ORPHANED AGAIN: REVISITING THE ORPHAN DRUG ACT AND PRIORITIZING PATIENT ACCESS TO MEDICINE

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ABSTRACT

In 1983, Congress passed the Orphan Drug Act ("ODA") as part of an effort to provide market incentives for pharmaceutical manufacturers to produce "orphan drugs," drugs for diseases that impact less than two hundred thousand people in the United States annually. Prior to the passage of the ODA, rare-disease patients had little to no treatment options. The ODA revolutionized the orphan drug space; therefore, the market for orphan drugs is becoming increasingly more lucrative for pharmaceutical manufacturers.

However, the recent prevalence of issues like "salami-slicing" and "indication stacking" provides pharmaceutical companies with excess market benefits and contributes to the prohibitively high cost of medicines. Both "salami-slicing" and "indication stacking" allow companies to obtain regulatory exclusivities for drugs already on the market, thus undercutting patient access by excluding competitors, thanks to the seven-year exclusivity period. Companies are free to raise the prices of their drugs how they see fit because they are now the only ones with regulatory exclusivity. As the market for orphan drugs has changed both domestically and globally, Congress must revisit the ODA to prioritize patient access to much-needed medicines. Congress should clarify the "same drug" language in the ODA by codifying the FDA's practice of granting orphan drug exclusivity for specific uses

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or indications that a drug is approved for, as well as increase the burden of proof for companies seeking market exclusivity for drugs with stacked indications.

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INTRODUCTION

In the United States, about four hundred people are affected by Lambert-Easton Myasthenic Syndrome ("LEMS").[1] Lore Wilkinson is one of the few suffering from this autoimmune disorder.[2] Patients suffering from LEMS are suffering from prohibitively high costs of medicines because of the existing ODA market exclusivity structures.[3] LEMS is a rare condition that causes a person's immune system to attack the points where the nerves and muscles connect, and there is no known cure.[4] Because these points are being attacked, individuals affected with LEMS cannot move their muscles normally.[5] In February 2023, USA Today chronicled Wilkinson's struggle with the rising costs of treatment for LEMS.[6] For almost ten years, Wilkinson obtained amifampridine phosphate,[7] free-of-charge, from Jacobus Pharmaceuticals.[8] In 2018, the United States Food and Drug Administration ("FDA") granted market exclusivity, subject to ODA requirements, to Catalyst Pharmaceuticals' brand-name amifampridine phosphate, Firdapse.[9] If Wilkinson were to get her medicine from Catalyst, her insurer, Medicare, would have

1. *Lambert-Eaton Myasthenic Syndrome (LEMS)*, CLEVELAND CLINIC, https://my.clevelandclinic.org/health/diseases/23202-lambert-eaton-myasthenic-syndrome-lems [https://perma.cc/68P6-TF7K] (May 21, 2022).

2. Sarah Jane Tribble, *'Who Can Afford That'? Patients Face Costly Bills Amid FDA's Battle over 'Orphan Drugs,'* USA TODAY, https://www.usatoday.com/story/news/health/2023/02/18/fda-orphan-drug-high-prescription-drug-prices/11257808002/ [https://perma.cc/G7XE-4DHP] (Feb. 23, 2023, 10:59 AM).

3. *Id.*

4. *Lambert-Eaton Syndrome*, JOHNS HOPKINS MED., https://www.hopkinsmedicine.org/health/conditions-and-diseases/lamberteaton-syndrome [https://perma.cc/R8KP-HKWH] (last visited Jan. 6, 2025).

5. *Id.*

6. Tribble, *supra* note 2.

7. Amifampridine phosphate treats LEMS and decreases the symptoms associated with muscle weakness. *Amifampridine Phosphate Tablet - Uses, Side Effects, and More*, WEBMD, https://www.webmd.com/drugs/2/drug-163809/amifampridine-phosphate-oral/details [https://perma.cc/L4SW-TQ9R] (last visited Jan. 6, 2025).

8. Tribble, *supra* note 2.

9. *Id.*

to pay $40,000 for a one-month supply of Firdapse, leaving Wilkinson with a $9,000 copayment.[10]

Similarly, patients suffering from Duchenne muscular dystrophy ("DMD") are among those feeling the consequences of the manufactured accessibility problem.[11] DMD is a rare condition that impacts the muscles, causing them to deteriorate and worsen over time.[12] As DMD progresses, both the heart and skeletal muscles continue to atrophy until the patient dies.[13] Unfortunately, there is no known cure for DMD.[14] Instead, all existing treatments focus on maintaining or improving the quality of life for affected patients.[15] DMD mainly affects young boys, with symptoms usually arising by age six.[16] Experts estimate that roughly fifty thousand people in the United States suffer from DMD.[17]

Until 2019, most patients suffering from DMD imported a drug, deflazacort, from abroad for about $1,200 annually.[18] However, in March of 2019, the FDA approved orphan drug status and, thus, granted market exclusivity for Marathon Pharmaceuticals' deflazacort subject to ODA requirements.[19] Because Marathon Pharmaceuticals now has a seven-year market exclusivity period on deflazacort, patients suffering from DMD are left with little option but to use Marathon Pharmaceutical's

10. *Id.*

11. *See* Shawn Radcliffe, *Why Are Drug Prices for Rare Diseases on the Rise?*, HEALTHLINE, https://www.healthline.com/health-news/critics-orphan-drug-law-ripe-for-abuse [https://perma.cc/CFG6-ERNG] (Apr. 5, 2019).

12. *Duchenne Muscular Dystrophy*, GENETIC & RARE DISEASE INFO. CTR. [hereinafter *GARD DMD Overview*], https://rarediseases.info.nih.gov/diseases/6291/duchenne-muscular-dystrophy [https://perma.cc/QN3N-PCAK] (Sept. 2024).

13. *Id.*; *Duchenne Muscular Dystrophy (DMD)*, CLEVELAND CLINIC [hereinafter *Cleveland Clinic DMD Overview*], https://my.clevelandclinic.org/health/diseases/23538-duchenne-muscular-dystrophy-dmd [https://perma.cc/8MNY-WPT4] (July 25, 2022).

14. *Cleveland Clinic DMD Overview*, *supra* note 13.

15. *Id.*

16. *Id.*

17. *GARD DMD Overview*, *supra* note 12.

18. Radcliffe, *supra* note 11.

19. *Id.*

drug.[20] After receiving approval, Marathon's CEO said that the net cost of deflazacort would be $54,000 annually.[21] This is a 4,500% increase in annual costs for patients suffering from DMD.[22]

In the United States, diseases or conditions that impact less than two hundred thousand patients a year are considered "rare diseases."[23] Prior to the passage of the Orphan Drug Act ("ODA" and "Act") in 1983, drugs for rare-disease patient populations were virtually unavailable because they cost too much to make and did not yield enough profits.[24] The Orphan Drug Act provided market incentives, including regulatory exclusivities, for pharmaceutical companies to pour resources into the rare-disease market and increased access for patients with rare diseases.[25] While the ODA revolutionized and revamped the rare-disease drug space, forty years after its passage, patients are stuck in almost the same pre-ODA situation because the prices of medicines are prohibitively expensive, thus creating the same accessibility problem that the ODA was intended to remedy.[26]

Congress originally passed the ODA to address the lack of available medicines to treat rare diseases in the United States.[27]

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20. *See id.*; Tribble, *supra* note 2.

21. Radcliffe, *supra* note 11.

22. *See id.* Both Catalyst's new drug and Marathon's drug could eventually be subject to the IRA Medicare Negotiation Plan, which could impact the prices each company can charge. *See Fact Sheet: Biden-Harris Administration Announces First Ten Drugs Selected for Medicare Price Negotiation*, THE WHITE HOUSE (Aug. 29, 2023) [hereinafter *Biden-Harris Fact Sheet*], https://www.whitehouse.gov/briefing-room/statements-releases/2023/08/29/fact-sheet-biden-harris-administration-announces-first-ten-drugs-selected-for-medicare-price-negotiation/ [https://perma.cc/3G6V-U5ZT]. For further discussion, see *infra* Section III.C.

23. *Rare Disease Database*, NAT'L ORG. FOR RARE DISORDERS, https://rarediseases.org/rare-diseases/ [https://perma.cc/NE5Y-RFPC] (last visited Nov. 24, 2024); Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983).

24. Koichi Mikami, *Orphans in the Market: The History of Orphan Drug Policy*, 32 SOC. HIST. OF MED. 609, 609–10 (2017).

25. *Id.* at 628.

26. *See* Tribble, *supra* note 2; Radcliffe, *supra* note 11.

27. Mikami, *supra* note 24, at 615.

Prior to the passage of the ODA, the existing structure of pharmaceutical regulation had resulted in many pharmaceutical manufacturers abandoning research and development of drugs for rare diseases.[28] As previously mentioned, the term "orphan drugs" refers to drugs that treat rare diseases, as in drugs whose production and development were abandoned by the pharmaceutical industry because of the lack of financial incentives.[29] According to the Genetic and Rare Disease Information Center ("GARD"), there are about ten thousand different rare diseases in the United States that impact thirty million Americans.[30] This means that more than one in ten Americans are living with a rare disease.[31]

Before the passage of the ODA, orphan drugs had little to no bearing on the U.S. pharmaceutical market, but today, such drugs account for almost a third of the global pharmaceutical market.[32] Forty years later, the demand for orphan drugs has blossomed, but the prohibitive cost of medicines creates the same problem the Act was meant to address—a lack of patient access to rare disease medicines.[33] From 2017 to 2021, the FDA approved 257 new drugs, and 127 of them were orphan drugs.[34] However, the monopolistic pricing tactics employed by pharmaceutical companies—and facilitated by the ODA—make rare disease drugs more *available*, but not more *accessible*.[35]

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28. *Id.* at 613.

29. *Id.* at 610.

30. *About GARD*, GENETIC & RARE DISEASES INFO. CTR., https://rarediseases.info.nih.gov/about [https://perma.cc/ZF6C-GK48] (last visited Nov. 24, 2024).

31. *Id.*; Hana Althobaiti, Enrique Seoane-Vazquez, Lawrence M. Brown, Marc L. Fleming & Rosa Rodriguez-Monguio, *Disentangling the Cost of Orphan Drugs in the United States*, HEALTHCARE, Feb. 2, 2023, at 1, 1.

32. *See* Mikami, *supra* note 24, at 610.

33. *See* Kavisha Jayasundara, Aidan Hollis, Murray Krahn, Muhammad Mamdani, Jeffrey S. Hoch & Paul Grootendorst, *Estimating the Clinical Cost of Drug Development for Orphan Versus Non-Orphan Drugs*, ORPHANET J. RARE DISEASES, Jan. 10, 2019, at 1, 1.

34. Althobaiti et al., *supra* note 31, at 3.

35. *See* Jayasundara et al., *supra* note 33, at 1.

The stories of deflazacort for patients with DMD and Firdapse for patients with LEMS exemplify how the impacts of the ODA have strayed from its intended purpose.[36] To remedy this discrepancy between the intended purpose—providing access to medications and treatments for rare disease patient populations—and the actual consequences of the Act, Congress must revisit and amend the Orphan Drug Act to prioritize patient access to much-needed medicines. Congress should clarify the "same drug" language in the ODA and codify the FDA's practice of granting orphan drug exclusivity for specific uses or indications that a drug is approved for,[37] as well as increase the burden of proof for companies seeking market exclusivity for drugs with stacked indications. Specifically, Congress should define the term "same drug" as referring to a drug approved for the same indication, as opposed to the same disease or condition.

