

7-29-2019

Robbing the Cradle: The Implications of Depleting Financial Incentives for Orphan Drug Manufacturers and Imposing Stricter Research Guidelines for Rare Pediatric Diseases

Cheryl L. Kozdrey

Follow this and additional works at: <https://scholarlycommons.law.cwsl.edu/cwlr>

Recommended Citation

Kozdrey, Cheryl L. (2019) "Robbing the Cradle: The Implications of Depleting Financial Incentives for Orphan Drug Manufacturers and Imposing Stricter Research Guidelines for Rare Pediatric Diseases," *California Western Law Review*: Vol. 55 : No. 2 , Article 4.

Available at: <https://scholarlycommons.law.cwsl.edu/cwlr/vol55/iss2/4>

This Article is brought to you for free and open access by CWSL Scholarly Commons. It has been accepted for inclusion in California Western Law Review by an authorized editor of CWSL Scholarly Commons. For more information, please contact alm@cwsl.edu.

**ROBBING THE CRADLE: THE IMPLICATIONS OF DEPLETING
FINANCIAL INCENTIVES FOR ORPHAN DRUG
MANUFACTURERS AND IMPOSING STRICTER RESEARCH
GUIDELINES FOR RARE PEDIATRIC DISEASES**

CHERYL L. KOZDREY*

ABSTRACT

Controversy surrounding drug pricing is ever-present. However, the focus on pricing practices has shifted with the influx of orphan drug designations. Many big players in the pharmaceutical and biotech industries have harvested enormous profits by finding unique ways to manipulate the Orphan Drug Act's incentive program. Meanwhile, scientific research startups have viewed the Act as a gateway to break into the pharmaceutical sector. As a result of the industry's growing interest in the orphan drug market, patients suffering from rare diseases enjoy tremendous benefits from medicinal innovation that would have otherwise gone undiscovered. In addition, the Act's financial incentives make market entry more feasible for young pharmaceutical and biotech companies, thereby expanding industry competition. So, why have politicians begun to attack the orphan drug market? Through the Tax Cuts and Jobs Act, the current Administration has slashed tax incentives for orphan drug manufacturers in half. In addition, the FDA issued a Guidance that recommends eliminating research exemptions previously available to pediatric subpopulations under the Pediatric Research Equity Act. These joint measures attempt to address

* Cheryl L. Kozdrey earned a J.D., magna cum laude, from California Western School of Law in 2018 and is currently an Associate Attorney at Saxe Doernberger & Vita, P.C. She extends her utmost gratitude to Professor Robert Bohrer, a true and passionate mentor. She also wishes to thank Eric Clarkson and Hana Willard for their insight and assistance throughout the editing process.

profitable exploitation of the Orphan Drug Act. However, they continue to ignore patient price concerns as well as the undeniable innovative benefits that flow from the Orphan Drug Act. Reducing tax credits and forcing drug makers to engage in more extensive pediatric research for rare diseases may reduce big pharma's profits. However, it will not save patients money or make more treatments available to them. Instead, pharmaceutical and biotech firms are incentivized to continue operating free from transparency while price-gouging orphan drug consumers, or to reduce their engagement in the pediatric orphan drug market and seek more profitable ventures. In the end, the only groups that stand to lose are children suffering from rare diseases.

TABLE OF CONTENTS

INTRODUCTION	389
I. ORPHANS AND TWINS: AN OVERVIEW OF THE ODA AND CONTIGUOUS PEDIATRIC DRUG LEGISLATION	392
A. <i>History of the Orphan Drug Act</i>	392
1. <i>The ODA's Impact on Pediatric Drug Development</i> ...	394
2. <i>The ODA's Incentive Structure</i>	395
B. <i>BPCA and PREA: The Contiguous Pediatric Drug Statutes</i>	396
II. FILLING THE PIGGYBANK: AN EXPLANATION OF ODA MISUSES, THE PREA LOOPHOLE, AND THE INTERPLAY OF PHARMA-ECONOMICS.....	398
A. <i>Exploiting Orphans: How Big Pharma Misuses the ODA to Render Big Profits</i>	399
B. <i>Neglecting the Children: How the PREA Loophole Exempts Drug Makers from R&D Requirements in Pediatric Subpopulations</i>	401
III. TAKING CANDY FROM A BABY AND IMPOSING STRICTER RULES: HOW THE TAX BILL CUT INCENTIVES FOR ORPHAN DRUG SPONSORS, AND THE GUIDANCE EXPANDED PEDIATRIC R&D REQUIREMENTS UNDER PREA	404
A. <i>The Tax Cuts and Jobs Act Slashes Orphan Drug Incentives</i>	405
B. <i>The FDA Guidance Elevates R&D Requirements and Eliminates Orphan Designations for Some Pediatric Subpopulations</i>	408
IV. THE PROOF IS IN THE PUDDING: OUTLINING THE EVIDENCE FOR AND AGAINST PROPOSED EFFECTS ON PRICE AND DEVELOPMENT	

2019]	ROBBING THE CRADLE	389
OF PEDIATRIC ORPHAN DRUGS.....		410
A. <i>Raising Big Pharma’s Allowance: Will Orphan Drug Prices Increase?</i>		410
1. <i>Examining the Industry’s Lack of Transparency</i>		411
2. <i>A Brief Comparison of Orphan Drug Development Costs Versus Pricing</i>		413
B. <i>A Time-Out for Drug Development: Will the Tax Bill and Guidance Lead to Reduced Engagement in the Pediatric Orphan Drug Market?</i>		415
1. <i>Using PREA’s Waiver System to Avoid Pediatric Testing in Orphan Subpopulations</i>		416
2. <i>The Prohibitive Effect on Small Bio-Pharma Companies</i>		418
CONCLUSION		421

INTRODUCTION

The National Organization for Rare Diseases (“NORD”) kick-started 2018 with a commemoration, celebrating the 35th anniversary of the Orphan Drug Act (“ODA”), a law that provides incentives for the development of treatments for rare diseases.¹ However, NORD may have less to celebrate and more to advocate for in coming years due to reduced financial incentives under the Tax Cuts and Jobs Act (“Tax Bill”), as well as stricter research guidelines proposed in the Food and Drug Administration’s (“FDA”) guidance entitled “Clarification of Orphan Designations of Drugs and Biologics for Pediatric Subpopulations of Common Diseases” (“Guidance”). The same is true for Tasha Nelson, Courtney Waller, and Rebecca Mauldin, all mothers of children afflicted with rare diseases.

Ms. Nelson, whose son Jack was only one-month old when he was diagnosed with cystic fibrosis, explains, “[a]ny dime you take from a company that is working toward saving my son’s life is an insult to my

1. National Organization for Rare Diseases, *NORD and the Orphan Drug Act Celebrate 35th Anniversaries*, CISION PR NEWSWIRE (Jan. 4, 2018), <https://www.prnewswire.com/news-releases/nord-and-the-orphan-drug-act-celebrate-35th-anniversaries-300577648.html> [hereinafter NORD].

family.”² Yet, that is precisely what the Tax Bill has done by slashing tax credits for the research and development (“R&D”) of orphan drugs in half.³ Nelson fears that drug companies “may not have the resources” to help Jack fight cystic fibrosis if tax breaks are reduced or eliminated.⁴ While there may be some debate about the pharmaceutical industry’s access to abundant financial resources, Nelson’s belief that the industry will reduce its participation in the orphan drug market is merited. Indeed, a June 2015 analysis prepared for NORD and the Biotechnology Innovation Organization (“BIO”) found that without the orphan drug tax credit, approximately 33% fewer orphan therapies will be developed and approved over the next ten years.⁵

Another argument in opposition of reduced tax incentives for orphan drug manufacturers stems from pricing concerns. Orphan drugs are notorious for their hefty price tags. However, some drug manufacturers have alleviated the burden on consumers by offering company-sponsored copays, which can significantly reduce out-of-pocket expenses for patients.⁶ For example, through a drug company’s copay program, Jack’s mother pays a mere \$25 per month for his cystic fibrosis treatment, Pulmozyme — a deep discount compared to its market price of \$6,000 per month.⁷ If the tax credit has a significant enough impact on manufacturers’ profit margin, some fear consumer pricing for orphan drugs will increase or company-sponsored discount programs will be eliminated.

