit shocking results.[242] A pharmaceutical company can obtain orphan drug designation and seven years of exclusivity for its drug to treat rare disease X.[243] Before its seven years of exclusivity end, the company can then obtain orphan drug designation and seven years of exclusivity for its drug to treat rare disease Y, which may even be related to rare disease X.[244] The regulations do not limit the amount of times a drug company can proffer the same drug for the ODA's incentives.[245] Instead, exclusivity may be endless.[246]

But the real abuse comes when the drug manufacturer, which has stacked incentives for the same drug for the treatment of different indications or uses, raises the price of the drug to an astronomical amount.[247] Pharmaceutical company AbbVie has flagrantly committed such an abuse with its drug Humira.[248] Humira was originally approved in 2002 to treat rheumatoid arthritis,[249] which affects millions of people.[250] Three years later, AbbVie requested orphan designation for Humira to treat juvenile rheumatoid arthritis.[251] AbbVie claimed that juvenile rheumatoid arthritis affected between thirty thousand to fifty thousand Americans, a figure within the threshold of the statutory definition of a rare disease or condition.[252]

But this begs the question: What is the difference between adult and juvenile rheumatoid arthritis?[253] Some children with juvenile rheumatoid arthritis outgrow the illness, while adults usually have lifelong symptoms.[254] Yet, the FDA approved this second designation in 2008.[255]

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241. *Id.*
242. *See* §§ 316.25, 316.31.
243. *See id.*
244. *See id.*
245. *See id.*
246. *See id.*
247. Sarah Jane Tribble & Sydney Lupkin, *Drugmakers Manipulate Orphan Rules to Create Prized Monopolies*, KHN (Jan. 17, 2017), https://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies.
248. *See id.*
249. *Id.*
250. *Id.*
251. *Id.*
252. *Id.*; *see supra* note 25 and accompanying text.
253. David Zelman, *What Is the Main Difference Between Juvenile and Adult Rheumatoid Arthritis?*, WEBMD, https://www.webmd.com/rheumatoid-arthritis/qa/what-is-the-main-difference-between-juvenile-and-adult-rheumatoid-arthritis (Jan. 30, 2019).
254. *Id.*
255. Tribble & Lupkin, *supra* note 247.

AbbVie then requested orphan designation for the same drug to treat four other statutorily rare diseases, including Crohn's disease and uveitis, thereby extending market exclusivity and the other incentives offered by the ODA to Humira until 2023.[256]

Many of the drugs with orphan designation listed on the FDA's website are commonly known drugs, including Humira.[257] When one searches for Humira on the database, eight entries are listed under its generic name, adalimumab.[258] Currently, Humira is designated as an orphan drug to treat the following diseases or conditions: moderate to severe hidradenitis suppurativa, moderate to severe Hurley stage disease, Crohn's disease, rheumatoid arthritis, chronic plaque psoriasis, and ulcerative colitis.[259] As a result of Humira's long-term market exclusivity, Sandoz, Inc., a manufacturer of the generic version of Humira, must wait until the beginning of 2023 to bring its drug to the United States market, twenty-one years after the drug was first approved, and once it does, Sandoz must pay AbbVie a royalty fee.[260] Thus, AbbVie faced a complete lack of competition for nearly two decades, enabling it to charge a premium for its drug—which rails against the ODA's original purpose and resulted in AbbVie's global sales totaling $19.9 billion in 2018 alone.[261]

This application of the ODA is also seen in the oncology branch of medicine.[262] Keytruda is a drug produced by Merck & Co. and is used to treat cancer patients.[263] Merck & Co. currently holds exclusivity over Keytruda for seven different uses, at least one of which extends to 2026, and at least three of which are related to the same disease—malignant melanoma.[264] Keytruda's list price for each dose is $9,869.94 when

256. *Id.*

257. *See Search Orphan Drug Designations & Approvals*, *supra* note 161. On the website, the drugs are sorted by their generic names. *Id.* The generic name for Humira is adalimumab. *Id.*

258. *Id.*

259. Gale Scott, *New Indication for Adalimumab*, HCP LIVE (Sept. 10, 2015), https://www.mdmag.com/product-news/new-indication-for-adalimumab.