This Note will proceed in four parts. Part I will address the historical context, both pre- and post-enactment of the ODA. Part II will introduce and expand upon some of the current issues plaguing the ODA and the FDA's enforcement of the Act. Part III will illustrate how Congress should amend the ODA to re-prioritize patient access to orphan drugs, and Part IV will address the central counterarguments to amending the ODA. Finally, Part V will synthesize the specifics of how Congress should revisit the Orphan Drug Act to prioritize patient access to much-needed medicines.

36. *See* Radcliffe, *supra* note 11; Tribble, *supra* note 2.

37. *See* discussion *infra* Section II.A, Part III.

I. HISTORICAL CONTEXT

A. Pre-Enactment

Understanding the origin and history of the Act is necessary to address the problems that exist today as a result of the Act's enforcement. This section addresses the pre-and post-enactment events of the ODA that have led to the current climate and the clear need for further change. The evolution of the Orphan Drug Act began almost twenty years before its enactment in 1983.[38] In 1962, Congress passed the Kefauver–Harris Amendments ("Amendments") to the Food, Drug, and Cosmetic Act.[39] In their originally proposed form, the Amendments provided the federal government with stronger regulatory authority over the pharmaceutical industry and lowered the price of prescription medicines.[40] However, in their final iteration, the Amendments instead focused on "ensur[ing] the safety and efficacy of drugs" and less on costs.[41] More than half a century later, this theme has governed most regulatory legislation in the pharmaceutical world and placed patient access to affordable medicines on the back burner.[42]

The Amendments made the FDA the sentinel of the pharmaceutical market.[43] In turn, the process of conducting clinical trials and bringing drugs to market became highly rigorous and heavily scrutinized, thus increasing the cost of production of all drugs.[44] The passage of the Amendments resulted in pharmaceutical companies across the nation abandoning research,

38. *See* Mikami, *supra* note 24, at 611.

39. *See id.*; Drug Amendments of 1962 (Kefauver–Harris Amendments), Pub. L. No. 87-781, 76 Stat. 780 (1962) (codified as amended in scattered sections of 21 U.S.C. §§ 301–81).

40. Mikami, *supra* note 24, at 611.

41. *Id.*

42. *See id.* at 610–11.

43. *Id.* at 611.

44. *See id.* at 611–12.

development, and production of drugs labeled "unprofitable."[45] Drugs used to treat rare diseases often fell into this category because the costly price of research and development for those drugs was not offset by the comparatively small patient populations in need of said drugs.[46] By abandoning research and development on drugs aimed at combatting rare diseases, pharmaceutical companies effectively orphaned these drugs—and the patients that need them most.[47]

Before the Amendments were passed, and before their regulatory consequences took effect, the pharmaceutical industry addressed rare-disease patient populations by providing "public service drugs."[48] Public service drugs are drugs that manufacturers produced and provided to rare-disease patient populations even though the manufacturers were suffering a financial loss.[49] However, the increased rigor of the new regulatory system put in place by the FDA made it too cost-prohibitive for pharmaceutical companies to continue producing public service drugs.[50] In addition, brand-name pharmaceutical companies lacked the incentive to produce orphan drugs because the compounds needed for these rare disease drugs are frequently discovered during the research and development of different drugs.[51] Even though a company that found the compound may not be using it to treat a rare disease, that company could include the possibility of the compound being used to treat rare diseases in publications they print, thus barring other pharmaceutical companies from patenting the compound for

45. *Id.* at 613.
46. *See id.* at 612, 615.
47. *Id.* at 613.
48. *Id.* at 612.
49. *Id.*
50. *See id.*
51. Sumin Kim, *The Orphan Drug Act: How the FDA Unlawfully Usurped Market Exclusivity*, 11 NW. J. TECH. & INTELL. PROP. 541, 542 (2013).

use in treating rare diseases.[52] The printed publications would preclude the condition of novelty needed for patentability.[53] For brand-name manufacturers, unpatentable drugs are not profitable.[54]

In 1975, the FDA considered passing regulations to provide pharmaceutical companies with incentives to produce more "unprofitable" drugs for rare-disease patient populations, but eventually declined to do so, citing the reasons for the issue as being "too diverse to permit meaningful recommendations."[55] In the years following, and leading up to the passage of the ODA, increased pressure from patient advocacy groups, like the National Organization for Rare Disorders ("NORD"),[56] created the opportunity for expanded patient visibility on the lack of available orphan drugs.[57] Specifically, in 1981, an episode that addressed the struggles of Tourette's patients and their search for available treatment aired on the show "Quincy, M.E."[58] Compounding the increased patient visibility of the issue was the pressure from the generic drug industry, who wanted the FDA to approve an "abbreviated new drug application" ("ANDA").[59] When a brand-name manufacturer seeks to apply for approval of a new drug, they need to conduct clinical trials

52. *Id.*

53. *See* 35 U.S.C. § 102. Under United States patent law, novelty is a condition of patentability. *Id.* If the possibility that a specific drug could be used to treat rare diseases has already been disclosed in published studies, that publication will preclude competitors from satisfying the novelty required for patent protection. *See id.*

54. *See* Marcia Angell & Arnold S. Relman, *Patents, Profits & American Medicine: Conflicts of Interest in the Testing & Marketing of New Drugs*, DAEDALUS, Spring 2002, at 102, 102–03. *But see* Mikami, *supra* note 24, at 614 (understanding the industry's unwillingness to produce such drugs as coming from "a fear of litigation and adverse publicity in the event of mishap, rather than their unprofitability").

55. *See* Mikami, *supra* note 24, at 613.

56. *See* John Swann, *The Story Behind the Orphan Drug Act*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/industry/fdas-rare-disease-day/story-behind-orphan-drug-act [https://perma.cc/PHV2-QX7L] (Feb. 23, 2018).

57. *See* Mikami, *supra* note 24, at 620.

58. Swann, *supra* note 56. Quincy, M.E. was a popular show during the 1980s. *Id.*

59. *See* Mikami, *supra* note 24, at 621.

and provide extensive research and findings supporting the efficacy and safety of the drug.[60] The generic industry, represented by the Generic Pharmaceutical Industry Association ("GPIA"), wanted the ANDA process to be approved so generic manufacturers would only have to prove the generic's "bioequivalence" to the brand-name to which the generic was related.[61] To solidify that hope, the GPIA supported Representative Henry Waxman's (D-CA) bill, the bill that would become the Orphan Drug Act.[62]

Waxman's bill made it through Congress with only a few amendments, and in January of 1983, President Ronald Reagan signed the Orphan Drug Act into law.[63] Reagan described the bill as "exemplif[ying] the proper role of government in helping meet legitimate needs in those cases where the free market alone can't do the job."[64] Representative Waxman touted the Act as "an example of government at its finest, demonstrating how Congress applies itself to solve overlooked, but deeply important, problems that affect millions of Americans."[65]

B. Post-Enactment

Today, an orphan drug is understood as one that treats a rare disease patient population.[66] However, the version of the ODA passed in 1983 did not include the "prevalence-based definition of rare disease" that serves as the metric for orphan

60. *See id.* at 611; *The FDA's Drug Review Process: Ensuring Drugs Are Safe and Effective*, U.S. FOOD & DRUG ADMIN., https://www.fda.gov/drugs/information-consumers-and-patients-drugs/fdas-drug-review-process-ensuring-drugs-are-safe-and-effective [https://perma.cc/P49D-SUS9] (Nov. 24, 2017).

61. Mikami, *supra* note 24, at 621.

62. *Id. See generally* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (codified as amended at 21 U.S.C. § 360aa–360ee).

63. Mikami, *supra* note 24, at 621.

64. Presidential Statement on Signing the Orphan Drug Act, 1 PUB. PAPERS 9, 9 (Jan. 4, 1983).

65. Mikami, *supra* note 24, at 609.

66. Matthew Herder, *What Is the Purpose of the Orphan Drug Act?*, PLOS MED., Jan. 3, 2017, at 1, 1.

drugs today.[67] Rare diseases were originally defined as conditions that "occur[] so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States such a drug for disease or condition will be recovered from the sales in the United States of such a drug."[68] The original definition of "orphan drug" is a reflection of the problem that Waxman and Congress attempted to address: a case of market failure.[69] In 1984, Congress amended the ODA, and changed the definition of rare disease to diseases that affect "less than 200,000 persons in the United States" or, if the drug was used to treat populations with more than two hundred thousand affected patients, "for whom '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 sale in the United States.'"[70] The former of these two definitions is commonly referred to as the "prevalence-based" definition, and the latter as the "commercial viability" definition.[71]

The change in definition reflects a flaw in an underlying assumption in ODA enforcement and implementation.[72] Congress enacted the ODA with the understanding that market failure had caused a lack of patient access to rare disease medicines, but even still, pharmaceutical manufacturers were required to prove that there was, in fact, commercial non-viability before a certain drug could be granted orphan drug status.[73] However, the new, and current, definition assumes that commercial non-viability is *inherent* to drugs for rare-disease patient

67. *Id.*
68. *Id.*
69. *See* Mikami, *supra* note 24, at 619.
70. Herder, *supra* note 66, at 2.
71. *Id.*
72. *See id.*
73. *Id.* at 1–2.

populations.[74] While there may have been some truth to the assertion that orphan drugs were inherently commercially nonviable prior to 1983 when the Act was passed, things have since changed.[75] Today, the global orphan drug market has skyrocketed, and orphan drugs "account[] for 21.4% of total branded prescription drug sales."[76] The existing definitions allow for a broader swath of companies to apply for drugs, and the existing definitions allow for the prevalence of techniques like "salami-slicing"[77] and "indication stacking"[78] that undercut patient access.[79]

1. Provisions

The Orphan Drug Act provides a seven-year market exclusivity period to a pharmaceutical company that produces an approved orphan drug, even if the drug has not yet been patented.[80] Typically, the only way for a company to avoid market competition is by obtaining a patent,[81] and even then, patents are subject to ANDA litigation from generic companies that is

74. *See id.* at 2.

75. *See id.*

76. Jayasundara et al., *supra* note 33, at 1.

77. *See* Sven Bostyn, *Tackling Salami Slicing and Indication Stacking in Orphan Drug Innovation Incentives*, BILL OF HEALTH (Sept. 15, 2021), https://blog.petrieflom.law.harvard.edu/2021/09/15/orphan-drug-innovation-incentives/ [https://perma.cc/PA6E-X92B]. "Salami-slicing" refers to the incidence of pharmaceutical companies intentionally "splitting certain common diseases into many artificial subsets" in order to gain additional approvals. *Id.*; Sarah Jane Tribble & Sydney Lupkin, *Drugmakers Manipulate Orphan Drug Rules to Create Prized Monopolies*, KFF HEALTH NEWS (Jan. 17, 2017), https://kffhealthnews.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/ [https://perma.cc/V4EC-VCRQ].

78. Bostyn, *supra* note 77. "Indication stacking" occurs when companies seek approval for multiple indications for a specific drug. *Id.* This, in effect, prevents cross-label prescriptions of generics, thus limiting patient choice and accessibility because it delays the arrival of generic drugs to the market. *See id.*

79. *See* Herder, *supra* note 66, at 2; *see also* discussion *infra* Section II.A (discussing the effects of salami-slicing on medicine prices and consumer access).

80. 21 U.S.C. § 360cc(a); Swann, *supra* note 56 (emphasizing that this protection extends even to non-patented medications).