Although families of children afflicted with rare diseases vehemently oppose orphan tax credit reductions, curiously, pharmaceutical companies are not fighting back against these

2. Meghan Holohan, *Unlikely Lobbyists: Parents of Kids with Rare Diseases Fight Against Tax Bill*, TODAY (Nov. 13, 2017, 3:38 PM), <https://www.today.com/parents/parents-kids-rare-diseases-rally-against-tax-bill-t118672>.

3. See Tax Cuts and Jobs Act, Pub. L. No. 115-97, pt. V, sec. 13401, § 45C, 131 Stat. 2054 (2017) (reducing the orphan drug tax credit from 25% to 50%).

4. Holohan, *supra* note 2.

5. BIOTECH. INDUSTRY ORG. & NAT. ORG. FOR RARE DISORDERS, IMPACT OF THE ORPHAN DRUG TAX CREDIT ON TREATMENTS FOR RARE DISEASES (June 2015), <https://rarediseases.org/assets/files/white-papers/2015-06-17.nord-bio-ey-odtc.pdf>.

6. Holohan, *supra* note 2.

7. *Id.* (explaining, additionally, that under a similar program, Ms. Mauldin, whose son Jonathan has spent most of his life battling a rare cancer called Langerhans cell histiocytosis, pays only \$10 of the \$1,500 monthly cost of his treatment).

diminished incentives. This is largely attributed to the Tax Bill's accompanying provisions, which provide the companies with an even greater benefits through reduced corporate tax rates and special repatriation rates.⁸

Pharmaceutical companies are, however, voicing concerns over the FDA's Guidance that seeks to eliminate Pediatric Research Equity Act ("PREA") exemptions previously available to some orphan subpopulations. For over fifteen years, drugs with a pediatric-subpopulation orphan designation were exempt from PREA. Meaning, manufacturers were not required to conduct additional safety and efficacy trials on children when applying for FDA approval on an adult indication. At least one drug maker fears that a departure from this exemption "is likely to impede and delay development of important new medicines for children because without an orphan drug designation, developing novel drugs and biologics for children is more difficult and[,] in many cases, practically impossible."⁹

This article draws attention to the anticipated adverse implications of depleting financial incentives for orphan drug manufacturers and imposing stricter research guidelines for rare pediatric diseases. Part I provides an overview of the ODA, as well as pediatric drug legislation including the Best Pharmaceuticals for Children Act ("BPCA") and PREA. Part II focuses on the loopholes imbedded in these statutes and the opportunistic efforts drug manufactures have used to exploit them. Part III discusses the current administration's two-fold effort to address these abuses using the Tax Bill and FDA's Guidance. Part IV observes that these administrative efforts could have an adverse impact on the pricing and availability of orphan drugs for pediatric subpopulations and analyzes the evidence supporting and opposing these predictions.

8. See U.S. FOOD & DRUG ADMIN., CLARIFICATION OF ORPHAN DESIGNATION OF DRUGS AND BIOLOGICS FOR PEDIATRIC SUBPOPULATIONS OF COMMON DISEASES: GUIDANCE FOR INDUSTRY (July 27, 2018) [hereinafter GUIDANCE].

9. Letter from Carry A. Neil, M.D., Chief Scientific Officer, Aevi Genomic Medicine, to Docket Management Branch, U.S. Food & Drug Admin., Re: Docket No. FDA-2017-D-6380, Clarification of Orphan Drug Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases; Draft Guidance for Industry (Feb. 17, 2018), <https://www.regulations.gov/document?D=FDA-2017-D-6380-0015> [hereinafter Aevi Letter]; see also *Developers Voice Concerns Over Draft Guidance Closing Orphan Drug Loophole*, FDA NEWS: DRUG DAILY BULLETIN (Feb. 27, 2018), <https://www.fdanews.com/articles/185776-developers-voice-concern-over-draft-guidance-closing-orphan-drug-loophole>.

The article concludes by suggesting that the Tax Bill and Guidance may have an unsubstantial effect on pricing patterns in the orphan drug market. However, these joint administrative efforts are likely to cause reduced engagement in the pediatric orphan drug market, thereby diminishing access to and availability of treatments for children suffering from rare diseases.

I. ORPHANS AND TWINS: AN OVERVIEW OF THE ODA AND CONTIGUOUS PEDIATRIC DRUG LEGISLATION

While the Tax Bill and Guidance are independent administrative efforts, their joint impact threatens to have an adverse effect on the cost and accessibility of orphan treatments for ill children. The Tax Bill slashes tax incentives for *all* orphan drugs, while the PREA Guidance makes it more difficult for drug manufacturers to receive orphan designations for *pediatric* treatments. To properly analyze the potential effects of the Tax Bill and PREA Guidance, it is necessary to understand the history of the ODA, and the legislation specific to pediatric patient populations including PREA and its predecessor, BPCA.

A. *History of the Orphan Drug Act*

Pharmaceutical research in the United States relies on a combination of government funding and private investment.¹⁰ “The revenue potential of a drug in treating a particular disease can influence for-profit manufacturers’ willingness to devote necessary resources to its development.”¹¹ Rare diseases, also commonly referred to as “orphan diseases,” are defined as those which affect 200,000 or fewer patients within the United States.¹² Traditionally, diseases that affect

10. Aaron S. Kesselheim, *Innovation and the Orphan Drug Act, 1983-2009: Regulatory and Clinical Characteristics of Approved Orphan Drugs*, in RARE & ORPHAN PRODUCTS: ACCELERATING RESEARCH AND DEVELOPMENT, a report by INST. OF MED. U.S. COMM. ON ACCELERATING RARE DISEASE RESEARCH & ORPHAN PROD. DEV., (Field MJ & Boat TF eds., 2010), <https://www.ncbi.nlm.nih.gov/books/NBK56187>.

11. *Id.*

12. 21 U.S.C. § 360bb(a)(2) (1997) (“[T]he term ‘rare disease or condition’ means any disease or condition which (A) affects less than 200,000 persons in the United States, or (B) affects more than 200,000 in the United States and for which

such a limited population do not permit recovery of private research investment.¹³ “As their name implies, ‘orphan’ drugs were drugs that nobody wanted to produce . . . because too few people had the different diseases.”¹⁴ Consequently, pharmaceutical companies believed that R&D expenditures on such drugs could not be recouped.¹⁵ Without adequate incentives available to entice participation in the orphan drug market, therapeutic products for orphan conditions developed slowly if at all.¹⁶ To address these concerns and stimulate private-industry R&D for treatments with modest project potential, a three-fold effort was set in place between 1982 and 1983.¹⁷ First, the FDA created the Office of Orphan Products Development, which is “dedicated to promoting the development of products that demonstrate promise for the diagnosis and/or treatment of rare diseases.”¹⁸ Shortly thereafter, Congress passed the ODA and, on January 4, 1983, President Reagan signed it into law.¹⁹ Finally, “the coalition of patient advocates formally established NORD as a nonprofit organization to provide advocacy, education, research and patient/family services for all Americans affected by rare diseases.”²⁰ Central to these efforts was the ODA,²¹ which was aimed at solving an important problem – “how to induce a

there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.”).

13. Kesselheim, *supra* note 10.

14. RONALD J. VOGEL, PHARMACEUTICAL ECONOMICS AND PUBLIC POLICY 206 (2007).

15. *Id.*

16. Kesselheim, *supra* note 10.

17. STUART O. SCHWEITZER, PHARMACEUTICAL ECONOMICS AND POLICY 39 (2d ed. 2007).

18. PHARMACEUTICAL INNOVATION 147 (Frank A. Sloan & Chee-Ruey Hsieh eds., Cambridge Univ. Press 2007).

19. *See* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) [hereinafter ODA]; *see also* 21 U.S.C. § 360aa-ff (2017) (addressing drugs for rare diseases or conditions under the Orphan Drug Act).

20. NORD, *supra* note 1.

21. ODA, *supra* note 19.

market-driven pharmaceutical industry to develop new therapeutics for diseases affecting relatively small numbers of persons.”²²

The ODA has succeeded in many of its goals.²³ It increased the availability and approval of drugs to treat low-prevalence conditions,²⁴ decreased mortality rates for persons with orphan conditions,²⁵ and made market participation more feasible for startup bio-pharma manufacturers.²⁶ The ODA has also been instrumental in the development of treatments for pediatric subpopulations.²⁷

1. *The ODA’s Impact on Pediatric Drug Development*

In a study published by the American Academy of Pediatrics in 2012, researchers provided a ten-year analysis focused on the ODA’s progress in stimulating pediatric drug production.²⁸ The study reports “increasing pediatric orphan product designations and approvals from 2000 to 2009,” indicating that “the [ODA] has continued to address this important unmet need.”²⁹ Specifically, the study reports that, from 2000 to 2009, 26% of all orphan drugs that received marketing approval were for pediatric diseases.³⁰ Further, “[t]he proportion of approvals for pediatric products increased from 17.5% . . . in the first half of the

22. Robert A. Bohrer, *It’s the Antigen Stupid: A Risk/Reward Approach to the Problem of Orphan Drug Act Exclusivity for Monoclonal Antibody Therapeutics*, 5 COLUM. SCI. & TECH. L. REV. 1, 1 (2003).