260. Joe Nocera, *Drug-Price Transparency Won't End the Patent Games*, BLOOMBERG (Oct. 16, 2018, 2:00 PM), https://www.bloomberg.com/opinion/articles/2018-10-16/humira-patents-show-why-fda-s-drug-price-shaming-won-t-work.

261. AHIP, *supra* note 171, at 7.

262. *Id.*

263. Nicholas Huntington, *Weekly Dose: Keytruda May Be a Miracle Cancer Drug, but can Those Who Need It Afford It?*, CONVERSATION (Apr. 11, 2018, 3:39 AM), https://theconversation.com/weekly-dose-keytruda-may-be-a-miracle-cancer-drug-but-can-those-who-need-it-afford-it-74757. Specifically, Keytruda works as an immunotherapy drug, meaning it increases the patient's own immune response to the cancer. *Id.*

264. Gregory J. Glover, *How Drug Companies Get Multiple Exclusivity Periods for One Orphan Indication*, PHARM. L. GRP. (July 19, 2019), https://www.pharmalawgrp.com/blog/5/how-drug-companies-get-multiple-exclusivity-periods-for-1-orphan-indication. Currently, Merck & Co.

administered every three weeks.[265] Typically, treatments of Keytruda last up to twenty-four months in patients without disease progression.[266] In 2018, Keytruda was the third top-selling drug in the world, with global sales totaling $7.3 billion just four short years after it was originally designated as an orphan drug in 2014.[267]

Orphan drugs have seen a four-fold increase in their share of all new drug approvals from 1988 to 2017.[268] Drug launch prices across the board continue to increase year after year.[269] While the average drug costs for traditional and specialty drugs have doubled in this twenty-year period, the average costs for orphan drugs have grown far more exponentially.[270]

The big pharmaceutical companies proffer a seemingly compelling justification for high orphan drug prices: low prices will not permit the company to recoup its research and development costs due to the small patient populations the orphan drugs are meant to treat.[271] At a 2019 congressional hearing, Senator Ron Wyden of Oregon noted that drug prices are higher in the United States than in other developed countries, including France and Germany.[272] In response, Richard Gonzalez, CEO of AbbVie, admitted that while the company still turns a profit in other countries, despite European patients paying less for Humira than American patients, AbbVie is dependent on this variety of pricing to support its research and development model.[273]

This justification is questionable at best.[274] According to a 2015 study, the fifteen drug companies that made the top twenty best-selling

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has exclusivity over Keytruda through 2024 for Hodgkin lymphoma and gastric cancer; 2025 for primary mediastinal B cell lymphoma, hepatocellular carcinoma, and Markel cell carcinoma; and 2026 for Stage IIB through IV malignant melanoma. The exclusivity end date for metastatic small cell lung cancer is to be determined. *Id.*

265. *Cost Info & Financial Help*, KEYTRUDA, https://www.keytruda.com/financial-support (last visited Feb. 8, 2021). In 2014, Keytruda's launch price was $12,500 per patient per month, or $150,000 per year. *See* Arlene Weintraub, *Updated: Merck's Melanoma 'Game-Changer' Keytruda Likely to Bolster Drug Pricing Debate*, FIERCE PHARMA (Sept. 5, 2014, 10:07 AM), https://www.fiercepharma.com/pharma/updated-merck-s-melanoma-game-changer-keytruda-likely-to-bolster-drug-pricing-debate. When Keytruda was originally approved, it was hailed as a "game changer." *Id.* Roger Perlmutter, president of Merck Research Laboratories, stated that the company factored in the cost of developing the drug when setting its list price. *Id.*

266. Huntington, *supra* note 263.

267. AHIP, *supra* note 171, at 7.

268. *Id.* at 4.