81. Gary A. Pulsinelli, *The Orphan Drug Act: What's Right with It*, 15 SANTA CLARA HIGH TECH. L.J. 299, 310 (1999).

often costly and can effectively undercut the patent period.[82] However, under the ODA, pharmaceutical companies are entitled to a seven-year market exclusivity period, after the drug is approved to treat a rare disease, where the FDA will not approve a generic drug for the product that was granted orphan drug status.[83] The Act also provides tax incentives and user fee waivers for the research and development of these drugs.[84] The FDA approval process is rigorous, highly scrutinized, and costly.[85] The ODA seeks to address this by providing pharmaceutical companies with guidance on which specific tests and studies are necessary for obtaining FDA approval for orphan drug status.[86] In addition, the Act provides funding for new rare disease treatments through the Orphan Product Grant program.[87] Bringing a new drug to market can cost pharmaceutical companies between $161 million and $4.5 billion, and the

82. *See* Robert Silver, *ANDA Litigation Basics Under the Hatch-Waxman Act and Medicare Prescription Drug, Improvement, and Modernization Act of 2003*, CEASAR RIVISE, P.C. (Nov. 16, 2015), https://www.caesar.law/news-resources/anda-litigation-basics-under-the-hatch-waxman-act-and-medicare-prescription-drug-improvement-and-modernization-act-of-2003/ [https://perma.cc/6KW5-QGYF]; *see also* KEVIN J. HICKEY, CONG. RSCH. SERV., IF12644, PATENT LISTING IN THE FDA'S ORANGE BOOK (2024) (noting that a Paragraph IV ANDA for a generic drug can be challenged by a brand-name drug patent holder and start an automatic thirty-month stay of the ANDA). ANDA filers seeking Paragraph IV certifications are attempting to prove that a sponsor's brand-name patent is invalid, thus allowing a generic to enter the market, or that the generic drug would not infringe on the brand-name sponsor's patent. *See* Silver, *supra*. If an ANDA filer can successfully prove that the brand-name sponsor's patent is invalid or that the generic does not infringe on the brand-name sponsor's patent, the generic enters the market earlier than the sponsor planned, since the patent period has not run. *See* Bruce H. Kobayashi, Joshua D. Wright, Douglas H. Ginsburg & Joanna Tsai, *Actavis and Multiple ANDA Entrants: Beyond the Temporary Duopoly*, 29 ANTITRUST 89, 90 (2015).

83. 21 U.S.C. § 360cc(a).

84. Swann, *supra* note 56; *see also* Orphan Drug Act sec. 4, § 44H(a) (amending the IRS code to allow manufacturers of approved orphan drugs to claim a tax credit of fifty percent of their "qualified clinical testing expenses" for the fiscal year).

85. *See* discussion *supra* Section I.A.

86. *See* H.R. REP. NO. 97-840(I), pt.1, at 10 (1982), *as reprinted in* 1982 U.S.C.C.A.N. 3577, 3582; Pulsinelli, *supra* note 81, at 310, 313.

87. MURRAY AITKEN, MICHAEL KLEINROCK, ELYSE MUÑOZ & URVASHI PORWAL, IQVIA INSTITUTE, ORPHAN DRUGS IN THE UNITED STATES 3 (2020).

process takes around ten years.[88] Therefore, these incentives are significant.

Under the Act, there are only two exceptions to the market exclusivity clause: (1) the Secretary of Health and Human Services may approve another drug and breach the market exclusivity if the original manufacturer cannot "meet the needs of persons with the disease or condition for which the drug was designated" or (2) if the original holder of the exclusivity provides written consent to the Secretary.[89] Scholars have cautioned that these exceptions clearly provide the power of a "monopoly market" and are a "potential target for abuse," but to date, there are no Congressional provisions to address this potential issue.[90]

While the Act itself provides for only two exceptions, the Act also establishes a board within HHS that has supervisory powers over the Orphan Drug Act.[91] Specifically, the Orphan Products Board is in charge of "promot[ing] the development of drugs and devices for rare diseases," and for "coordinat[ing] among Federal, other public, and private agencies in carrying out their respective functions relating to the development of such articles for such diseases or conditions."[92] In 1992 (almost ten years after the Act was originally passed), the FDA issued a

88. Michael Schlander, Karla Hernandez-Villafuerte, Chih-Yuan Cheng, Jorge Mestre-Ferrandiz & Michael Baumann, *How Much Does It Cost to Research and Develop a New Drug? A Systematic Review and Assessment*, 39 PHARMACOECONOMICS 1243, 1263 (2021); Kim, *supra* note 51, at 542.

89. 21 U.S.C. § 360cc(b).

90. Kim, *supra* note 51, at 543.

91. 42 U.S.C. § 236(a)–(b) (establishing that the board is comprised of representatives selected by federal agencies including FDA, National Institutes of Health ("NIH"), and Center for Disease Control ("CDC")). The Supreme Court's overturning of the *Chevron* doctrine will undoubtedly impact how the FDA continues to issue approvals and guidance, but the specific effects remain speculative. *See generally* Loper Bright Enters. v. Raimondo, 144 S. Ct. 2244, 2270–73 (2024) (overturning Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837 (1984), which established a system of judicial deference to agency interpretation).

92. 42 U.S.C. § 236(a)–(b).

series of rules governing the implementation of the ODA.[93] One of the most significant rules is the "clinical superiority" exception.[94] The rules hold that the FDA will not approve and grant orphan drug designation to "subsequent drugs for the same rare disease or condition" unless the sponsor can prove through a "plausible hypothesis that its drug may be clinically superior to the first drug."[95] The FDA has regularly construed "same drug" in this exception to mean drugs that have the same indications, [96] not drugs used for the same disease.[97]

Under this rule, there are three avenues for a drug to be labeled "clinically superior."[98] A drug may be found clinically superior if it "provide[s] a significant therapeutic advantage over and above . . . [the] approved drug" by: (1) demonstrating "[g]reater effectiveness than [the] approved drug," (2) demonstrating "[g]reater safety in a substantial portion of the target populations," or (3) demonstrating "that the drug otherwise

93. *See generally* 21 C.F.R. §§ 316.1–.25 (1992) (offering regulations and guidance for orphan drug development).

94. *See* § 316.25(a)(3).

95. *Id.*

96. The indication a drug is approved for refers to what the drug may be used for, whether it be "treatment, prevention, mitigation, cure, or diagnosis of a recognized disease or condition, or of a manifestation of a recognized disease or condition, or for the relief of symptoms associated with a recognized disease or condition." 21 C.F.R. § 201.57(c)(2) (2024). While an indication may sometimes refer to an entire disease or condition, for orphan drugs, the indication often refers to specific aspects of the disease. *See* U.S. DEP'T OF HEALTH & HUM. SERVS., FOOD & DRUG ADMIN., CTR. FOR DRUG EVALUATION & RSCH. & CTR. FOR BIOLOGICS EVALUATION & RSCH., INDICATIONS AND USAGE SECTION OF LABELING FOR HUMAN PRESCRIPTION DRUG AND BIOLOGICAL PRODUCTS—CONTENT AND FORMAT: GUIDANCE FOR INDUSTRY 7 (2018). For example, the FDA states that insomnia drugs' indicators should specifically say whether the drug helps people fall asleep, stay asleep, or both. *Id.* Treatment for the specific indications covers a narrower scope than treatment for the entire disease. *Id.* at 6–7.

97. *FDA Doubles Down on Its Pre-Catalyst Stance on Orphan Drug Exclusivity*, COOLEY (Jan. 27, 2023) [hereinafter *FDA Doubles Down*], https://www.cooley.com/news/insight/2023/01-27-23-fda-doubles-down-on-its-pre-catalyst-stance-on-orphan-drug-exclusivity [https://perma.cc/WZ2Z-W26V]. The difference in the interpretation of "same drug" is significant. If the FDA were to grant orphan drug status, and therefore market exclusivity provisions, to manufacturers based on the entire disease or condition, rather than for the specific indication, it would grant those manufacturers a wider market exclusivity, thereby limiting patient choice. *See* discussion *infra* Section II.C.

98. *See* 21 C.F.R. § 316.3(b)(3)(i)–(iii) (2024).

makes a major contribution to patient care."[99] In practice, because there is not a statutory definition of "same drug" in the ODA context, the FDA lacks consistency in its approval process for what counts as both "clinically superior" and the "same drug."[100] Congress must address the lack of consistency between these interpretations by revisiting and clarifying the ODA to reestablish the goal of providing accessible medications to rare disease patient populations. Further, Congress should clarify the "same drug" language in the ODA by codifying the FDA's practice of granting orphan drug exclusivity for specific uses or indications that a drug is approved for, as well as increase the burden of proof for companies seeking market exclusivity for drugs with stacked indications.

II. CONCERNS ABOUT THE ACT: ISSUES WITH IMPLEMENTATION AND ENFORCEMENT

Former U.S. Representative Henry Waxman stated that while the ODA has had "great success" in providing access to treatment for rare disease patient populations, "[the ODA has] been in some ways turned on its head when it becomes the basis of manipulating the system for the drug company to make much more money than they would in an open, competitive market."[101] Well-reported concerns regarding the impacts of the ODA are the fears of "salami-slicing" and pharmaceutical companies being able to reap excess market benefits, as well as the issue of prohibitive costs of rare disease drugs that limit patient accessibility to these medicines.[102]

99. *Id.*

100. *FDA Doubles Down*, *supra* note 97; *see also* discussion *infra* Section II.C.

101. Tribble & Lupkin, *supra* note 77.

102. *See* Herder, *supra* note 66, at 2; Mikami, *supra* note 24, at 610.

A. Salami-Slicing and Indication Stacking

The ODA provides significant market incentives for pharmaceutical companies that are able to obtain orphan drug status for their products.[103] As mentioned above, patentable drugs are the most lucrative for pharmaceutical manufacturers, and the ODA strengthens existing patent protection for rare disease manufacturers through the seven-year market exclusivity provisions.[104] Since the Act was passed in 1983, the FDA has approved "more than 600 orphan drug indications from greater than 450 distinct drug products."[105] The increased prevalence of issues like "salami-slicing" and "indication stacking" provides pharmaceutical companies with excess market benefits and contributes to the prohibitively high cost of medicines.[106] Both salami-slicing and indication stacking allow companies to obtain regulatory exclusivities for drugs already on the market, thus undercutting patient access by excluding competitors because of the seven-year exclusivity period.[107] Companies are free to raise the prices of their drugs how they see fit because regulatory exclusivity provides monopolistic control over the market.[108] Salami-slicing refers to the incidence of pharmaceutical companies intentionally "splitting certain common diseases into many artificial subsets" of less than two hundred thousand people in order to gain additional approvals for each subset.[109]

103. *See* Herder, *supra* note 66, at 1. Both issues are briefly addressed below, as they correlate and impact one another, but much of the further discussion focuses mainly on the prohibitive costs and addresses potential solutions to the cost issue.

104. *See* Mikami, *supra* note 24, at 618; Swann, *supra* note 56.

105. Michael Gabay, *The Orphan Drug Act: An Appropriate Approval Pathway for Treatments of Rare Diseases?*, 54 HOSP. PHARMACY 283, 283 (2019).

106. *See* Bostyn, *supra* note 77; Ryan Marling, *Salami-Slicing, Precision Medicine and the Orphan Drug Act*, CHRISTENSEN INST. (Feb. 23, 2017), https://www.christenseninstitute.org/blog/salami-slicing-precision-medicine-orphan-drug-act/ [https://perma.cc/F2ZB-KTAA].

107. *See* Radcliffe, *supra* note 11.

108. *Id.*

109. *See* Tribble & Lupkin, *supra* note 77; 21 C.F.R. § 316.25(a)(1)(i) (2024) (stating that FDA will refuse orphan authorization if the "disease or condition" is not shown to affect less than 200,000 people in the United States).