23. *Id.* at 2 (“Although some drugs for small patient populations have been exceedingly profitable, the need for special incentives to spur pharmaceutical manufacturers to undertake the costly and risky process of drug development and research for less common diseases was clear to the Congressional sponsors of the Act and the Act has been largely judged a success.”).

24. PHARMACEUTICAL INNOVATION, *supra* note 18, at 121.

25. *Id.*

26. Aevi Letter, *supra* note 9 (noting that incentives under the ODA are extremely important to small pharmaceutical companies).

27. See generally Chandana Thorat, et al., *What the Orphan Drug Act Has Done Lately for Children with Rare Diseases: A 10-Year Analysis*, 29 PEDIATRICS 516 (2012); see also 21 C.F.R. § 201.57(c)(9)(iv) (2015) (defining pediatric populations as including patients aged “birth to 16 years, including age groups often called neonates, infants, children, and adolescents”).

28. Thorat, *supra* note 27, at 516–21.

29. *Id.* at 516.

30. *Id.*

decade, to 30.8% . . . in the second.”³¹ Although there have been very few systematic studies quantifying the ODA’s contribution to drug development for children with rare diseases, these calculations provide a promising outlook on the improvement of drug availability for pediatric subpopulations.³²

2. *The ODA’s Incentive Structure*

The ODA’s success in expanding the availability of drugs for ailments afflicting small patient populations is derived from the four extremely generous financial incentives it offers orphan drug manufactures.³³ First, no patent is necessary to gain market exclusivity.³⁴ Once the FDA’s Office of Orphan Products Development grants orphan drug status to a new product, the drug company receives exclusive marketing rights for seven years.³⁵ This means that the FDA will not grant approval to any other drug for the same indication within that seven-year period.³⁶ Second, the FDA provides grant money to companies in order to defray the costs of testing the drugs.³⁷ Third, the FDA provides assistance in “protocol design and new drug applications (NDA) or product license approval (PLA) applications.”³⁸ Finally, the ODA offers a tax credit for clinical R&D expenditures, which has raised great concern after being significantly reduced from 50% to 25% by the newly enacted Tax Bill.³⁹

31. *Id.*

32. *Id.* at 517 (reporting that “there have been *no* systematic analysis” quantifying the ODA’s contribution to pediatric drug development) (emphasis added).

33. VOGEL, *supra* note 14, at 207.

34. *See id.*

35. 21 U.S.C. §360cc(a) (2017); *see also* VOGEL, *supra* note 14, at 207.

36. 21 U.S.C. § 360cc(a)(2) (2017) (“[T]he Secretary may not approve another application . . . for the same drug for the same disease or condition for a person who is not the holder of such approved application or of such license until the expiration of seven years form the date of the approval of the approved application or the issuance of the license.”).

37. 21 U.S.C. § 360ee (2017); *see also* VOGEL, *supra* note 14, at 207.

38. SCHWEITZER, *supra* note 17, at 39; 21 U.S.C § 360aa (2017); *see also* Bohrer, *supra* note 22, at 18 n.32.

39. Tax Cuts and Jobs Act, Pub. L. No. 115-97, pt. V, sec. 13401, § 45C, 131 Stat. 2054 (2017).

B. BPCA and PREA: The Contiguous Pediatric Drug Statutes

Another area of contention arises where the ODA and pediatric drug legislation intersect. Through the ODA, Congress effectively addressed the once disparate availability of treatments for patients with rare diseases.⁴⁰ However, many years passed before Congress recognized the inadequate availability of safe and effective drugs for another underserved population – children.⁴¹ “[I]n 2001, only twenty percent of prescription medications were tested and approved for use in children.”⁴² Children nonetheless required treatment, and physicians engaged in “off-label”⁴³ prescription practices whereby children received drugs approved exclusively for adults.⁴⁴ It became common practice to dose children with adjusted quantities of the medication calculated solely according to their lower body weight.⁴⁵ However, this dosing standard was highly inaccurate and problematic because it did not take into account the metabolic differences between a child and an adult.⁴⁶ Additionally, “the lack of age-appropriate formulations, such

40. Bohrer, *supra* note 22, at 2 (noting the ODA is judged as a success).

41. The ODA was passed in 1983. Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983). Meanwhile, the first legislative effort that specifically addressed the need for adequate clinical studies in children came in 1997 with the Food and Drug Administration Modernization Act of 1997 (FDMA), which was subsequently reenacted through the BPCA in 2002. *See* Food and Drug Administration Modernization Act of 1997, Pub. L. No. 105-115, 111 Stat. 2296 (1997); *see also* Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002).

42. Lisa Jerles, Note, *The Best Pharmaceuticals for Children Act and the Pediatric Research Equity Act – Helping or Hurting America’s Children*, 6 CARDOZO PUB. L. POL’Y & ETHICS J. 515, 516 (2008) (citation omitted).

43. Off-label use refers to the use of an “FDA-approved medical product for a use that has not been studied yet” and is also referred to as “unapproved use of an approved product.” U.S. FOOD AND DRUG ADMIN., GLOSSARY OF TERMS, <https://www.fda.gov/ForPatients/ClinicalTrials/ucm410359.htm#O-1> (last visited May 1, 2019).

44. *See* Joanna K. Sax, *Reforming FDA Policy for Pediatric Testing: Challenges and Changes in the Wake of Studies Using Antidepressant Drugs*, 4 IND. HEALTH L. REV. 61, 65 (2007) (“[B]ecause relatively few drugs are tested on pediatric populations, doctors tend to ‘dose down’ adult dosages to account for the lower body weight in children.”).

45. Jerles, *supra* note 42, at 516; *see also* Sax, *supra* note 44, at 62.

46. Sax, *supra* note 44, at 76 (“The protocol of ‘down dosing’ adult prescriptions to account for the smaller size of children does not address physiological

2019]

ROBBING THE CRADLE

397

as liquid forms for children who cannot yet swallow drugs in pill form, [made] it difficult to administer medication to children.”⁴⁷

To curb these problems, Congress created several programs to promote pediatric studies and changed the regulatory landscape.⁴⁸ Today, the most important of these legislative efforts are the BPCA⁴⁹ and PREA⁵⁰, enacted in 2002 and 2003 respectively. Although both Acts are intended to promote pediatric studies, each operates differently. The BPCA operates as a “carrot,” *incentivizing* drug manufacturers with an additional six months of market exclusivity when it submits reports of pediatric studies that fairly respond to a written request from the FDA and are conducted in accordance with generally applicable scientific principles and protocols.⁵¹ Meanwhile, PREA operates as the “stick,” *requiring* drug makers to conduct studies that reflect “an assessment of safety and effectiveness (including dosing information) for the proposed indication in all relevant pediatric subpopulations.”⁵²

The combined impact of BPCA and PREA has been highly successful in providing parents and providers with essential information on the safety and efficacy of drugs used to treat children.⁵³ In fact, the American Academy of Pediatrics asserts that “[c]hildren are safer

differences between adults and children.”); Jerles, *supra* note 42, at 517 n.9 (“The drug Cyclosporine was approved for adults to counter organ rejection following transplants. The drug was then used in children without testing and without the same success. Researchers eventually discovered that children metabolize Cyclosporine much faster than adults, therefore needing more frequent dosing.”) (citations omitted).