269. *Id.* at 3.

270. *See supra* note 171 and accompanying text.

271. *Id.* at 7.

272. *Drug Pricing in America: A Prescription for Change, Part II: Hearing Before the S. Comm. on Fin.*, 116th Cong. III 20 (2019).

273. *Id.*

274. *See* Rachel Z. Arndt, *High U.S. Drug Prices Cannot Be Explained by R&D Spending*

drugs globally brought in $116 billion in excess revenue from drug prices in the United States, despite spending $76 billion dollars on global research and development.[275] If those companies lowered their prices in the United States so that they were proportional to the cost of research and development, American patients, businesses, and taxpayers would have saved about $40 billion dollars that year.[276]

AbbVie CEO Gonzalez also testified that AbbVie "spend[s] $5.2 billion dollars" on research and development and "make[s] $5.6 billion dollars in earnings. So [its research and development costs are] almost equivalent to what [its] earnings are."[277] In a report to Congress, however, the Department of HHS found that average development costs for an orphan drug are approximately $1 billion, compared to an estimated $2.6 billion for a mass-market drug.[278] Thus, the question still remains: Why are orphan drugs priced astronomically higher than mass-market drugs?[279]

IV. CHANGING THE RULES: AMENDMENTS TO DECREASE PRICES AND INCREASE COMPETITION

At the same 2019 congressional hearings to address drug prices, the CEO of pharmaceutical company AstraZeneca, Pascal Soriot, called for increased government regulation, stating "[t]he government has to step up and change the rules."[280] Due to the extensive abuse of the current legislation, congressional leaders should take control over the ODA and restore it to its original purpose.[281]

First, this Part argues that the FDA should refuse to grant orphan drug designation and exclusivity to a drug that is the same as an

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Alone, MODERN HEALTHCARE (Mar. 7, 2017, 12:00 AM), https://www.modernhealthcare.com/article/20170307/NEWS/170309919/high-u-s-drug-prices-cannot-be-explained-by-r-d-spending-alone.

275. *Id.*

276. *Id.*

277. *Drug Pricing in America: A Prescription for Change, Part II: Hearing Before the S. Comm. on Fin.*, 116th Cong. III, 21 (2019).

278. U.S. DEP'T OF HEALTH & HUM. SERVS., PRESCRIPTION DRUGS: INNOVATION, SPENDING, AND PATIENT ACCESS 25 (2016).

279. *See* Radcliff, *supra* note 57; *see also* Joshua Cohen, *Drug Pricing Should Reflect Value, Not Recoupment of Investment*, FORBES (June 20, 2019, 9:33 AM), https://www.forbes.com/sites/joshuacohen/2019/06/20/drug-pricing-should-reflect-value-not-recoupment-of-investment/?sh=1e257811680c (arguing that high drug prices should "relate to meaningful clinical advantages over current existing standards of care," rather than the cost that went into developing them).

280. *Drug Pricing in America: A Prescription for Change, Part II: Hearing Before the S. Comm. on Fin.*, 116th Cong. III 61 (2019).

281. *See infra* Part IV.A–C.

already-approved drug on the market, even if the new drug is clinically superior to the already-approved drug.[282] Next, it argues that the FDA should refuse to grant orphan drug designation and exclusivity to a drug for different uses and, instead, orphan drug designation should only be available once to a particular drug.[283] It also proposes an amendment that will permit market exclusivity until the sales of the orphan drug reach a set dollar threshold, or the company recoups its costs for the research and development of the drug, rather than the seven years currently authorized by statute.[284] Finally, this Part argues for revocation of market exclusivity should an orphan drug treat a population in excess of 200,000 individuals.[285]

A. Limitations on Orphan Drug Designation

The current ODA permits a pharmaceutical company to request orphan designation and exclusivity for a drug that is the same as one already on the market, so long as the subsequent drug is clinically superior.[286] This practice contravenes the original purpose of the ODA: to encourage innovative research and development to produce treatments for rare diseases and conditions.[287]