As a result, the prices of these medications for these particularly small patient groups become excessively expensive.[110] One of the more illustrative case studies of this issue is seen with Amgen and the drug EPO.[111] In 1989, Amgen obtained orphan drug status for EPO as used "to treat anemia associated with end-stage renal disease."[112] However, EPO is useful for treating anemias other than those associated with end-stage renal disease, meaning that Amgen had essentially artificially carved the market for EPO into different "slices" for the purpose of gaining and profiting from exclusivity.[113] In effect, Amgen gets exclusivity for each subset of patients under two hundred thousand that the drug can be used to treat.[114] Amgen can get exclusivity for creating a subset of patients who suffer from end-stage renal failure and those who are not yet at the end stage.[115]

Commentators have argued that salami-slicing negatively impacts rare-disease patient populations by "undermin[ing] precision medicine efforts."[116] In other words, salami-slicing shifts the focus from addressing unmet patient needs to providing profits for pharmaceutical companies by allowing companies to essentially repurpose previously approved drugs.[117] In the end, the patients suffering from rare diseases once again draw the short stick. The financial advantages provided by the ODA are meant to encourage companies to "respond to . . . diagnostic breakthroughs with *novel treatments* proven to be *more effective* than the former one-treatment-fits-all solution."[118] One

110. *See* Tribble & Lupkin, *supra* note 77.

111. Pulsinelli, *supra* note 81, at 321–22.

112. *Id.* at 321; Diane Gershon, *Amgen Scores a Knockout*, 350 NATURE 99, 99 (1991) (reviewing Amgen's unlikely patent victory for the genetically modified version of the naturally occurring molecule erythropoietin ("EPO") after its approval for renal disease management in 1989).

113. Pulsinelli, *supra* note 81, at 321–22.

114. *Id.*

115. *Id.*

116. *See* Marling, *supra* note 106.

117. *Id.*

118. *See id.*

critique of the allowance of orphan drug status for "one-size-fits-all" treatments is that it discourages the precise type of research needed to address subtypes of rare diseases.[119] The focus shifts from providing targeted treatments for actual subtypes of rare diseases to splitting up the condition into as many subsets as possible for the purpose of broadening the range and impact of the market exclusivity provisions.[120] Critics also argue that the prevalence of salami-slicing goes beyond offering market incentives for pharmaceutical companies and instead encourages monopolistic tactics, as both patients and third-party payers have previously lacked negotiating ability.[121]

The FDA has previously attempted to address salami-slicing by promulgating regulations that state disease subsets must be "medically plausible," but even this definition does not provide the kind of clear-cut guidance that is necessary to solve the issue.[122] Specifically, with respect to the case of Amgen and EPO, there may be "medically plausible" patients with anemia from end-stage renal failure, but their incidence may still be reflective of salami-slicing.[123] While finding the perfect solution to the salami-slicing issue is unlikely, it still needs to be addressed, and increasing the burden of proof for manufacturers who are seeking stacked indications is a potentially workable solution.[124]

The prevalence of indication stacking also contributes to the prohibitively high cost of rare disease drugs.[125] Indication

119. *Id.*

120. *Id.*

121. Taeho Greg Rhee, *Policymaking for Orphan Drugs and Its Challenges*, 17 AMA J. ETHICS 776, 777 (2015).

122. Pulsinelli, *supra* note 81, at 322 ("The effect of this rule on the EPO designation is not clear. The end-stage renal disease patients may be a medically plausible subset, or they may instead be the result of salami slicing.").

123. *Id.* at 321–22.

124. *See id.* at 322; H.R. 456, 118th Cong. (2023) (proposing amending the federal Food, Drug, and Cosmetic Act to provide limitations on the requisite approval and licensure of orphan drugs).

125. *See* Bostyn, *supra* note 77.

stacking occurs when companies seek product approval for two or more orphan indications.[126] The indications "often overlap in their practical application" even though they are approved for distinguishable orphan diseases.[127] Companies then are entitled to two seven-year periods of exclusivity (even though said period may run concurrently).[128] Indication stacking creates the same problems as salami-slicing, ultimately restricting patient access to medicines.[129] Dr. Sven Bostyn writes extensively on indication stacking and salami-slicing and points out that in the European system, prescribers help patients get cheaper medicine by prescribing generics for their indications that are still protected by exclusivity through "cross-label prescribing." This is when prescribers take a drug that was given exclusivity for one specific indication of a disease and prescribe its generic form to a current patient whose indication is still protected by exclusivity, so long as the indications are safely interchangeable.[130] Dr. Bostyn claims indication stacking "de facto delay generic entry," where allowing companies to get a second period of market exclusivity on their old indication keeps those cross-

126. *See id.*

127. *See id.*

128. *See id.*; *see also* Eagle Pharms. v. Azar, 952 F.3d 323, 325–30, 337 (D.C. Cir. 2020) (accepting that a drug automatically receives periods of exclusivity as long as it is designated an orphan drug, either by indication or molecule). In *Eagle Pharms.*, the Court explicitly blamed the FDA for this problem because it claimed the FDA granted orphan status without considering indication stacking and tried to address the issue in a way at odds with the statute. *Id.* at 336–37 ("[T]he serial exclusivity and self-evergreening concerns do not result purely from a literal reading of the statutory text of § 360cc(a) but from the way the FDA has decided to regulate its definitions for designation and the scope of exclusivity."). Interestingly, the Eleventh Circuit in *Catalyst Pharms.* then went on to hold that the FDA's regulations regarding approving orphan drug status based on different patient populations went against the statute too. Catalyst Pharms., Inc., v. Becerra, 14 F.4th 1299, 1311–13 (11th Cir. 2021).

129. *See* Bostyn, *supra* note 77; Marling, *supra* note 106. Again, by shifting the focus on expanding the breadth of the market exclusivity protection, as opposed to precision medicine efforts, patients are harmed. *See* Marling, *supra* note 106.

130. Bostyn, *supra* note 77. In the United States, off-label, or cross-label prescriptions account for 21% to 32.3% of all prescriptions. Gail A. Van Norman, *Off-Label Use vs Off-Label Marketing of Drugs*, 8 JACC: BASIC TO TRANSLATIONAL SCI. 224, 225 (2023).

label drugs out for a second round of exclusivity.[131] Essentially, this means that indication stacking delays the entry of generics into the market, and while this is a benefit for brand-name manufacturers, it undercuts patient accessibility and places a greater financial burden on the patient.[132] "[D]elaying the entry of generic products into the marketplace" allows manufacturers to "keep prices high . . . [for] patients," ultimately limiting access for many.[133]

An illustrative example of indication stacking is seen in the case of Gleevec.[134] Gleevec (imatinib mesylate) is manufactured by Novartis.[135] One of its indications is for intestinal stoma tumors, and another is for chronic myeloid leukemia; both of these conditions fall under the category of rare diseases.[136] By stacking indications, Novartis reaps a higher profit.[137] When the prices of the drugs with these stacked indications are tempered by generic drugs and, therefore, made accessible to patient

131. Bostyn, *supra* note 77; *see, e.g.*, Caitlin Owens, *Blockbuster Drugs Are Stacking up Orphan Approvals*, AXIOS (Feb. 19, 2019), https://www.axios.com/2019/02/19/blockbuster-drugs-are-stacking-up-1550264427 [https://perma.cc/SZV4-LAS6] (showing that Humira, which has been in the United States's market since 2002, has been given seven further orphan drug indication approvals, which gives it exclusivity until October 2025).

132. *See* Bostyn, *supra* note 77; James D. Chambers, Katherine A. Clifford, Daniel E. Enright & Peter J. Neumann, *Follow-On Indications for Orphan Drugs Related to the Inflation Reduction Act*, JAMA NETWORK OPEN, Aug. 15, 2023, at 1, 1 (noting that even in the U.S., the FDA is approving additional orphan indications for drugs after their initial period of market exclusivity); Owens, *supra* note 131.

133. Kerstin Noëlle Vokinger, Aaron S. Kesselheim, Jerry Avron & Ameet Sarpatwari, *Strategies That Delay Market Entry of Generic Drugs*, 177 JAMA INTERNAL MED. 1665, 1668 (2017).

134. *See* André Côté & Bernard Keating, *What Is Wrong with Orphan Drug Policies?*, 15 VALUE HEALTH 1185, 1188 (2012). The article refers to "Glaive" and "Glove" as Novartis' brands of imatinib but uses "Gleevec" in its data comparisons. *Id.* at 1187–88. Novartis currently manufactures the drug under the name Gleevec. *Gleevec® (Imatinib Mesylate)*, NOVARTIS, https://www.novartis.com/us-en/content/gleevec%C2%AE-tablets [https://perma.cc/38B5-4UB9] (last visited Jan. 21, 2025).

135. *Gleevec® (Imatinib Mesylate)*, *supra* note 134.

136. *Id.*; *Gastrointestinal Stromal Tumors*, NAT'L ORG. FOR RARE DISORDERS, https://rarediseases.org/rare-diseases/gastrointestinal-stromal-tumors/ [https://perma.cc/A8WR-VNBQ] (Apr. 12, 2024); *Chronic Myelogenous Leukemia*, NAT'L ORG. FOR RARE DISORDERS, https://rarediseases.org/rare-diseases/chronic-myelogenous-leukemia/ [https://perma.cc/6MC6-C2PR] (June 11, 2018).

137. *Gleevec® (Imatinib Mesylate)*, *supra* note 134.

populations, the benefits are widespread—more patients can afford the medications, and companies can increase their exclusivity periods.[138] However, in practice, the stacked indications allow pharmaceutical companies to set prohibitively high costs of medicines and limit patient choice by keeping generics out of the market.[139] Companies profit to the detriment of patients who cannot afford medicines.[140]

B. Prohibitive Costs of Medicines

The ODA has largely been successful in bringing orphan drugs to market; from 2017 to 2021, the FDA approved 257 new drugs—127 orphan drugs and 130 non-orphan drugs.[141] In other words, the ODA has made orphan drugs more *available*, but the lack of regulation on drug pricing and monopolistic tendencies has not made orphan drugs more *accessible* to patient populations.[142] One of the biggest complaints about the impact of the ODA is its resulting market of prohibitively high-cost medicines.[143] For instance, Cerezyme is a drug used for treating Gaucher disease and treats about two thousand patients in the United States.[144] Depending on the patient's age, the drug can cost between $100,000 and $400,000 a year.[145] One recent study found that the median cost of treatment for orphan drugs was 4.3 times the median cost of non-orphan drugs.[146] Fabrazyme is used to treat Farby disease, which affects one out of forty thousand individuals assigned male at birth in the United States,

138. *See* Vokinger et al., *supra* note 133, at 1668.
139. *See id*.
140. Rhee, *supra* note 121, at 177.
141. Althobaiti et al., *supra* note 31, at 3.
142. *See* Jayasundara et al., *supra* note 33, at 1.
143. *See* Rhee, *supra* note 121, at 777; Côté & Keating, *supra* note 134, at 1185.
144. Côté & Keating, *supra* note 134, at 1186.
145. *Id.*
146. Althobaiti et al., *supra* note 31, at 4.

and can cost upwards of $300,000 annually.[147] The two sides of this argument are that pharmaceutical companies are engaging in monopoly-building tactics with how they choose to price their orphan drugs.[148] Alternatively, others argue that the high prices of orphan drugs simply reflect the cost of research and development to produce those drugs.[149] The more likely reality is a combination of both of these reasonings.[150]

The criticism of orphan drug pricing is exacerbated by the "blockbuster" status that certain orphan drugs have achieved for manufacturers.[151] The orphan drug market is expanding at almost twice the rate of the non-orphan market, and by 2026, orphan drugs are expected to account for 20% of drug sales globally.[152] By 2026, the top-selling orphan drugs are projected to produce profits ranging from $3 billion to $13 billion annually.[153] The existence of blockbuster orphan drugs runs contradictory to the reason the market incentives were first provided for orphan drugs.[154] The ODA was enacted to address the lack of orphan drugs available, an issue largely attributable to market failure.[155] The existence of blockbuster orphan drugs

147. *See* Côté & Keating, *supra* note 134, at 1186; *Fabry Disease*, CLEVELAND CLINIC, https://my.clevelandclinic.org/health/diseases/16235-fabry-disease#How%20Common%20Is%20Fabry%20Disease? [https://perma.cc/P8YU-8J7T] (Aug. 21, 2023).