47. Jerles, *supra* note 42, at 517 (citation omitted).

48. GUIDANCE, *supra* note 8, at 3.

49. Best Pharmaceuticals for Children Act, Pub. L. No. 107-109, 115 Stat. 1408 (2002).

50. Pediatric Research Equity Act, Pub. L. No. 108-155, 117 Stat. 1936 (2003).

51. See 21 U.S.C. § 355a (2017).

52. GUIDANCE, *supra* note 8, at 2–3 (citing Pub. L. No. 108-155 (2003), codified at 21 U.S.C. § 355c (2017)).

53. Letter from American Academy of Pediatrics, et al., to Scott Gottlieb, Commissioner, U.S. Food & Drug Admin., RE: Docket No. FDA-2017-D-6380, Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases; Draft Guidance of Industry; Availability, 1 (Jan. 19, 2018), <https://www.regulations.gov/document?D=FDA-2017-D-6380-0010> [hereinafter AAP Letter] (“[M]ore than 640 drugs and biologics [have been] relabeled with important information about their use in children”).

because of what we have learned through BPCA and PREA studies, and the pediatricians who care for them are better equipped to make clinical decisions for their patients.”⁵⁴ However, PREA contains a “loophole,” which permits orphan drug manufacturers to seek exemptions from some of their obligations to conduct pediatric studies.⁵⁵ The American Academy of Pediatrics and its partners explain:

Currently, a drug for a common disease, that would otherwise not be eligible for orphan status, can receive orphan status for just the pediatric population with that disease, if such population is under 200,000. After receiving that designation, the sponsor can decide not to pursue pediatric drug studies at all, despite requesting the pediatric designation.⁵⁶

Recognition of this loophole has given rise to increased scrutiny of the pharmaceutical industry’s opportunistic exploitation of ODA incentives.⁵⁷

II. FILLING THE PIGGYBANK: AN EXPLANATION OF ODA MISUSES, THE PREA LOOPHOLE, AND THE INTERPLAY OF PHARMA-ECONOMICS

Because “[t]he pharmaceutical industry is a competitive and potentially very lucrative marketplace,” the high-stakes business challenges it faces can harness significant risks as well as substantial rewards.⁵⁸ Despite projections from EvaluatePharma’s World Preview estimating that worldwide pharmaceutical drug sales will reach more than \$1 trillion by 2022, this forecast actually reflects a decrease for the same period last year.⁵⁹ This is the first time in ten years that drug sales

54. *Id.*

55. *Id.*; see *infra* Part I, sec. B (explaining the operative details of the PREA “loophole”).

56. AAP Letter, *supra* note 53, at 1; see also *infra* Part I, sec. B.

57. AAP Letter, *supra* note 53, at 1 (“This loophole allows sponsors to exploit the process and this must change.”).

58. Matthew J. Seamon, *Antitrust and the Biopharmaceutical Industry: Lessons From Hatch-Waxman and an Early Evaluation of the Biologics Price Competition and Innovation Act of 2009*, 34 NOVA L. REV. 629, 640 (2010).

59. *Biotech Industry Moves Towards a Patent Cliff*, THE BIO REPORT, at 0:58 (July 13, 2017) (download through iTunes podcast query) [hereinafter THE BIO REPORT] (interviewing Antonio Iervolino, head of forecasting for EvaluatePharma).

2019]

ROBBING THE CRADLE

399

have been projected to fall instead of rise, a phenomenon that forecasters attribute to pricing pressures as well as the advent of more biosimilar products.⁶⁰ While price-gouging and concerns about consumer affordability in the capitalistic pharmaceutical market are nothing new to the political pulpit, “pushback from consumers, [pharmacy benefit managers], payers and lawmakers has become much stronger as of late.”⁶¹

In the drug development market, “[p]rofits are measured in billions of dollars in annual sales and unexpected, sudden market collapses are not uncommon.”⁶² This juxtaposition incentivizes big-players in the pharmaceutical and biotech industries to engage in unconventional and creative strategies. Specifically, drug makers caught the attention of political forces due to their exploitation of the orphan drug system, as well as their use of the PREA “loophole” to avoid mandatory R&D testing in children.

A. Exploiting Orphans: How Big Pharma Misuses the ODA to Render Big Profits

The exploitation of ODA incentives did not begin with the pediatric market and certainly does not end there either. These efforts are far more expansive. For example, although ODA policies were intended to incentivize drug companies to participate in markets for underrepresented and otherwise less profitable diseases, ironically, “[s]even of the [ten] best-selling drugs in the country in 2015 were orphan drugs.”⁶³ Critics claim that these high yield returns on orphan drugs are a result of drug manufacturers gaming the system by seeking an orphan designation for drugs that were “first approved for the mass

60. *Id.* at 3:18; see also EVALUATEPHARMA, WORLD PREVIEW 2017, OUTLOOK TO 2022 EXECUTIVE SUMMARY 2 (10th ed. June 2017), <http://info.evaluategroup.com/rs/607-YGS-364/images/WP2017-SUM.pdf>.

61. Jacob Bell, *Pricing Pressures Lower Drug Sales Forecasts, New Report Finds*, BIOPHARMADIVE.COM (June 21, 2017), <https://www.bropharmadive.com/news/evaluatepharma-pricing-report-world-preview/445516>.

62. Seaman, *supra* note 58, at 640.

63. Sarah Janes Tribble & Sydney Lupkin, *Drugs for Rare Diseases Have Become Uncommonly Rich Monopolies*, NPR: HEALTH INC. (Jan. 17, 2017, 4:59 AM), <http://www.npr.org/sections/health-shots/2017/01/17/509506836/drugs-for-rare-diseases-have-become-uncommonly-rich-monopolies>.

market and later won approval for a rare disease.”⁶⁴ Conversely, some drugs have been introduced with an orphan status to gain financial subsidies and market exclusivity, then are continuously reintroduced to treat other ailments, thereby making the “leap from orphan to rolling blockbuster.”⁶⁵

Critics say these drugs are not “true” orphans but are being misused to give manufacturers a market monopoly.⁶⁶ Botox, Allergan’s best-selling product, provides an illustration of this practice. Botox received orphan approval in 1984 to treat painful muscle spasms of the eye, uncontrolled blinking, and neck pain.⁶⁷ Since then, the FDA has approved Botox for two additional orphan designations and as a “mass market drug to treat a variety of ailments, including chronic migraines and wrinkles.”⁶⁸ “Today, there are 5 million doses of Botox administered annually in North America, which translates into approximately \$1.5 billion in sales.”⁶⁹

Another “concern that has long plagued the ODA is the potential for drug developers to . . . artificially subdivide diseases to create subgroups of patients that fall under the orphan drug prevalence threshold – a practice referred to as ‘salami slicing.’”⁷⁰ For example, Epogen received an orphan designation in 1986 and final FDA approval in 1989 to treat anemia caused by end-stage renal failure.⁷¹ Shortly thereafter, Epogen became widely prescribed for a broad range of patients with anemia unrelated to end-stage renal failure.⁷² “Consequently, through off-label use . . . in patients without end-stage

64. *Id.*

65. Michael N. Abrams & Rita E. Numerof, *The Growing Orphan-Drug Paradigm*, 25 BIOPHARM INTERNATIONAL.COM (Apr. 1, 2012), <http://www.biopharminternational.com/growing-orphan-drug-paradigm-0>.

66. Tribble & Lupkin, *supra* note 63.

67. Abrams & Numerof, *supra* note 65.

68. Tribble & Lupkin, *supra* note 63.

69. Abrams & Numerof, *supra* note 65.

70. Shannon Gibson & Barbara von Tigerstrom, *Orphan Drug Incentives in the Pharmacogenomic Context: Policy Responses in the US and Canada*, 2 J.L. & BIOSCIENCES 263, 268 (2015), <https://doi.org/10.1093/jlb/lsv013> (citing David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?*, 31 AM. J. L. & MED. 365 (2005)).

71. *Id.*

72. *Id.*

renal disease, Epogen became a blockbuster drug and generated billions of dollars in revenue for its manufacturer.”⁷³ Similarly, Genentech developed human growth hormone (hGH) to treat children with hypopituitary dwarfism, then later received mass profits for the drug’s use to treat other growth deficiencies.⁷⁴

Due to the high profitability, more compelling market value propositions, and a faster route to market, “[t]he orphan drug market is expected to almost double during the 2016-22 period, peaking at \$209bn in 2022.”⁷⁵ “No one disputes that orphan drugs have helped or saved hundreds of thousands of patients suffering from debilitating or even fatal rare diseases.”⁷⁶ Yet, as former Representative Henry Waxman points out, drug manufacturers have turned the ODA on its head by using it as the “basis of manipulating the system . . . to make much more money than they would in an open competitive market.”⁷⁷

B. Neglecting the Children: How the PREA Loophole Exempts Drug Makers from R&D Requirements in Pediatric Subpopulations

Beyond creative abuses of the ODA, politicians have identified a secondary problem that lies at the intersection of PREA and the ODA. “Section 505B(k) of the Food Drug and Cosmetics Act contains a statutory exemption from the requirement to conduct pediatric studies under PREA for certain drugs with orphan designations.”⁷⁸ The FDA explains, this unintended “loophole” allows sponsors to “submit a marketing application for use of its drug in the non-orphan adult population,” then use the ODA to get a pediatric-subpopulation

73. *Id.*

74. Robert A. Bohrer & John T. Prince, *A Tale of Two Proteins: The FDA’s Uncertain Interpretation of the Orphan Drug Act*, 12 HARV. J. L. & TECH. 365, 381 (1999) (quoting JOHN HENKEL, ORPHAN DRUG PRODUCTS: NEW HOPE FOR PEOPLE WITH RARE DISORDERS, FDA SPECIAL REPORT ON NEW DRUG DEVELOPMENT IN THE UNITED STATES (1995)).