Section 360cc(c) and its enforcing regulation, which requires clinical superiority in order for the same drug to be approved for market exclusivity, should be repealed.[288] Permitting drug companies to tweak existing drugs just enough to satisfy the requirement of clinical superiority, and thus obtain exclusive marketing rights over such drugs and charge astronomical prices, is not the innovation the ODA was designed to encourage.[289] Should a drug company wish to provide an advanced version of an already-existing, approved drug, the drug company is free to do so; however, it should not be able to engage in anticompetitive practices and increase drug prices ten-fold.[290] This type of arbitrary and unpredictable inflation is not sustainable and is not in line with American capitalism.[291] Instead, a drug company that improves

282. *See infra* Part IV.A.
283. *See infra* Part IV.B.
284. *See infra* Part IV.B.
285. *See infra* Part IV.C.
286. *See supra* Part III.A.
287. Waddill, *supra* note 47.
288. 21 U.S.C. § 360cc(c).
289. Tribble & Lupkin, *supra* note 247.
290. *See* Erin Fox, *How Pharma Companies Game the System to Keep Drugs Expensive*, HARV. BUS. REV. (Apr. 6, 2017), https://hbr.org/2017/04/how-pharma-companies-game-the-system-to-keep-drugs-expensive.
291. *Id.*

upon an already-existing drug should intelligently market the drug as an improved version of an already-existing drug.[292] In other words, there should be competition.[293]

In addition to repealing Section 360cc(c), the following provision is necessary to stop the ongoing abuses of the ODA at the hands of pharmaceutical giants[294]:

> If a sponsor of a drug that is designated under section 360bb of this title and is otherwise the same, as determined by the Secretary, as an already-approved or licensed drug is seeking exclusive approval or licensure described in subsection (a) for the same rare disease or condition as the already-approved drug, the Secretary shall deny such approval or licensure.[295]

This amendment will first prevent drug companies, like Depomed, Inc. and Eagle Pharmaceuticals, Inc., from taking advantage of the ODA prior to the FDARA.[296] Second, this amendment will create competition among drug companies who seek to improve upon existing drugs in order to obtain orphan drug exclusivity.[297] Instead of an opportunity to engage in anticompetitive practices, drug companies are forced, under this proposed provision, to drive down prices, therefore benefitting the millions of sick Americans for whom the ODA was originally designed to help.[298] Additionally, this amendment may encourage pharmaceutical companies to put time, effort, and resources into treatments waiting to be developed, as was the original intent of the ODA, instead of expending costs and research on already-approved drugs.[299]

Further, the ODA permits drug manufacturers to stack incentives, thereby exponentially increasing market exclusivity for decades, with just a single product.[300] This endless exclusivity can be easily prohibited through regulatory action.[301] To resolve this issue, the FDA should

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292. *See* Michael Kades, *To Combat Rising U.S. Prescription Drug Prices, Let's Try Competition*, WASH. CTR. FOR EQUITABLE GROWTH (Mar. 5, 2019), https://equitablegrowth.org/to-combat-rising-u-s-prescription-drug-prices-lets-try-competition.

293. *Id.*

294. *See infra* text accompanying note 295.

295. *See* 21 U.S.C. § 360cc (serving as an amended model as part of the solution to this Note).

296. *See supra* Part III.A.

297. *See* Kades, *supra* note 292.

298. *See supra* Part II.B.

299. *See generally* Joshua M. Liao & Mark Pauly, *Orphan Drugs: Pursuing Value and Avoiding Unintended Effects of Regulations*, HEALTH AFFS. (May 4, 2017), https://www.healthaffairs.org/do/10.1377/hblog20170504.059899/full (exploring the connection between government regulation and drug company output).

300. *See supra* Part III.B.