148. Jayasundara et al., *supra* note 33, at 1.

149. *Id.*

150. *See id.*

151. *See* Melanie Senior, *Orphan Drugs: From Niche to Mainstream*, PHARMEXEC.COM (June 15, 2022), https://www.pharmexec.com/view/orphan-drugs-from-niche-to-mainstream [https://perma.cc/XCR3-KKQ2]. "Blockbuster" drugs are drugs that have produced annual sales totaling more than $1 billion. Alexander Schuhmacher, Markus Hinder, Nikolaj Boger, Dominik Hartl & Oliver Gassmann, *The Significance of Blockbusters in the Pharmaceutical Industry*, 22 NATURE REVS. DRUG DISCOVERY 177, 177 (2023).

152. Senior, *supra* note 151.

153. *Id.*

154. *See* Mikami, *supra* note 24, at 619.

155. *See id.*

suggests, at the very least, that the market for orphan drugs has changed, and that updated legislation is warranted.[156]

Generally speaking, bringing an orphan drug to market costs more than a non-orphan drug.[157] Clinical trials for orphan drugs have fewer subjects and can often take longer, and thus be more costly, because of factors including difficulty obtaining information on disease prevalence and incidence, "lack of data on natural disease progression," participant recruitment difficulties, lack of eligible participants in a concise geographic area, and "low medical expertise in the community."[158] Researchers André Côté and Bernard Keating identify six factors that exacerbate the high prices of orphan drugs by providing rare business opportunities to pharmaceutical companies.[159] These factors are indication stacking, "appreciable support for biotechnology companies," the potential for profitable new molecules, off-label prescriptions, basing pricing off patient/third-party payer willingness to pay, and "fast-tracking the development and marketing of new molecules."[160] Côté and Keating conclude that the policies in place for enforcement of the ODA result in a system geared towards providing market opportunities for pharmaceutical companies—a system that, in turn, often leaves patients without access to necessary medicines.[161]

156. *See* AHIP, THE RISE OF ORPHAN DRUGS 8 (2019) (claiming that "we are treating common diseases at orphan-high prices").

157. *See* Jayasundara et al., *supra* note 33, at 6, 8 (estimating that developing unsuccessful orphan drugs costs more than unsuccessful non-orphan drugs, but also finding that successful orphan drugs had lower development costs than successful non-orphan drugs).

158. *Id.* at 6.

159. Côté & Keating, *supra* note 134, at 1186–87.

160. *Id.*

161. *See id.* at 1190.

1. Previous and ongoing attempts to regulate

The high cost of medicines as a result of the ODA's market incentives has been an issue since the late 1980s.[162] There were attempts in the late 80s and early 90s to address the high costs of medicines through congressional action, but they were largely unsuccessful.[163] In 1990, the House Subcommittee on Health and the Environment held hearings to assess whether three drugs that had orphan drug status and whose sponsors had seen huge commercial success were instances of abuse of the Orphan Drug Act.[164] Later that year, both houses of Congress passed more amendments to the ODA that allowed "shared exclusivity," which permitted companies to demonstrate "that their product was developed simultaneously to a designated orphan drug."[165] Additionally, the amendments held that if the population the drug was meant to treat exceeded two hundred thousand, the orphan drug status was to be removed.[166] President George H.W. Bush, however, "pocket-vetoed" [167] the amendments, in line with his general opposition to regulating the free market.[168]

In 1991, both the Senate Subcommittee on Antitrust, Monopolies and Business Rights, as well as the Subcommittee on Labor and Human Resources, conducted a hearing on a bill that proposed a ceiling on the sale of orphan drugs at $200 million.[169]

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162. *See* Mikami, *supra* note 24, at 625.

163. *See id.* at 625–27.

164. *Id.* at 625. The argument was that because these drugs had been commercial successes, and because they would have been made without the incentives from the ODA, the fact that the manufacturers got to benefit from the ODA incentives was an abuse of the provisions. *Id.*

165. *Id.* at 626.

166. *Id.*

167. *Pocket Veto*, BRITANNICA, https://www.britannica.com/topic/pocket-veto [https://perma.cc/GV8N-X6V5] (last visited Sept. 26, 2024). A pocket veto effectively kills legislation. *Id.* In the United States, when the President fails to sign a bill within ten days, and Congress has adjourned within that ten-day period, the bill is automatically vetoed absolutely. *Id.*

168. *See* Mikami, *supra* note 24, at 626.

169. *Id.*

The bill died in committee.[170] One of the more recent bipartisan attempts to combat the prohibitively high cost of rare disease medicines has been the proposed Retaining Access Restoring Exclusivity ("RARE") Act.[171] In May of 2022, Senators Bill Cassidy (R-LA) and Tammy Baldwin (D-WI) introduced the RARE Act.[172] The Act intends to "codify[] the FDA's longstanding interpretation of the Orphan Drug Act . . . to ensure that the scope of the orphan drug exclusivity is clarified to apply only to the same approved use or indication within [a specific] rare disease."[173] The RARE Act is supported by the National Organization for Rare Disorders ("NORD"), the same association responsible for the proliferation of the Orphan Drug Act in the 1980s.[174] Senators Braun and Baldwin also introduced the Fair Accountability and Innovative ("FAIR") Drug Pricing Act.[175] Senator Baldwin's office described the FAIR Drug Pricing Act as follows:

> The FAIR Drug Pricing Act would require drug manufacturers to notify the U.S. Department of

170. *See id.* at 627.

171. Press Release, Tammy Baldwin, U.S. Sen., Baldwin's Bills to Increase Prescription Drug Transparency and Boost Access to Treatments for Rare Diseases Advance in Senate (May 11, 2023) [hereinafter Press Release, Baldwin's Bills], https://www.baldwin.senate.gov/news/press-releases/baldwins-bills-to-increase-prescription-drug-transparency-and-boost-access-to-treatments-for-rare-diseases-advance-in-senate [https://perma.cc/9DQ9-DE5T].

172. Press Release, Tammy Baldwin, U.S. Sen., Senators Baldwin and Cassidy Introduce Bipartisan Legislation to Preserve Access to Treatments for Rare Disease Patients (May 11, 2022) [hereinafter Press Release, Baldwin & Cassidy Introduce Bipartisan Legislation], https://www.baldwin.senate.gov/news/press-releases/senators-baldwin-and-cassidy-introduce-bipartisan-legislation-to-preserve-access-to-treatments-for-rare-disease-patients- [https://perma.cc/RFN5-XUAZ].

173. Press Release, Baldwin's Bills, *supra* note 171.

174. *See* Karin Hoelzer, *Congress Should Protect the Intent of the Orphan Drug Act and Pass the RARE Act*, NAT'L ORG. FOR RARE DISORDERS (Apr. 24, 2023), https://rarediseases.org/pass-the-rare-act/ [https://perma.cc/J4W6-P47N]; Swann, *supra* note 56.

175. Press Release, Tammy Baldwin, U.S. Sen., Baldwin, Braun Leading Bill to Require Transparency for Skyrocketing Drug Prices (Mar. 22, 2023) [hereinafter Press Release, Baldwin & Braun Bill to Require Transparency], https://www.baldwin.senate.gov/news/press-releases/baldwin-braun-lead-bill-to-require-transparency-for-skyrocketing-drug-prices [https://perma.cc/62M2-EZ2G].

> Health and Human Services (HHS) and submit a transparency and justification report 30 days before they increase the price of drugs that cost at least $100 by more than ten percent over one year or 25 percent over three years. For drugs that have a list price that is higher than median family income, or $70,784 in 2021, manufacturers will also be required to submit a transparency and justification report.[176]

The RARE Act was not voted on in its original form.[177] However, in April 2023, the Act was reintroduced as a part of another bill.[178] Since then, the Senate Committee on Health, Education, Labor, and Pensions has recommended that the bill be considered by the full chamber.[179]

Representative Earl "Buddy" Carter (R-GA) addressed a different aspect of the ODA and introduced the Fairness in Orphan Drug Exclusivity Act ("FODEA").[180] Instead of focusing on the way the FDA enforced the ODA, FODEA would require drug manufacturers to prove that they cannot reasonably expect to recover the costs of researching and developing drugs through U.S. sales to receive seven-year market exclusivity.[181] Representative Carter's office explained that this bill was meant to eliminate a loophole in the ODA that allows companies to gain orphan drug status and the accompanying market exclusivity

176. *Id.*

177. Retaining Access and Restoring Exclusivity Act, S. 4185, 117th Cong. (2022).

178. *See* Retaining Access and Restoring Exclusivity Act, S. 1214, 118th Cong. (2023).

179. *See id.* On February 15, 2024, Representative Doris Matsui (D-CA), introduced H.R. 7383, the RARE Act, to the House. *See* Retaining Access and Restoring Exclusivity Act, H.R. 7383, 118th Cong. (2024). The text of this bill is the same as the one introduced by Senator Baldwin. *Compare id.*, *with* S. 1214. The bill was referred to the House Committee on Energy and Commerce. H.R. 7383.

180. Press Release, Buddy Carter, U.S. Cong. Rep., Carter Introduces Bill to Close Loophole Blocking Rare Disease Treatments from Market (Jan. 24, 2023) [hereinafter Press Release, Buddy Carter Introduces Bill to Close Loophole], https://buddycarter.house.gov/news/documentsingle.aspx?DocumentID=10861 [https://perma.cc/GHH9-6438].

181. *Id.*

for old or "recycled" medicines.[182] In effect, patients are again stuck with limited access and virtually no choice because of consecutive market exclusivity periods that allow companies to set prices as they wish.[183] Since its introduction, the bill has been referred to the Subcommittee on Health, but no further action has been taken.[184]

C. Catalyst Pharmaceuticals, Inc. v. Becerra

As previously mentioned, Lore Wilkinson struggled to receive medicine to treat LEMS because of Catalyst Pharmaceuticals' ("Catalyst") newly obtained orphan drug exclusivity for Firdapse.[185] Ms. Wilkinson's story highlights the negative impact the ODA can have on patients' access to orphan drugs.[186] Catalyst's battle to uphold its orphan drug status culminated in a controversial Eleventh Circuit ruling that the FDA is attempting to avoid.[187]

In 2018, Catalyst was granted orphan drug exclusivity for its drug, Firdapse, used to treat LEMS.[188] The high price point attached to the drug created a significant backlash within the rare disease community.[189] In 2019, the FDA approved Jacobus Pharmaceuticals' drug only for treating LEMS in children, instead of

182. *Id.*; *see also* Côté & Keating, *supra* note 134, at 1189 (highlighting that under current legislation, manufacturers that recycle drugs gain seven years of market exclusivity from the FDA, which allows them to keep charging high prices for their drug).

183. Press Release, Buddy Carter Introduces Bill to Close Loophole, *supra* note 180.

184. Fairness in Orphan Drug Exclusivity Act, H.R. 456, 118th Cong. (2023).

185. *See supra* Introduction.

186. Tribble, *supra* note 2.

187. *See* Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1301 (11th Cir. 2021); *FDA Doubles Down*, *supra* note 97.