75. EVALUATEPHARMA, *supra* note 60, at 3.

76. Tribble & Lupkin, *supra* note 63.

77. *Id.*

78. GUIDANCE, *supra* note 8, at 4 (citing 21 U.S.C. § 355c(k) (2017)).

designation for the juvenile subset of the disease.⁷⁹ By way of example, for “a condition like inflammatory bowel disease (IBD), a drug may be approved to treat the large population of adults with the condition but then the same drug may be granted an orphan designation to treat a subset of children suffering from IBD.”⁸⁰ Due to this designation, the drug’s sponsor is “exempt from conducting the pediatric studies normally required under PREA when seeking approval of the adult indication.”⁸¹

This means, when a sponsor seeks FDA approval for a drug intended to treat a common adult illness, it can use an orphan designation get around PREA testing requirements if that illness occurs rarely in children. FDA Commissioner Dr. Scott Gottlieb explains, “once a drug receives an orphan designation for a pediatric population of the adult disease, the drug then becomes statutorily exempt from the requirements of PREA.”⁸²

For example, if FDA grants pediatric-subpopulations designation for a sponsor’s drug for pediatric ulcerative colitis and the sponsor submits an NDA . . . for its drug to treat ulcerative colitis in adults, the sponsor would be exempt from having to conduct pediatric studies under PREA by virtue of having the pediatric-subpopulation designation for pediatric ulcerative colitis. This is despite the fact that prevalence of the ulcerative colitis indication as a whole is greater than 200,000 and despite the fact that pediatric ulcerative colitis does not meet the definition of an orphan subset under 21 C.F.R. § 316.3(b)(13).⁸³

79. Announcement of the Availability of Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases; Guidance for Industry, 83 Fed. Reg. 35655 (July 27, 2018).

80. Zachary Brennan, *FDA to Close Loophole Allowing Companies to Skirt Pediatric Study Requirements*, RAPS: REGULATORY FOCUS (Sept. 12, 2017), <https://www.raps.org/regulatory-focus%e2%84%a2/news-articles/2017/9/fda-to-close-loophole-allowing-companies-to-skirt-pediatric-study-requirements>.

81. GUIDANCE, *supra* note 8, at 4.

82. Scott Gottlieb, M.D., *FDA is Advancing the Goals of the Orphan Drug Act*, U.S. FOOD & DRUG ADMIN.: FDA VOICES (Sept. 12, 2017), <https://www.fda.gov/NewsEvents/Newsroom/FDAVoices/ucm612012.htm>; *see also* Brennan, *supra* note 80.

83. GUIDANCE, *supra* note 8, at 4; 21 C.F.R. § 316.3(b)(13).

Gottlieb contends that this creates a “loophole” which directly opposes congressional intent.⁸⁴ He asserts, “[n]obody envisioned this unintended conflict between the original ODA and the provisions outlined in PREA,” which effectively provides drug makers with a “free pass from having to study drugs in pediatric uses.”⁸⁵ Gottlieb continues, “rather than ensuring more pediatric research, as Congress envisioned, we can end up with fewer pediatric studies.”⁸⁶

Although this “loophole” has existed for the entire fifteen years since PREA’s enactment, it has only recently fostered negative attention. This leaves some with the impression that Gottlieb is sensationalizing the problem. For example, NORD contends that the FDA has “not provide[d] sufficient evidence of the perceived loophole;” accordingly, the organization has asked the FDA for further evidence that this loophole is being exploited, including information about how many therapies were exempted from PREA, while also receiving a pediatric subpopulation orphan designation, and not being subject to additional pediatric testing.⁸⁷ In addition, the Guidance itself makes clear that, although drugs with ODA designations are exempt from PREA, they nonetheless can be the subject of a written request for pediatric testing under BPCA.⁸⁸ This mechanism seems to undermine Gottlieb’s argument that drug makers are receiving a “free pass” from studying drugs in pediatric uses.⁸⁹ Nevertheless, the FDA continues to scrutinize the pharmaceutical industry’s use of the PREA “loophole” as

84. Gottlieb, *supra* note 82.

85. *Id.*; see also Brennan, *supra* note 80.

86. Gottlieb, *supra* note 82.

87. *NHGRI Launches Strategic Planning Process for Genomic Research and Funding*, CENTERWATCH (Feb. 26, 2018), <https://www.centerwatch.com/cweekly/2018/02/26/nhgri-launches-strategic-planning-process-genomic-research-funding>.

88. GUIDANCE, *supra* note 8, at 3 (explaining that BPCA provides “an additional six months of market exclusivity when a sponsor submits reports of pediatric studies that fairly respond to a written request from FDA and are conducted in accordance with generally applicable scientific principles and protocols”); see also *SAFE & EFFECTIVE MEDICINES FOR CHILDREN: PEDIATRIC STUDIES CONDUCTED UNDER THE BEST PHARMACEUTICALS FOR CHILDREN ACT & THE PEDIATRIC RESEARCH EQUITY ACT* (Marilyn J. Field & Thomas F. Boat, eds., National Academies Press 2012), <https://www.nap.edu/read/13311/chapter/3#34> (“Drugs with designations under the Orphan Drug Act are exempt under PREA but can be the subject of written requests”).

89. See Gottlieb, *supra* note 82 (emphasis added).

a measure to avoid the added time and monetary investments for R&D in limited pediatric subpopulations.

Yet, as discussed in Part I, these strategic measures do not always result in detrimental effects on patients. One benefit is shown through the influx of treatments for pediatric populations regardless of the shortcomings that flow from the “loophole.” Another benefit flows from the orphan drug system, which has undoubtedly incentivized the development of treatments for rare ailments that may have otherwise gone unattended. This is true despite concerns about excess profitability and repurposing.⁹⁰ Notwithstanding these positive advancements, the high price of brand-name prescription drugs in the mass market, as well as the orphan drug market, remains an ever-present and significant concern that cannot be ignored. In fact, “[s]crutiny of drug prices around the globe is expected to exert growing pressure on the biopharmaceutical sector” in the coming years.⁹¹

Unfortunately, several challenges stand in the way of accomplishing reasonable pricing models in the pharmaceutical sector. Brett Saunders, Chief Executive Officer of Allergan, points out that one of the problems lies with opposition from some drug companies who resist voluntary price capping⁹² and continue to increase list prices to exorbitant levels. However, the greater challenge lies with incompatible regulatory structures that fail to balance the economic interests of pharmaceutical manufacturers with important patient protections.

III. TAKING CANDY FROM A BABY AND IMPOSING STRICTER RULES: HOW THE TAX BILL CUT INCENTIVES FOR ORPHAN DRUG SPONSORS, AND THE GUIDANCE EXPANDED PEDIATRIC R&D REQUIREMENTS UNDER PREA

The current administration has taken a two-fold approach to addressing some of the problems that plague the industry’s pediatric orphan drug sector. The first approach uses the Tax Bill to reduce the

90. See Tribble & Lupkin, *supra* note 63.

91. THE BIO REPORT, *supra* note 59, at 0:53.

92. See Jared S. Hopkins, *Allergan CEO Pushes for Trump to Lead Drug Price Discussions*, BLOOMBERG (Feb. 24, 2017, 6:02 AM), <https://www.bloomberg.com/news/articles/2017-02-23/allergan-ceo-pushes-for-trump-to-lead-drug-price-restraint-talks>.

orphan tax credit and deter excessive uses of the ODA.⁹³ The second approach flows from the FDA Guidance, which would impose stricter pediatric research requirements for orphan drugs and reduce the number of juvenile treatments that qualify for an orphan designation.⁹⁴ Before evaluating the compatibility and effect of these administrative efforts, it is important to understand some of their intricacies.