301. *See generally* 21 C.F.R. § 316.31 (2020) (offering no current provision that prohibits this practice).

amend the regulation to bar drug manufacturers from obtaining successive exclusivity periods for the same drug in order to treat different indications or uses.[302] Specifically, the regulation should permit the FDA to grant orphan drug designation one single time for one particular drug, even if the sponsor contends it is being used to treat a different rare disease than the one the drug was already approved to treat.[303] This, too, will increase competition in the market and drive down drug prices since a company will be unable to submit the same drug for orphan designation multiple times under the guise of several different uses, therefore preventing serial exclusivity.[304]

B. Revocation of Orphan Drug Designation and Market Exclusivity Based on Drug Profits

In order to further protect American consumers, the ODA and its regulations should be amended to include a provision permitting the FDA to revoke orphan drug designation, and thus market exclusivity, when an orphan drug's profit either (1) reaches a certain dollar threshold, or (2) equals the amount the sponsor spent on the research and development of said drug.[305]

Similar to a 1992 congressional proposal, automatically revoking market exclusivity once a drug's total sales exceed a set dollar amount will limit abuse of the ODA.[306] Obviously, the drug could and would still be sold; however, it would not allow big pharmaceutical

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302. *See* 21 C.F.R. § 316.31(b) (serving as an amended model as part of the solution to this Note).

303. *See id.*

304. *See supra* Part III.B.

305. *See infra* Part IV.B.

306. *See* 138 Cong. Rec. 9194 (1992) (setting forth Rep. Henry A. Waxman's proposal to withdraw a drug's market exclusivity if its total sales exceed $200 million, unless research costs are greater than sales). Waxman noted this proposal would "allow for competition in these important markets which should lower the prices of these drugs." *Id.* "The resulting benefits," he continued, "will flow to consumers, the Federal Government, and other institutions that purchase drugs." *Id.* The limit would have allowed a drug to turn profits of $25 million to $30 million annually for seven years and rank among the top global sellers, but after a period of such monopoly, the limit would allow for competition. Philip J. Hilts, *Seeking Limits to a Drug Monopoly*, N.Y. TIMES, May 14, 1992, at D1. The bill was introduced in the Senate in 1992, but it did not receive a vote. *S. 2060 (102d): Orphan Drug Amendments of 1992*, GOVTRACK, https://www.govtrack.us/congress/bills/102/s2060 (last visited Feb. 8, 2021). Additionally, it is worthwhile to note that at a March 1992 hearing, then FDA Commissioner David A. Kessler testified that "the [Bush] Administration strongly opposes" the bill and "the Secretary would recommend that it be vetoed" because the bill "would undermine the [ODA's] primary incentives." *Orphan Drug Amendments of 1991: Hearing on S. 2060 Before the Comm. on Lab. & Hum. Res.*, 102d Cong. 40 (1992) (statement of David A. Kessler).

manufacturers and their shareholders to hold the market captive.[307] This would encourage manufacturers to continue to improve the drug and would allow for competition.[308]

This proposal is particularly appropriate since one study found that the clinical costs of orphan drugs were actually lower than the non-orphan drugs, thus there is currently little to no additional risk to develop orphan drugs as compared to non-orphan drugs.[309] The study found that "the capitalized clinical cost per approved orphan drug was half that of a non-orphan drug."[310] More specifically, the out-of-pocket clinical costs per approved orphan drug was $166 million, compared to $291 million per non-orphan drug.[311]

Alternatively, if a drug company does not reach the dollar threshold needed to revoke market exclusivity, the ODA should permit revocation once a company recoups its losses stemming from research and development.[312] This answers the contested justification proffered by the pharmaceutical giants: that low drug prices will not permit the company to make back the costs of research and development due to the small populations of potential consumers.[313] This alternative is also more functional than setting a dollar threshold amount due to the inconsistent costs of developing a drug.[314] The cost of research and development depends mostly on the cost of clinical studies, which can range from $10 million to $2 billion, depending on the drug.[315] Thus, the regulations should provide that when a sponsor submits its application for orphan drug designation, it is required to produce data showing the cost of research and development of the drug, including any failed clinical trials.[316] The regulations should also include a subsection within 21 C.F.R. § 316.29, providing that should the drug sponsor fail to report

307. *See* Liao & Pauly, *supra* note 299.