188. Tribble, *supra* note 2.

189. *Id.*; *see also* Manas Mishra, *Catalyst Pharmaceuticals Defends $375,000 Drug Price After Bernie Sanders Rebuke*, REUTERS (Feb. 21, 2019, 2:33 PM), https://www.reuters.com/article/us-usa-healthcare-catalyst-idUSKCN1QA1XT/ [https://perma.cc/6ADNZDVC] (highlighting that patients who at one point could receive the drug during its experimental phase for free, are now having to ration their medication because of the high prices). Senator Bernard Sanders (D-VT) chastised the company for its $375,000 price tag. *Id.*

in both children and adults.[190] Catalyst then filed suit against the FDA, alleging a violation of the ODA's market exclusivity provision when it approved Jacobus's drug.[191] The Southern District of Florida granted the FDA's motion for summary judgment and dismissed the case.[192] The district court found the terms "the same disease or condition" in the ODA to be ambiguous as to whether the term referred to a specific indication or the disease as a whole.[193] The court found that either interpretation was a reasonable one, so it applied *Chevron* deference to abide by the FDA's interpretation.[194] On appeal, the U.S. Court of Appeals for the Eleventh Circuit reversed.[195] The Eleventh Circuit held that Catalyst was entitled to summary judgment because by granting approval to Jacobus's drug, the FDA had acted "contrary to the unambiguous language of the Orphan Drug Act," and that Catalyst was entitled to the seven-year

190. News Release, U.S. Food & Drug Admin, FDA Approves First Treatment for Children with Lambert-Eaton Myasthenic Syndrome, a Rare Autoimmune Disorder (May 6, 2019), https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-children-lambert-eaton-myasthenic-syndrome-rare-autoimmune-disorder [https://perma.cc/E5RD-BLAQ]. Jacobus Pharmaceuticals was the company that had been providing Lore Wilkinson with her LEMS medication, free of charge, for almost ten years before Fridapse was granted orphan-drug status. Tribble, *supra* note 2.

191. Tribble, *supra* note 2; *see Catalyst Pharms.*, 14 F.4th at 1305.

192. *See* Catalyst Pharms. v. U.S. Food & Drug Admin., No. 19-cv-22425-BLOOM/Louis, 2020 WL 5792595, at *1 (S.D. Fl. Sept. 29, 2020) (granting FDA summary judgment).

193. *See id.* at *5–8 (analyzing under step one of the *Chevron* doctrine analysis).

194. *Id.* at *9. The FDA interprets "same disease or condition" to mean the same indication. *See id.* at *6 (finding that the FDA's focus on indications and specific uses is not an unreasonable interpretation of the phrase "same disease or condition" under the statute); HANNAH-ALISE ROGERS & HASSAN Z. SHEIKH, CONG. RSCH. SERV., IF12605, THE ORPHAN DRUG ACT: LEGAL OVERVIEW AND POLICY CONSIDERATIONS 1–2 (2024). *Chevron* deference refers to the judicial deference previously given to administrative agency decisions where the court finds the agency's decision not to be unreasonable. *See* Chevron, U.S.A., Inc. v. Nat. Res. Def. Council, Inc., 467 U.S. 837, 865–66 (1984) (explaining that when Congress uses ambiguous terms, the court will give the agency deference as to the meaning of the term if the agency's interpretation is deemed reasonable). The term was coined after the Supreme Court decided *Chevron, U.S.A., Inc. v. Nat. Res. Def. Council*. *Id.* In June 2024, the Supreme Court overruled the *Chevron* doctrine in *Loper Bright Enters. v. Raimondo* and held that courts may no longer defer to an agency's interpretation of the law when the statute is ambiguous. 144 S. Ct. 2244, 2273 (2024). The future of FDA decisions regarding approval in situations where the statute is ambiguous will remain unclear pending further litigation.

195. *Catalyst Pharms.*, 14 F.4th at 1313.

market exclusivity period.[196] The Eleventh Circuit further explained that because none of the statutory exceptions for approving another drug applied, the FDA was not allowed to approve the "same drug manufactured by [Jacobus] to treat the same autoimmune disease" while Catalyst's market exclusivity period was still running.[197] The court said that the actions of the FDA were "arbitrary, capricious, and not in accordance with [the] law," and set aside Jacobus's approval.[198]

The FDA and several lawmakers were upset by this holding, claiming that it undercut a "decades-long" FDA process.[199] One of the main frustrations with the Eleventh Circuit's ruling is the practical impact.[200] Jacobus's drug was the only approved product to treat LEMS in pediatric patients, whereas Firdapse was never specifically indicated for children.[201] In January of 2023, the FDA issued new regulations meant to "address the uncertainty" resulting from the Eleventh Circuit's holding in *Catalyst*.[202] The FDA said that it would abide by the decision in *Catalyst* with respect to Jacobus's drug; however, it would be confining the decision to this specific set of facts.[203] The FDA has maintained that it intends to continue implementing its current rules and "long-standing approach to grant orphan drug exclusivity based on the indications for which the drug is approved

196. *Id.* at 1312.

197. *Id.* at 1312–13.

198. *Id.* at 1313; *see also* 5 U.S.C. § 706(2)(A). The Administrative Procedure Act provides the framework under which agency decisions are evaluated. *Id.*

199. *See* Sara W. Koblitz, Catalyst Pharmaceuticals, Inc. v. Becerra, FOOD & DRUG L. INST., https://www.fdli.org/2022/06/catalyst-pharmaceuticals-inc-v-becerra/ [https://perma.cc/QL75-PTNC] (last visited Jan. 6, 2025); HANNAH-ALISE ROGERS, CONG. RSCH. SERV., R47653, THE ORPHAN DRUG ACT AND CATALYST PHARMACEUTICALS, INC., V. BECERRA 15–16 (2023) (claiming that a group of senators proposed legislatively overruling the decision).

200. *See* Tribble, *supra* note 2 ("Now, there is no competitive drug on the market that treats Wilkinson's disease.").

201. *Catalyst Pharms.*, 14 F.4th at 1304–05. Shortly after the decision, Catalyst bought the licensing rights from Jacobus. *See* Tribble, *supra* note 2.

202. Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms., Inc. v. Becerra; Notification, 88 Fed. Reg. 4086, 4087 (Jan. 24, 2023) (to be codified at 21 C.F.R. pt. 316).

203. *FDA Doubles Down*, *supra* note 97.

rather than granting the exclusivity for the entire rare disease or condition that was the subject of the orphan drug designation."[204] The FDA asserts that its decision to limit the *Catalyst* ruling and maintain its previous approval process is the best way to balance the interests of and incentives for pharmaceutical companies with the need for patient access to drugs.[205]

The problem with the *Catalyst* decision is that it weighs almost entirely in favor of pharmaceutical manufacturers and allows them to broaden the scope of their market exclusivity, thus keeping out generics and constricting patient choice.[206] While the FDA's response to constrain the breadth of potential market exclusivity periods is important, it does not provide strong enough measures to combat indication stacking or salami-slicing.[207] The Eleventh Circuit's decision in *Catalyst* addresses both of those issues by creating a first-come, first-served mentality, in that the drug manufacturer that can get approval for a specific disease will have exclusivity over medications for that entire disease, not just for the specific indication.[208] However, this approach creates an exaggerated monopoly impact.[209] Because Catalyst has complete regulatory exclusivity over all indications relating to LEMS, they can justify pricing their medications at $375,000, as they have no real competitors and patients

204. *Id.*

205. Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms., Inc. v. Becerra; Notification, 88 Fed. Reg. at 4087.

206. *See Catalyst Pharms.*, 14 F.4th at 1313; *see also* Koblitz, *supra* note 199 ("This decision undoubtedly increases the value of orphan drug exclusivity . . . . [T]he expansion of orphan drug exclusivity to block approval of the entire designated disease or condition could also limit treatment options for patients where few exist.").

207. *See FDA Doubles Down*, *supra* note 97. The existing FDA policy does not address indication stacking or salami-slicing. *See generally* Bostyn, *supra* note 77 (defining indication stacking and salami-slicing); Marling, *supra* note 106 (describing the dangers of drug companies' use of salami-slicing).

208. *FDA Doubles Down*, *supra* note 97.

209. *See id.*; ROGERS, *supra* note 199, at 14.

have virtually no alternatives.[210] The result is that patients cannot reasonably access their medications.[211]

III. PROPOSED SOLUTIONS

A. Clarifying the ODA

Clarifying the ODA will require Congress to add stronger language that prioritizes patient accessibility to medicines. Specifically, Congress should define the term "same drug" as referring to a drug approved for the same indication, as opposed to the same disease or condition. Recently, there have been different legislative efforts to clarify the ODA,[212] but these efforts alone will not do enough to further patient access to medicines. An effective approach will require a combination of previously proposed solutions.[213] The conflict between the Eleventh Circuit's holding in *Catalyst* and the FDA's interpretation of "same disease" is indicative of the fact that Congress needs to revisit the ODA and clearly define this provision.[214] As discussed above, there have been recent efforts in Congress to codify that the same drug for the "same disease or condition" language in the ODA does actually mean that orphan drug status cannot be granted to the same drug for the "same approved use or

210. *See, e.g.*, Mishra, *supra* note 189 (describing how Catalyst raised price due to lack of competition); Tribble, *supra* note 2 (describing high costs faced by patients).

211. *See, e.g.*, Tribble, *supra* note 2 (explaining that production exclusivity leads to drastic increases in prices beyond what would constitute reasonable access for patients in need).

212. *See* Press Release, Baldwin's Bills, *supra* note 171; Press Release, Buddy Carter Introduces Bill to Close Loophole, *supra* note 180.

213. *See* Press Release, Baldwin's Bills, *supra* note 171 (discussing the bipartisan package of bills designed to tackle the ultimate problem of prescription drug prices); Press Release, Buddy Carter Introduces Bill to Close Loophole, *supra* note 180 (advocating for the elimination of companies' ability to recycle their old orphan drug exclusivity periods via "piggybacking").

214. *See* Catalyst Pharms., Inc. v. Becerra, 14 F.4th 1299, 1301–02 (11th Cir. 2021); *FDA Doubles Down*, *supra* note 97. Catalyst is only the latest development in the schism between the courts and the FDA. *See, e.g.*, Eagle Pharms., Inc. v. Azar, 952 F.3d 323, 328 (D.C. Cir. 2020) (citations omitted) ("The FDA initially appealed the *Depomed* decision but ultimately withdrew its appeal, opting instead to nonacquiesce to the decision in future cases."). Without legislation, this cycle will likely continue.

indication within such rare disease or condition."[215] Conversely, there are stakeholders (companies like Catalyst) that would rather Congress codify the Eleventh Circuit's ruling in *Catalyst*.[216]

Congress should amend the ODA and codify the FDA's practice of granting orphan drug exclusivity for specific uses or indications for which the drug is approved.[217] However, in focusing on the approval-for-indication approach, Congress needs to clarify the approval guidelines to ensure that companies cannot create subsections within a disease to stack exclusivity periods (salami-slicing).[218] Specifically, when companies seek to stack multiple subsections of disease or multiple indications, Congress should specify in the ODA that those companies are subject to a higher burden of proof.[219] In other words, companies seeking to stack should provide demonstratable evidence that without exclusivity, they would be unable to recoup the research and development costs of these drugs.[220] This proposed solution combines the most effective parts of the proposed RARE Act and the FODEA Act.[221]

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215. S. 4185, 117th Cong. § 2(a)(1) (2022); S. 1214, 118th Cong. § 2(a)(1) (2023) (containing the same language as S. 4185).