A. *The Tax Cuts and Jobs Act Slashes Orphan Drug Incentives*

The Tax Bill is a broad and multi-dimensional piece of legislation with wide-ranging effects on personal, as well as business economics.⁹⁵ Although the Tax Bill does not exclusively target the pharmaceutical industry, three of its key provision have significant impacts on the industry by lowering corporate tax rates,⁹⁶ providing a special repatriation rate,⁹⁷ and reducing the orphan tax credit.⁹⁸ The first two provisions have the potential to provide enormous benefits to drug manufacturers. For instance, the corporate tax rate has been slashed from a variable rate peaking at 35% to a flat rate of 21% for most large corporations.⁹⁹ While this provision has been revered as the “largest reduction in U.S. corporate tax rates in our nation’s history[.]”¹⁰⁰ some analysts predict the reduced corporate tax rate, on its own, will have a

93. Sarah Jane Tribble, *Advocates for Patients with Rare Diseases Defend Tax Credits for Orphan Drugs*, NPR: HEALTH-SHOTS (Nov. 29, 2017, 4:16 PM), <https://www.npr.org/sections/health-shots/2017/11/29/567052592/advocates-for-patients-with-rare-diseases-defend-tax-credits-for-orphan-drugs> (discussing the Tax Bill, and asserting that “[w]e need to think about ways we can improve the [ODA] and stop people from gaming the system and exploiting it”).

94. *See generally* GUIDANCE, *supra* note 8.

95. *See generally* Tax Cuts and Jobs Act, Pub. L. No. 115-97, 131 Stat. 2054 (2017).

96. *Id.* pt. I, sec. 13001, § 11(b).

97. *Id.* § 904(E).

98. *Id.* pt. V, sec. 13401, § 45C.

99. *Id.* pt. I, sec. 13001, § 11(b); *see also* *Tax Cuts and Jobs Act: Overview of Provisions Affecting Business*, MAXWELL, LOCKE, & RITTER (Jan. 11, 2018), <https://www.mlrpc.com/articles/tax-cuts-jobs-act-overview-provisions-affecting-businesses>.

100. Zachary Brennan, *Senate, House Agree to Cut Orphan Drug Research Credit in Half in Tax Bill*, RAPS: REGULATORY FOCUS (Dec. 18, 2017), <https://www.raps.org/regulatory-focus%E2%84%A2/news-articles/2017/12/senate,-house-agree-to-cut-orphan-drug-research-credit-in-half-in-tax-bill>.

negative or insubstantial impact on pharmaceutical cash.¹⁰¹ However, most agree that coupling it with the repatriation provision provides a windfall for large pharmaceutical companies and their investors.¹⁰² The special repatriation rate encourages corporations to bring overseas cash back to the U.S. Instead of paying the corporate tax rate on profits held overseas, companies will get a one-time deal that taxes them approximately 15.5% on funds they bring back to the United States economy.¹⁰³ “Companies such as Johnson & Johnson, Amgen, Gilead, Pfizer and Merck all keep more than 80% of their cash overseas.”¹⁰⁴ Accordingly, the decreased cost of bringing overseas cash back to the U.S. is considered a major victory for the bio-pharma industry.¹⁰⁵ However, this bonus does not come without sacrifice.

Since 1983, the tax credit for orphan drug manufacturers has been issued at a rate of 50% of all R&D costs.¹⁰⁶ This was one of the greatest financial incentives available to bio-pharma manufacturers under the

101. The corporate tax rate is likely to have little impact on the biotechnology and pharmaceutical industries because the average effective tax rate across all companies in these sectors is already estimated at approximately 20%. See Aswarth Damodaran, TAX RATES BY SECTOR (US), NYU: STERN SCHOOL OF BUSINESS (Jan. 2018), http://pages.stern.nyu.edu/~adamodar/New_Home_Page/datafile/taxrate.htm; but see Trefis Team, *A Look at Big Pharma’s Value Sensitivity to Changes in Tax Rates*, FORBES (Jan. 11, 2018, 3:49 PM), <https://www.forbes.com/sites/greatspeculations/2018/01/11/a-look-at-big-pharmas-value-sensitivity-to-changes-in-tax-rates/#705523e614d5> (noting “many companies will see a significant impact from changes in their effective tax rates . . . it will boil down to the expected taxable income growth and the expected change in their effective tax rate”).

102. *Editorial: Drug Firms Lead the Way on Pocketing Tax Cuts*, ST. LOUIS POST-DISPATCH (Feb. 26, 2018), http://www.stltoday.com/opinion/editorial/editorial-drug-firms-lead-the-way-on-pocketing-tax-cuts/article_f88c2f67-8ec6-5875-9230-ec7260fad95.html (“A new survey of U.S. companies from analysts at Morgan Stanley estimates that 43 percent of the savings from the [Tax Bill] will be paid to investors in the form of higher dividends and stock buybacks.”); see also @jimtankersley, TWITTER (Feb. 10, 2018, 7:59 AM), <https://twitter.com/jimtankersley/status/962370393016291328>.

103. *Editorial*, *supra* note 102; see Tax Cuts and Jobs Act, Pub. L. No. 115-97, pt. I, sec. 13001, § 904(E), 131 Stat. 2054 (2017).

104. Brennan, *supra* note 100; see also @bradloncar, TWITTER (Nov. 29, 2017, 11:45 AM), <https://twitter.com/bradloncar/status/935957450481717255>.

105. Brennan, *supra* note 100.

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

ODA.¹⁰⁷ But, after thirty-five years of substantial savings on the R&D of drugs for rare diseases, the Tax Bill slashed this handsome reward in half.¹⁰⁸ “The House bill had originally sought to eliminate the tax credit entirely, meanwhile the Senate bill sought reforms that would reduce the credit rate to 27.5% of qualified clinical testing expenses.”¹⁰⁹ Ultimately, legislators agreed to reduce the credit to 25% of qualified clinical testing expenses.¹¹⁰ Proponents of the cut flaunt its \$32.5 billion in projected government savings over the next ten years.¹¹¹ Meanwhile, those opposed to cutting the orphan drug credit argue that it could both “stifle research on new medications and make the cost of prescriptions even more expensive.”¹¹² Thirty-six patient organizations, including NORD, banded together in opposition of the weakened orphan tax credit.¹¹³ Surprisingly, biopharma leaders did not oppose the Tax Bill, likely due to the Bill’s favorable repatriation rate and corporate tax provisions.

107. Tribble & Lupkin, *supra* note 63 (noting “advocates as well as critics of the industry say tax credits have been an important motivation for companies”).

108. Tax Cuts and Jobs Act, Pub. L. No. 115-97, pt. V, sec. 13401, § 45C, 131 Stat. 2054 (2017).

109. Brennan, *supra* note 100.

110. Tax Cuts and Jobs Act, Pub. L. No. 115-97, § 45C. Stat. 2054 (2017).

111. Brennan, *supra* note 100.

112. Jessica Waltman, *President Trump Signs Tax Cuts and Job Act: Impact on Health Care and Benefits*, KISTLER, TIFFANY BENEFITS (Dec. 26, 2017), <https://ktbenefits.com/2017/12/congress-passes-tax-reform-impact-on-health-care-and-benefits>.

113. Christina Jensen, *Statement by 36 Patient Organizations in Opposition to Senate’s Proposed Weakening of the Orphan Drug Tax Credit*, NORD (Nov. 14, 2017), <https://rarediseases.org/statement-36-patient-organizations-opposition-senates-proposed-weakening-orphan-drug-tax-credit>. *See also* Letter from Nat. Org. for Rare Disorders, to Division of Dockets Management, U.S. Food & Drug Admin., Re: Docket No. FDA-2017-D-6380-0005: Guidance: Clarification of Orphan Drug Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases (Feb. 18, 2018), <https://www.regulations.gov/document?D=FDA-2017-D-6380-0016> [hereinafter NORD Letter].