308. *Id.*

309. *See* Mark Terry, *Report: Evaluating the Cost-Effectiveness and Controversies of Orphan Drugs*, BIOSPACE (Jan. 14, 2019), https://www.biospace.com/article/report-clinical-costs-for-orphan-drugs-lower-than-expected.

310. *Id.*

311. *Id.* The study noted, however, that "[f]urther research is required to better quantify the overall costs of drug development and obtain consensus on what cost categories should be included in such an analysis." *Id.*

312. *See supra* text accompanying notes 271-76.

313. *See supra* text accompanying note 271.

314. *See* Matthew Herper, *The Cost of Developing Drugs Is Insane. That Paper that Says Otherwise Is Insanely Bad*, FORBES (Oct. 16, 2017, 10:58 AM), https://www.forbes.com/sites/matthewherper/2017/10/16/the-cost-of-developing-drugs-is-insane-a-paper-that-argued-otherwise-was-insanely-bad/?sh=61826e942d45.

315. *Id.*; *see also supra* text accompanying notes 114-24.

316. *See generally* 21 C.F.R. § 316.20 (2020) (offering no current provision that requires this information).

total sales of the orphan drug to the FDA for each fiscal year, or should the total sales of the drug exceed the cost of research and development as reported in its initial application for orphan drug designation, the FDA may revoke a drug's orphan drug designation, thus revoking market exclusivity.[317]

C. Revocation of Orphan Drug Designation and Market Exclusivity Based on a Drug's Patient Population

Under the current regulations, a sponsor will receive orphan drug designation if it meets the requirements of 21 C.F.R. Part 316.[318] In order to limit abuse of the ODA, the regulation should be amended to permit the FDA to revoke orphan drug designation should the patient population of the drug exceed 200,000 Americans.[319] The regulation currently permits revocation of orphan drug designation in several instances, however, it specifically states:

> Where a drug has been designated as an orphan drug because the prevalence of a disease or condition . . . is under 200,000 in the United States at the time of designation, its designation will not be revoked on the ground that the prevalence of the disease or condition (or the target population) becomes more than 200,000 persons.[320]

By measuring what a "rare disease or condition" is based upon the number of persons affected, the total number of Americans living with a rare disease is estimated at between 25-30 million, making these diseases not so rare.[321] This definition does not take into account that the number of people affected by a disease may change, or that a drug may be used to treat a condition it was not originally intended to treat.[322]

First, the regulation should instead take into account that, despite a drug qualifying as an orphan, it is not guaranteed that the drug will *not* be highly profitable.[323] Some orphan drugs must be administered chronically and, over time, patients are increasingly reliant on the

317. *See generally* 21 C.F.R. § 316.29 (offering no current provision that permits this practice).
318. 21 C.F.R. § 316.2.
319. *See* 21 C.F.R. § 316.29.
320. 21 C.F.R. § 316.29(c). According to the regulation,

> FDA may revoke orphan-drug designation for any drug if the agency finds that: (1) [t]he request for designation contained an untrue statement of material fact; or (2) [t]he request for designation omitted material information required by this party; or (3) FDA subsequently finds that the drug in fact had not been eligible for orphan-drug designation at the time of submission of the request therefor.