216. ROGERS, *supra* note 199, at 16.

217. *See* Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms, Inc. v. Becerra; Notification, 88 Fed. Reg. 4086, 4087 (Jan. 24, 2023) (to be codified at 21 C.F.R. pt. 316); S. 1214 § 2(a)(1). Overturning *Chevron* has seemingly taken a great deal of deference away from the FDA, but codifying the FDA's existing practice by defining "same drug" to refer to a specific indication as opposed to an entire disease or condition will circumvent the issue by removing an important ambiguity from the statute. *See generally* Loper Bright Enters. v. Raimondo, 144 S. Ct. 2244 (2024); Rachel Rodman & Alec Albright, *U.S. Supreme Court Strikes Down Chevron Doctrine–What You Need to Know*, WHITE & CASE (July 8, 2024), https://www.whitecase.com/insight-alert/us-supreme-court-strikes-down-chevron-doctrine-what-you-need-know [https://perma.cc/7MH3-FZ78].

218. *See* discussion *supra* Section II.A.

219. *See* H.R. 456, 118th Cong. (2023).

220. *See id.*

221. *See* Bostyn, *supra* note 77 (advocating for the eradication of salami-slicing and indication stacking); H.R. 7383, 118th Cong. (2024) (attempting to cabin the monopoly given to drugs to only their specific indications); H.R. 456 (fighting salami-slicing of diseases into hyper-defined subsets by requiring companies to prove that they are unlikely to be able to turn a profit on the drug being developed). The RARE Act was once again introduced to the House on February 15,

B. Price Caps

It is helpful to compare how other countries around the world are addressing orphan drugs to determine what kinds of changes could be made to the U.S. ODA. In 2019, orphan drugs accounted for 16% of the market for prescription drugs across the globe.[222] This figure is expected to increase by 2026.[223] In the past, the United States had been one of the only countries in the world that did not have a structured pharmaceutical price regime.[224] Understandably, the United States still has some of the world's most expensive medicines; a 2019 House Ways and Means Committee Report found that U.S. drug prices were "nearly four times higher than [the] average prices in comparative countries."[225] Because most pharmaceutical companies compete on the global market, critics of U.S. drug policy argue that patients in the United States end up subsidizing the cost of medicine in the rest of the world.[226]

In the European Union, most countries have some kind of price regulations ranging from fixed prices to price negotiation

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2024, by Representative Doris Matsui (D-CA). H.R. 7383. It has since been referred to the House Committee on Energy and Commerce. *Id.*

222. Paweł Żelewski, Michał Wojna, Katarzyna Sygit, Elżbieta Cipora, Izabela Gąska, Mateusz Niemiec, Mateusz Kaczmarski, Tomasz Banaś, Beata Karakiewicz, Artur Kotwas, Paulina Zabielska, Olga Partyka, Monika Pajewska, Edyta Krzych-Fałta, Ewa Bandurska, Weronika Ciećko & Aleksandra Czerw, *Comparison of US and EU Prices for Orphan Drugs in the Perspective of the Considered US Orphan Drugs Act Modifications and Discussed Price-Regulation Mechanisms Adjustments in US and European Union*, INT'L J. ENV'T RSCH. & PUB. HEALTH, Sept. 24, 2022, at 1, 2.

223. *See id.* (claiming that sales of orphan drugs accounted for 16% of all money spent in the global prescription drug market in 2019); Senior, *supra* note 151 (claiming that orphan drugs already make up a sizeable portion of the volume of the prescription drug market).

224. Moshe Levy & Adi Rizansky Nir, *The Pricing of Breakthrough Drugs: Theory and Policy Implications*, PLOS ONE, Nov. 25, 2014, at 1, 1.

225. *Id.*; Żelewski et al., *supra* note 222, at 2.

226. Levy & Rizansky Nir, *supra* note 224, at 2; Olivier Wellman-Labadie & Youwen Zhou, *The US Orphan Drug Act: Rare Disease Research Stimulator or Commercial Opportunity?*, 95 HEALTH POL'Y 216, 225 (2010).

problems.[227] Reference pricing is a form of price regulation used in many European Union countries.[228] To set prices for orphan drugs, countries that employ reference pricing contrast the price sought by the manufacturer with the price of the same drug in other countries.[229]

Mild regulation of drug prices can greatly benefit patient populations by increasing accessibility without resulting in excessive losses for pharmaceutical companies.[230] One suggested price cap strategy was a grant-and-access structure that would replace the existing tax credit system built into the ODA.[231] Instead of receiving tax credits associated with research and development costs, companies would apply for grant funding within the FDA to offset R&D costs.[232] Under this proposal, these companies would not qualify for tax credits if they were receiving grants, and the grants would be contingent on price caps, varying with the length and cost of the R&D process.[233] Conversely, in other countries, the prices of orphan drugs will be fixed at an "optimal" price by the regulatory agency of that country.[234] While the US is moving away from its "free" system, meaning that the prices are set by the manufacturer, the existing price caping mechanisms will be slow to implement, and

227. Todd Gammie, Christine Y. Lu & Zaheer Ud-Din Babar, *Access to Orphan Drugs: A Comprehensive Review of Legislations, Regulations, and Policies in 35 Countries*, PLOS ONE, Oct. 9, 2015, at 1, 16; Żelewski et al., *supra* note 222, at 3.

228. Gammie et al., *supra* note 227, at 16.

229. *Id.*

230. *See* Ana M. Valverde, Shelby D. Reed & Kevin A. Schulman, *Proposed 'Grant-and-Access' Program with Price Caps Could Stimulate Development of Drugs for Very Rare Diseases*, 31 HEALTH AFFS. 2528, 2530 (2012).

231. *Id.*

232. *Id.*

233. *Id.*

234. Gammie et al., *supra* note 227, at 16.

further regulation will be needed to lower the patient cost of drugs in the United States.[235]

C. The IRA and Drug Pricing

One of the more recent attempts at imposing regulations on drug prices comes from the Inflation Reduction Act ("IRA").[236] President Biden signed the IRA into law in 2022 to address many of the impacts of rising inflation.[237] One key goal of the legislation is to lower the cost of American health insurance.[238] One of these provisions is the controversial Medicare Drug Price Negotiation Program.[239] The program is meant to allow Medicare to negotiate directly with pharmaceutical companies about the "prices for certain high expenditure, single source Medicare Part B or Part D drugs."[240] The program is described as follows:

> For the first year of the Negotiation Program, the Secretary will select 10 Part D high expenditure, single source drugs for negotiation. The maximum fair prices that are negotiated for these drugs will apply beginning in initial price applicability year 2026. The Secretary will select an additional 15 Part D drugs for negotiation for initial price applicability year 2027, 15 Part B or Part D drugs for initial price applicability year 2028, and 20 Part B or Part D drugs for initial price

235. *See generally Biden-Harris Fact Sheet*, *supra* note 22 (discussing how the implementation of the Inflation Reduction Act will help lower the cost of drugs in the United States); Memorandum from Chiquita Brooks-LaSure, Adm'r, Ctrs. for Medicare & Medicaid Servs., to Interested Parties (Jan. 11, 2023) [hereinafter CMS Memorandum] (demonstrating the long timeline for implementing the Medicare Drug Price Negotiation Program).

236. Inflation Reduction Act of 2022, Pub. L. No. 117-169, sec. 11001, 136 Stat. 1818, 1833 (2022).

237. CMS Memorandum, *supra* note 235.

238. *Id.*

239. *Id.*

240. *Id.*

> applicability year 2029 and subsequent initial price applicability years.[241]

The IRA's Medicare Negotiation Plan is one of the first substantial attempts at regulating the prices of the pharmaceutical industry.[242] The drugs originally chosen for the Medicare Negotiation Plan are those that account for the highest spending amounts under Medicare Part D.[243] The Act as it exists exempts orphan drugs with single indications from negotiation.[244] However, as previously discussed, a staggering number of orphan drugs are approved for more than one indication,[245] meaning that most orphan drugs could eventually be subject to the negotiation program.

The IRA's Medicare Negotiation Program has been met with significant pushback. In June of 2023, Merck, a major pharmaceutical company, filed suit against the federal government to enjoin the negotiation program.[246] In its complaint, Merck alleged that the negotiation program is "tantamount to extortion," and that it violates the Fifth Amendment's Takings

241. *Id.*

242. *See Biden-Harris Fact Sheet*, *supra* note 22.

243. *Id.*

244. *This Bill Would Fix IRA Orphan Drug Incentives*, BIO (Sept. 19, 2023), https://www.bio.org/gooddaybio-archive/bill-would-fix-ira-orphan-drug-incentives [https://perma.cc/DNG6-MXPR]; *see* Inflation Reduction Act of 2022, Pub. L. No. 117-169, sec. 11001, § 1192(e)(3)(A), 136 Stat. 1818, 1840 (codified at 42 U.S.C. § 1320f-1(e)(3)(A)).

245. Tribble & Lupkin, *supra* note 77 (showing that, as of 2017, eighty-four orphan drugs were approved for multiple orphan diseases, compared to 302 for only one disease); Michael G. Daniel, Timothy M. Pawlik, Amanda M. Fader, Nestor F. Esnaola & Martin A. Makary, *The Orphan Drug Act: Restoring the Mission to Rare Diseases*, 39 AM. J. CLINICAL ONCOLOGY 210, 211 (2016) (decrying that "almost any cancer medication can be maneuvered into an orphan disease category" by focusing on genetic markers).

246. Michael Erman, *Merck Sues US Government to Halt Medicare Drug Price Negotiation*, REUTERS (June 6, 2023, 4:35 PM), https://www.reuters.com/business/healthcare-pharmaceuticals/merck-sues-us-government-halt-medicare-drug-price-negotiation-2023-06-06/ [https://perma.cc/DG4T-K3EU].

Clause, as well as the First Amendment's protection against compelled speech.[247]

The White House and HHS have maintained that they plan to stick with the plan and that the Medicare Negotiation Program is constitutional.[248] Because most orphan drugs have been approved with multiple indications, they will qualify for the Medicare Negotiation Program, and the success of the IRA will undoubtedly change the landscape of the orphan drug market.[249] The success of the IRA Medicare Negotiation Program could revolutionize the way drugs are priced in the United States.[250] Patients suffering from rare diseases would benefit greatly from this kind of drug pricing change, so the success of the Medicare Negotiation Program will be felt in the orphan drug space.

IV. CHALLENGES WITH AND FORCES OPPOSED TO ODA REVISION

Recent attempts to revise the ODA have been largely unsuccessful and, thus, are emblematic of the opposition to changing the existing orphan drug market-exclusivity regime.[251] In the 1990s, the proposed amendments to the ODA were ultimately unsuccessful because they could not maintain the balance

247. Complaint at 2–3, Merck & Co. v. Becerra, No. 1:23-cv-01615 (D.D.C. June 6, 2023) (arguing that "the IRA's mechanism for effecting this taking makes a mockery of the First Amendment").

248. *Inside the 2 Lawsuits Challenging the Inflation Reduction Act*, ADVISORY BD. (June 14, 2023), https://www.advisory.com/daily-briefing/2023/06/14/ira-lawsuits [https://perma.cc/SBN3-YK46]. Motions for summary judgment have been filed in the case, but no decisions have been made. Plaintiff's & Defendant's Respective Motions for Summary Judgment, Merck & Co. v. Becerra, No. 1:23-cv-01615 (D.D.C. June 6, 2023).

249. *See* Erman, *supra* note 246.

250. *See Biden-Harris Fact Sheet*, *supra* note 22 (discussing the potentially transformative impact of the negotiation program).