B. The FDA Guidance Elevates R&D Requirements and Eliminates Orphan Designations for Some Pediatric Subpopulations

The Tax Bill was introduced almost simultaneously with a draft Guidance issued by the FDA, which aims to close the PREA “loophole.”¹¹⁴ The Guidance explains the FDA’s approach as follows:

FDA intends to no longer continue to grant pediatric-subpopulation designation. Pediatric-subpopulation designation is no longer necessary to stimulate the study of drugs in pediatric populations, now that various programs, such as PREA and BPCA, have proven to be effective in achieving those ends. Therefore, if a sponsor requests orphan drug designation for a pediatric subpopulation of a common disease [in adults], and even if the pediatric subpopulation prevalence is below 200,000, FDA will not grant orphan drug designation to that pediatric subpopulation unless:

1. the disease in the pediatric population constitutes a valid orphan subset, and the drug meets all the other criteria for orphan designation; or
2. the sponsor can adequately demonstrate that the disease in the pediatric subpopulation is a different disease from the disease in the adult population, and the drug meets all other criteria for orphan designation. For example, if as a scientific matter, efficacy from clinical studies in the adult population could not be extrapolated to the pediatric subpopulation, such information may be considered a different disease.¹¹⁵

Ironically, the Guidance is titled “Clarification of Orphan Designations of Drugs and Biologics for Pediatric Subpopulations of *Common Diseases*[.]”¹¹⁶ It may seem oxy-moronic to clarify orphan designations for *common diseases* when the ODA makes clear that its incentives apply only to *rare diseases*.¹¹⁷ Yet, this is precisely where the controversy lies: where do you draw the line between rare and

114. See GUIDANCE, *supra* note 8, at 4 (explaining the Guidance was created “in order to close the loophole created by the interaction of the practice of granting pediatric-subpopulation designation and the PREA orphan exemption”).

115. *Id.* at 4–5.

116. *Id.* at 1 (emphasis added).

117. See generally Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983); 21 U.S.C. § 360aa-ff (2017).

common diseases when the prevalence of those ailments varies between adult and pediatric populations? More importantly, should ODA incentives be withheld for rare pediatric diseases merely because those diseases occur commonly in adults? If so, to what extent will withholding ODA incentives stifle the production of pediatric treatments? Curiously, the FDA leaves many of these questions unanswered.

In response, NORD issued a letter calling on the FDA to (1) provide substantive evidence detailing how the alleged “loophole” in PREA has been exploited, (2) offer “additional analysis on the possibility for pediatric drug development and research to actually be weakened by this move rather than strengthened,” and (3) clarify ambiguities in its Guidance to ensure “pediatric subpopulations of rare diseases continue to receive orphan designation since there are few other incentives for development.”¹¹⁸ Similarly, the Pharmaceutical Research and Manufacturers of America (“PhRMA”), as well as BIO, issued letters asking the FDA to “tailor the scope of the [G]uidance to preserve incentives for developing drugs for rare pediatric diseases,” and clarify the terms “pediatric subpopulation(s)” and “pediatric-subpopulation designation(s).”¹¹⁹ Like NORD, both PhRMA and BIO also question the pervasiveness of the industry’s alleged exploitation of the “loophole” highlighted in the Guidance.¹²⁰ At the crux of these

118. NORD Letter, *supra* note 113, at 2–3.

119. *See* Letter from PhRMA to Division of Dockets Management, U.S. Food & Drug Admin., Re: Docket No. FDA-2017-D-6380: Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases; Draft Guidance for Industry (Mar. 7, 2018), <https://www.regulations.gov/document?D=FDA-2017-D-6380-0017> [hereinafter PhRMA Letter]; *see also* Letter from BIO to Dockets Management Branch, U.S. Food & Drug Admin., Re: Docket No. FDA-2017-D-6380: Clarification of Orphan Designation of Drugs and Biologics for Pediatric Subpopulations of Common Diseases (Feb. 16, 2018), <https://www.regulations.gov/document?D=FDA-2017-D-6380-0012> [hereinafter BIO Letter].

120. *See* PhRMA Letter, *supra* note 119 (“PhRMA is concerned with the implication in the draft guidance that sponsors are acting inappropriately by taking advantage of a ‘loophole’ to avoid completing studies in pediatric subpopulations. PhRMA respectfully disagrees with this characterization and, to the extent such a ‘loophole’ exists, believes that it is a legal interpretation of the PREA exemption that has created this result”); *see also* BIO Letter, *supra* note 119 (“[T]he terminology used by the FDA in the draft guidance implies that sponsors are acting inappropriately by taking advantage of a ‘loophole.’ BIO respectfully disagrees and requests that the

concerns is the idea that limiting the groups of pediatric conditions that qualify for orphan designation reduces incentives to such a degree that it negatively affects the development and accessibility of treatments for rare childhood diseases.

IV. THE PROOF IS IN THE PUDDING: OUTLINING THE EVIDENCE FOR AND AGAINST PROPOSED EFFECTS ON PRICE AND DEVELOPMENT OF PEDIATRIC ORPHAN DRUGS

Unique issues arise when the concerns of patient advocacy groups align with the those of bio-pharma lobbyists. The concerns expressed by NORD,¹²¹ PhRMA,¹²² and BIO¹²³ about the Guidance correspond with fears surrounding the new Tax Bill. These groups' concerns focus on two common issues. First, how will reduced tax incentives and more extensive pediatric research requirements impact the price of drugs for rare childhood disorders? Second, how will these factors impact future production and development of pediatric orphan drugs?

A. *Raising Big Pharma's Allowance: Will Orphan Drug Prices Increase?*

According to one report, "the largest, most expensive clinical trials for orphan drugs cost about a quarter as much as those for non-orphan drugs, after the tax credits are factored in."¹²⁴ Yet, the average annual cost per patient for orphan drugs in the United States was over \$140,000, compared with \$27,756 for non-orphans.¹²⁵ Overall, orphan

FDA adjust this language within the guidance to reflect that it has been FDA's legal interpretation of the PREA that has allowed for such designations to be granted[.]").

121. See generally NORD Letter, *supra* note 113.

122. See generally PhRMA Letter, *supra* note 119.

123. See generally BIO Letter, *supra* note 119.

124. Carolyn Y. Johnson, *High Prices Make Once-Neglected 'Orphan' Drugs a Booming Business*, WASH. POST (Aug. 4, 2016), https://washingtonpost.com/business/economy/high-prices-make-once-neglected-orphan-drugs-a-booming-business/2016/08/04/539d0968-1e10-11e6-9c81-4be1c14fb8c8_story.html?noredirect=on&utm_term=.25a7a6514679.

125. EVALUATEPHARMA, ORPHAN DRUG REPORT 2017, 9 (4th ed. 2017), <http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf>.

drug sales increased by 12.2% between 2015 and 2016; meanwhile, non-orphan drug sales increased by a mere 2.4%.¹²⁶

Patient populations are much smaller for true orphan indications, and a smaller market makes it more difficult to recoup even discounted R&D costs. However, the exorbitant price mark-ups do not necessarily correspond with the cost of development.¹²⁷ It has long been understood that pharmaceutical companies charge what the market will bear,¹²⁸ rather than some calculated percentage of their clinical expenditures. This means reducing tax credits, or escalating R&D costs through mandated pediatric testing, may not have a significant impact on pediatric orphan drug pricing.

1. *Examining the Industry's Lack of Transparency*

Assessing the true R&D costs and fair price for a new drug is extremely difficult because the pharmaceutical industry operates free from transparency requirements.¹²⁹ This leads to increased scrutiny of the bio-pharma industry.¹³⁰ As a result, “companies such as Eli Lilly and Johnson & Johnson have given peaks [sic] behind the curtain of drug pricing decisions.”¹³¹ Meanwhile, other companies – including Allergan, AbbVie, and Novo Nordisk – have implemented “social contracts” with patients, pledging to limit the number of annual price increases and to keep price hikes in the single-digit percentages.¹³²

126. *Id.* at 8.

127. *See id.* at 11 (noting that, instead, prices correlate with patient population size).

128. Claude E. Barfield & Mark A. Groombridge, *Parallel Trade in the Pharmaceutical Industry: Implications for Innovation, Consumer Welfare, and Health Policy*, 10 FORDHAM INTELL. PROP. MEDIA & ENT. L.J. 185, 244 n.184 (1999) (citing Frederick T. Schut & Peter A.G. Van Bergeijk, *International Price Discrimination: The Pharmaceutical Industry*, 44 WORLD DEV. 1141, 1142 (1986)) (“the pharmaceutical industry charges what the market will bear”).

129. Gilbert Carrillo, *Drug Transparency Laws Will Not Drive Pharmaceutical Prices Down and Will Only Stifle Innovation*, 25 ANNALS HEALTH L. ADVANCE DIRECTIVE 77, 80 (2015).

130. *See* Bell, *supra* note 61 (“[P]ushback from consumers, PBMs, payers and lawmakers has become much stronger as of late[.]”).