21 C.F.R. § 316.29(a).
321. 21 U.S.C. § 360bb(a)(2).
322. *See* Dorman, *supra* note 167.
323. *See* Rohde, *supra* note 81, at 130.

medication to manage long-term conditions, thus creating a large profit for the pharmaceutical manufacturer.[324] Second, in the case of some drugs, the original patient population expands dramatically while the drug is on the market.[325] For example, Azidothymidine ("AZT") was the only approved treatment out of all first-generation treatments for AIDS.[326] At the time it was originally approved for market exclusivity as an orphan drug, approximately 50,000 people were afflicted with full-blown symptoms of AIDS.[327] AZT was later found to be helpful in treating HIV, which affected more than 600,000 people.[328] Nonetheless, AZT still enjoyed market exclusivity.[329]

In order to remedy this, the Act should be amended to include a requirement wherein each drug manufacturer that currently produces and markets a product with orphan drug designation must provide the FDA with an annual report detailing any changes in the patient population of the disease the drug is designed to treat.[330] Additionally, if the FDA finds that the patient population exceeds 200,000 people, or that the drug is being used to treat other diseases with a patient population in excess of 200,000 people, the FDA should be allowed to immediately revoke orphan drug designation, and thus revoke market exclusivity.[331] With the free and unrestricted ability to revoke orphan drug status should the patient population exceed 200,000 individuals, and thereby the ability to revoke a grant of market exclusivity, the FDA would be able to foster competition and decrease the number of pharmaceutical manufacturers abusing the Act's incentives.[332] This would be consistent with the Act's original purpose: to encourage drug manufacturers to develop drugs and

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324. *See* Abbey Meller & Hauwa Ahmed, *How Big Pharma Reaps Profits While Hurting Everyday Americans*, CTR. FOR AM. PROGRESS (Aug. 30, 2019, 9:03 AM), https://www.americanprogress.org/issues/democracy/reports/2019/08/30/473911/big-pharma-reaps-profits-hurting-everyday-americans.

325. *See* Marlene Cimons & Victor F. Zonana, *Manufacturer Reduces Price of AZT by 20%*, L.A. TIMES (Sept. 19, 1989, 12:00 AM), https://www.latimes.com/archives/la-xpm-1989-09-19-mn-111-story.html.

326. *Id.*

327. *Id.*; Rohde, *supra* note 81, at 135.

328. Rohde, *supra* note 81, at 135.

329. *See* Gary A. Pulsinelli, *The Orphan Drug Act: What's Right with It*, 15 SANTA CLARA HIGH TECH. L.J. 299, 323-24 (1999).

330. *See* 21 C.F.R. § 316.29 (2020) (displaying the absence of this requirement in the current law).

331. *Id.*

332. *See* Zachary Brennan, *FDA to Revoke Orphan Designation for Opioid Addiction Drug Sublocade*, REG. FOCUS (Nov. 8, 2019), https://www.raps.org/news-and-articles/news-articles/2019/11/fda-revokes-orphan-designation-for-opioid-addictio (citing a rare example where the FDA opted to lift a drug's exclusivity designation, thus increasing competition, which will likely result in trickle-down cost savings to the consumer).

treatment options for patients suffering from rare diseases or conditions.[333]

V. CONCLUSION

The abuse and manipulation of the ODA by greedy and grasping pharmaceutical manufacturers should be prohibited in the United States.[334] The current legislation clearly allows for the continued exploitation of a law that was originally designed to aid people afflicted by rare diseases.[335] Instead, in cruel irony, millions are afflicted by the orphan drug designation.[336] Drug companies and their shareholders should not be allowed to corner the market and exploit the pain and suffering of the millions of Americans who suffer from rare diseases and conditions, along with the millions more who suffer from everyday diseases and conditions but pay exorbitant prices for, or go without the benefit of, the medication they need.[337] These results are unconscionable.[338]

By restricting and limiting some of the incentives provided to drug companies under the Act, the American public can get the medicine it needs at lower drug prices through increased competition.[339] The ultimate beneficiaries are the patients—the original and intended beneficiaries of the ODA when Congress first passed it.[340]

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333. Waddill, *supra* note 47.
334. *See supra* Part IV.
335. *See supra* Part III.
336. *See supra* Part III.
337. *See supra* Parts II–III.
338. *See supra* Part III.
339. *See supra* Part IV.
340. *See supra* Part II.

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