251. Both the FODEA and the RARE Act were pieces of legislation introduced in 2023 aimed at revising the ODA. Fairness in Orphan Drug Exclusivity Act, H.R. 456, 118th Cong. (2023); Retaining Access and Restoring Exclusivity Act, S. 1214, 118th Cong. (2023). The RARE Act has made it out of committee and is waiting to be voted on by one of the chambers; FODEA has yet to make it out of committee. *See* S. 1214; H.R. 456.

between supporting patients' needs and accessibility while providing effective market incentives to pharmaceutical manufacturers.[252]

The response from the pharmaceutical industry to the IRA's Medicare Negotiation Program illustrates what pushback to price caps for orphan drugs would look like. For instance, as it stands, the IRA only exempts orphan drugs with single indications from the negotiation plans.[253] Critics argue that this provision quells innovation and prevents companies from engaging in research to see whether their drug can treat many indications.[254] Representatives from NORD, the patient advocacy group that backed the original iteration of the ODA in the 1980s and that has supported the recent attempts to revise the Act, have raised concerns specifically about the impact of the IRA on the orphan drug space.[255] Karen Hoelzer, NORD's Director of Policy and Regulatory Affairs, expressed that the single-indication exemption for the IRA could discourage pharmaceutical manufacturers from furthering research for additional diseases, therefore limiting patient access.[256]

Addressing indication stacking in light of the IRA's Medicare Negotiation Program and the exemption for single-indication drugs creates a double-edged sword problem for patients and pharmaceutical manufacturers alike.[257] As previously discussed, if multiple indications are created to carve up the market and keep generics out, then patients end up suffering from

252. *See* Mikami, *supra* note 24, at 625–27.

253. *This Bill Would Fix IRA Orphan Drug Incentives*, *supra* note 244; Inflation Reduction Act of 2022, Pub. L. No. 117-169, sec. 11001, § 1192(e)(3)(A), 136 Stat. 1818, 1840 (codified at 42 U.S.C. § 1320f-1(e)(3)(A)).

254. *This Bill Would Fix IRA Orphan Drug Incentives*, *supra* note 244.

255. *See* Jeannie Baumann, *Medicare Drug Price Guidance Leaves Murky Future for Rare Diseases*, BLOOMBERG L. (June 30, 2023, 12:20 PM), https://news.bloomberglaw.com/pharma-and-life-sciences/medicare-drug-price-guidance-leaves-murky-future-for-rare-drugs [https://perma.cc/55CC-68KP].

256. *Id.*

257. *See id.*; Marling, *supra* note 106.

prohibitively high costs.[258] Conversely, if companies are disincentivized from engaging in research to find actual existing subsets of patients that a drug could be used for, out of fear that the second indication will subject the drug to price negotiation, patients again end up suffering from a lack of treatment options.[259] Subjecting pharmaceutical manufacturers to a higher burden of proof, namely, requiring them to prove that they would not be able to recover the costs of the medicine for the second indication without ODA exclusivity, will address the issue of indication stacking for the purpose of excluding generics from the market.[260] After demonstrating the economic need for a second-indication's orphan drug status, companies would have more leverage to justify their prices in a negotiation scheme.[261]

The most common defense from pharmaceutical companies for the astronomical orphan drug prices is the cost of research and development, and that high pricing is the only way to recover profits when dealing with small patient populations.[262] Defenders of the pharmaceutical industry's monopolistic pricing tactics in the orphan drug market argue that orphan drugs would not be produced without these monopolistic guarantees.[263] They argue that reducing the reimbursement for the costs of research and development by controlling the prices of orphan drugs would, in turn, stifle innovation.[264]

Critics of amending the ODA also argue that the stated purpose and findings of the original act were not expressly to provide more access to orphan drugs but rather to "facilitate the

258. *See* discussion *supra* Section II.A.

259. *See* Baumann, *supra* note 255; *see also* discussion *supra* Section II.A.

260. Fairness in Orphan Drug Exclusivity Act, H.R. 456, 118th Cong. (2023).

261. *See* H.R. 456; CMS Memorandum, *supra* note 235 (offering an expansive list of elements to be considered in drug price negotiations, including "research and development costs").

262. Jayasundara et al., *supra* note 33, at 1.

263. David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?*, 55 FOOD DRUG L.J. 125, 133 (2000).

264. *See* Baumann, *supra* note 255.

development of" orphan drugs.[265] Congress explicitly noted the following under the findings section of the Act:

> (4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops and orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently incur a financial loss;
>
> (5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in applicable Federal laws to reduce the costs of developing such drugs . . . .[266]

They argued that the ODA does not explicitly mention increasing accessibility of medicines to patients, but instead, the focus is on providing incentives for pharmaceutical companies to develop these medicines, the objective is met with the existing framework.[267] After all, orphan drugs are set to make up 20% of the global pharmaceutical market by 2026, a number that would not have been thinkable before the enactment of the ODA.[268] Critics claim that patients are not worse off because of the monopolistic prices that the ODA market incentives create because those patients who cannot afford the medicines would simply not have had any access because the drugs did not exist prior to the enactment of the ODA.[269] For patients who can afford the high prices of orphan drugs, the Act has succeeded in

265. *See* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) (introducing the bill as, "amend[ing] the Federal Food, Drug, and Cosmetic Act to facilitate the development of drugs for rare diseases and conditions, *and for other purposes*" (emphasis added)); *see* Pulsinelli, *supra* note 81, at 318–19.

266. Orphan Drug Act, § 1(b)(4)–(5).

267. *See* Pulsinelli, *supra* note 81, at 318–19.

268. *See* Senior, *supra* note 151.

269. *See* Pulsinelli, *supra* note 81, at 318–19.

its intended purposes.[270] They maintain that the only way to provide patients with "the power and force of the high technology and sophistication" pharmaceutical companies provide to nonorphan drugs is through the existing market incentives of the ODA.[271]

This argument exemplifies a common logical fallacy associated with regulating pharmaceutical prices.[272] Those who argue that restricting the ODA to lower the prices of orphan drugs would simply result in pharmaceutical companies discontinuing their orphan drug manufacturing fail to consider that both the world and the global pharmaceutical market do not look the same as when the original act was passed.[273] Most of the globe already includes some kind of market regulation of drug pricing, and most pharmaceutical companies that operate in the United States are global producers.[274] Since the passage of the ODA, several orphan drugs have become "blockbuster" drugs so the orphan drug space now boasts the potential of a highly lucrative base.[275] Those in opposition are not unwarranted in claiming that the success of the orphan drug market is largely because of the market incentives provided in the Orphan Drug Act.[276] Amending and revising the ODA would not eliminate these market incentives; it would add extra levels of protection

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270. *See id*. at 318.

271. Mikami, *supra* note 24, at 627 (quoting the then-president of the Cystic Fibrosis Foundation's remarks in support of the ODA).

272. *See Logical Fallacies*, PURDUE ONLINE WRITING LAB, https://owl.purdue.edu/owl/general_writing/academic_writing/logic_in_argumentative_writing/fallacies.html [https://perma.cc/AHZ6-BUF5] (last visited Jan. 6, 2025) (describing hasty generalizations as a fallacy that occurs when the proponent of a claim fails to consider more evidence than just what is immediately available).

273. *See generally* Mikami, *supra* note 24, at 610 (describing how orphan products account for a larger portion of newly approved drugs within the market); Jayasundara et al., *supra* note 33, at 1 (stating that the global market for orphan drugs has greatly increased and evolved since the passage of the ODA).

274. *See* Żelewski et al., *supra* note 222, at 3; Gammie et al., *supra* note 227, at 1–2.

275. *See supra* note 151 and accompanying discussion of "blockbuster drugs."

276. *See* Baumann, *supra* note 255.

for patients so that manufacturers could still recover the costs of research and development and that patients could afford the medicines they need.[277]

Similarly, the result these monopolistic policies have created is one antithetical to the purpose of the ODA. The Act's stated purpose is to "facilitate the development of drugs for rare diseases and conditions, and for other purposes" and the Act's authors championed it as a mechanism for providing access to medicines that before did not exist.[278] While these medicines now do exist, the access part of the proposed goal has not yet been addressed. Patient access should be at the crux of rare disease regulations, and to center and realize this goal, the ODA needs to be restructured.

V. THE PROPOSED REVISIONS

The discussion and analysis above have expanded on why the ODA should be revised. Congress should amend the ODA by defining "same drug" as referring to the same approved indication, thus codifying the FDA's practice of granting orphan drug exclusivity for specific uses or indications for which a drug is approved.[279] However, in focusing on the approval-for-indication approach, Congress needs to clarify the guidelines for approval by ensuring that companies cannot create subsections within a disease for the purpose of stacking exclusivity period (salami-slicing).[280] Specifically, when companies seek to stack multiple subsections of disease or multiple indications, Congress should specify in the ODA that those companies are

277. *See id.*; Retaining Access and Restoring Exclusivity Act, S. 1214, 118th Cong. (2023); Fairness in Orphan Drug Exclusivity Act, H.R. 456, 118th Cong. (2023).

278. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983).

279. *See* Clarification of Orphan-Drug Exclusivity Following Catalyst Pharms, Inc. v. Becerra; Notification, 88 Fed. Reg. 4086, 4086–87 (Jan. 24, 2023) (to be codified at 21 C.F.R. pt. 316).

280. *See id.*; H.R. 456.

subject to a higher burden of proof.[281] In other words, companies seeking to stack indications or subsections should provide demonstratable evidence that without exclusivity, they would be unable to recoup the costs of research and development of these drugs.[282]

As mentioned above, the greatest pushback to revising the ODA is that altering or removing the market incentives provided in the act could quell innovation and production of orphan drugs.[283] These proposed solutions do not mean to quell the market incentives provided by the ODA, but rather the codification of the FDA's long-standing practice of granting exclusivity based on indications as opposed to the whole disease will provide greater patient access and choice.[284] There is necessarily a balance to be maintained between incentivizing pharmaceutical manufacturers to research and innovate new drugs for rare diseases, and maintaining the accessibility of those medicines.[285] The suggested proposals herein maintain that balance and seek to ensure the ODA serves its intended purpose: providing medicines for rare disease patient populations.[286]

CONCLUSION

The Orphan Drug Act revolutionized the marketplace of drugs for rare disease patient populations.[287] Since its enactment, the ODA transformed a sector of medicine that had little impact on United States pharmaceutical sales into a growing

281. *See* H.R. 456.

282. This proposed solution combines the most effective parts of the proposed RARE Act and the FODEA Act. *See supra* note 179 and accompanying discussion of Representative Matsui's RARE Act; H.R. 7383, 118th Cong. (2024).

283. *See* Baumann, *supra* note 255.

284. *See* discussion *supra* Section II.C.

285. *See* Marling, *supra* note 106; Baumann, *supra* note 255.

286. S*ee* discussion *supra* Part II.

287. *See, e.g.*, Baumann, *supra* note 255 ("[I]f IRA's provisions were in place 30 years ago, we wouldn't be where we are today as a company. We wouldn't be able to serve as many patients as we do today.").

20% of the global pharmaceutical market.[288] While the Act has encouraged new levels of innovation in the orphan drug space, the existing enforcement and approval structures in the Act encourage companies to create subsections of diseases and stack indications simply for the purpose of obtaining market exclusivity and not for prioritizing patient access to medicines.[289] The current structure of the Act allows companies to employ monopolistic tactics that create astronomical prices that patients cannot afford.[290]

Therefore, Congress must revisit the Orphan Drug Act to prioritize patients' access to much needed medicines. Further, the FDA should clarify the "same drug" language in the ODA by codifying the FDA's practice of granting orphan drug exclusivity for specific uses or indications that a drug is approved for, as well as increase the burden of proof for companies seeking market exclusivity for drugs with stacked indications. While there will be difficulties and costs associated with altering the existing market incentives and approval process of the ODA, the costs are greatly outweighed by the benefits of providing patients with access to medicines. The point of this legislation was to provide hope to patients with no options and the Act must be restructured to restore that hope.

288. *See* Jayasundara et al., *supra* note 33, at 1.

289. *See* discussion *supra* Part II.

290. *See* discussion *supra* Part II.