131. *Id.*

132. *Id.*; *see, e.g.*, Brent Saunders, *Our Social Contract with Patients*, CEO BLOG (Sept. 6, 2016), <https://www.allergan.com/news/ceo-blog/september-2016/our->

In September 2016, Allergan became the first company to voluntarily promise to limit its annual drug price increases to single-digit percentages. Although the use of social contracts as self-imposed price regulations is a new and unpopular practice among the majority of pharmaceutical leaders, the significant long-term impacts are already apparent.¹³³ However, effectuating a voluntary program that slashes financial returns in half requires a delicate balance between the regulatory restraints that seek to protect patient interests and the autonomous business interests of drug makers.¹³⁴ Unfortunately, neither the Tax Bill, nor the Guidance come anywhere close to addressing the issue of transparency or pharmaceutical pricing restraints. Meanwhile, some drug manufacturers have stopped pretending that R&D costs justify their price markers. For example,

In a slide deck released to a Senate committee last year, Valeant Pharmaceuticals International outlined its reasoning for a price hike for Syprine, a three-decade-old-rare-disease drug that ultimately went from \$652 for 100 capsules to \$21,267 over a five-year period. The slide explains the reason for the price hike: “Progressive pricing actions to bring in line with comparable Orphan products.”¹³⁵

Likewise, Martin Shkreli¹³⁶ attempted to justify his company’s exponentially high price-increase for Daraprim, an old drug used to

social-contract-with-patients (“Where we increase price on our branded therapeutic medicines, we will take price increases no more than once per year and, when we do, they will be limited to single digit percentage increases.”).

133. For example, Allergan “raised 2017 list prices by an average of only 6.7 percent” when the overall “average price increase for branded drugs was 12.92 percent in 2016.” Joanna Shepherd, *The Pharmaceutical Industry’s Social Contract With Patients*, MORNING CONSULT (Sept. 5, 2017), <https://morningconsult.com/opinions/pharmaceutical-industrys-social-contract-patients/>. The effect of annual price increases accumulates over time, “with a 12.92-percent annual price increase resulting in drug prices that are twice what a 6.7-percent annual price increase would produce in 15 years.” *Id.*

134. *Id.*

135. Johnson, *supra* note 124.

136. Martin Shkreli, criticized as “the most hated man in America,” is a former pharmaceutical executive who became notorious for raising the price of Daraprim from \$13.50 per pill to \$750 per pill. Zoe Thomas & Tim Swift, *Who is Martin Shkreli – “The Most Hated Man in America”?*, BBC NEWS (Aug. 4, 2017), <http://www.bbc.com/news/world-us-canada-34331761>.

fight a rare infection, by explaining “[t]his drug is priced similarly to other drugs for rare disease, and I think physicians understand that.”¹³⁷ The truth is, “[n]owhere are the strange economics of drug pricing more difficult to understand than when a drug invented decades earlier is granted orphan status – and an orphan price.”¹³⁸

When consumers are already being price-gouged for age-old drugs that required little to no R&D expenditures, how are we to arrive at the conclusion that decreased orphan tax incentives will do anything other than render even higher pricing? The practice is already in place, and pharmaceutical sponsors admit their pricing does not necessarily parallel their R&D costs.¹³⁹ Indeed, even a cursory review of clinical expenditures and profits for orphan drugs reinforces the notion that development costs do not correlate to increased drug prices.

2. *A Brief Comparison of Orphan Drug Development Costs Versus Pricing*

Although a lack of transparency in the pharmaceutical industry impedes access to abundant data sources, a holistic review of cost versus profit is still possible. A research study published by the Journal of the American Medical Association (“JAMA”) in September 2017 provided an estimate of R&D spending, as well as profits, for ten cancer drugs of which nine hold orphan designations.¹⁴⁰ The researchers explain, “[a] common justification for high cancer drug prices is the sizeable [R&D] outlay necessary to bring a drug to the U.S. market.”¹⁴¹ However, the study found that the approximate “cost to develop a cancer drug is \$648.0 million, a figure significantly lower than prior estimates.”¹⁴² Meanwhile, “the revenue since approval is substantial,” averaging \$1,658.4 million, and ranging from \$204.1 million to \$22,275.0 million.¹⁴³

137. Johnson, *supra* note 124.

138. *Id.*

139. *See id.*

140. Vinay Prasad & Sham Mailankody, *Research and Development Spending to Bring a Single Cancer Drug to Market and Revenues After Approval*, 177 JAMA INT’L MED. 1569 (2017).

141. *Id.* at 1569.

142. *Id.*

143. *Id.*

A separate study, issued by EvaluatePharma in 2016, noted a correlation between the available patient population and the revenue per patient for the top 20 selling orphan drugs.¹⁴⁴ The study also found that as the patient population got smaller (i.e. fewer than 10,000), the correlation became closer.¹⁴⁵ This confirms “industry perceptions that smaller patient groups allow a pricing premium to be achieved versus non-orphans.”¹⁴⁶ This reinforces the idea that orphan drug pricing is not tethered to R&D costs. Instead, the market is based on “innovation premiums for drugs that create a step change in treatment options and therapy outcomes.”¹⁴⁷

“The high prices of orphan drugs have been detached from the [ODA’s] original rationale – that incentives are necessary for companies to recoup the costs of [R&D] of treatments with tiny markets.”¹⁴⁸ The pricing schema has also been removed from consumer idealism, i.e., the idea that the profit margin should correspond with production costs. Today, the “[orphan] market has come to expect high prices for any drug that treats very few patients.”¹⁴⁹ What is worse is “the system lacks any real mechanism to counter the price increases.”¹⁵⁰ “Drug companies argue that any change to incentives could lead the industry to abandon orphans once more.”¹⁵¹ Patients and advocates have the same concern. However, these reports also demonstrate that “orphan drugs give companies virtually unlimited pricing power,”¹⁵² irrespective of the Tax Bill’s diminished incentives or the Guidance’s added R&D requirements.

144. EVALUATEPHARMA, *supra* note 125, at 11.

145. *Id.*

146. *Id.* (asserting “Soliris confirms the pricing power resulting from indications with the fewest number of patients”).

147. *Id.* (using the Gleevec product as an example).

148. Johnson, *supra* note 124.

149. *Id.*

150. *Id.*

151. *Id.*

152. *Id.*

B. A Time-Out for Drug Development: Will the Tax Bill and Guidance Lead to Reduced Engagement in the Pediatric Orphan Drug Market?

While pricing concerns appear unsubstantiated, suspicion that the Tax Bill and Guidance will impede innovation and deter participation in the already vulnerable pediatric orphan drug market is merited. In its letter to the FDA, NORD expressed concerns that there may be rare pediatric subpopulations that would have received R&D under the previous incentive structure that will now be ignored.¹⁵³ The organization explains, “[b]oth PREA and BPCA exist to encourage these studies, but PREA requirements can be avoided using the sometimes unpredictable waiver and deferral process, and the six months of exclusivity offered by BPCA has not shown to be an adequate incentive in every case.”¹⁵⁴ Essentially, NORD argues that despite the Guidance’s aim to encourage pediatric testing, drug makers can easily get around PREA research requirements through waivers.

In fact, by eliminating a company’s eligibility to receive ODA benefits for some pediatric subpopulations, the Guidance actually encourages business-minded drug makers to seek a PREA waiver. Now, instead of receiving the abundant financial incentives and seven years of added exclusivity under the ODA, the drug maker is left with a mere six months of additional exclusivity under BPCA. If the six-month incentive alone is not enough to satisfy its return on investment, the drug maker will be effectively deterred from pursuing R&D in the pediatric subpopulation. This problem is intensified for small-scale and startup pharmaceutical companies that rely heavily on the incentives accrued by orphan designations.¹⁵⁵ Aevi Genomic Medicine, in its responsive letter to the FDA Guidance, argues “[w]ithout these incentives, developing drugs for children can be prohibitively expensive and practically impossible for small companies.”¹⁵⁶

153. NORD Letter, *supra* note 113, at 2.

154. *Id.*

155. Aevi Letter, *supra* note 9, at 1.

156. *Id.*

1. *Using PREA's Waiver System to Avoid Pediatric Testing in Orphan Subpopulations*

PREA's waiver system provides a means for drug maker avoid its obligation to conduct pediatric testing even where the Guidance would otherwise impose such a requirement. A full waiver of PREA's requirement to submit pediatric assessments is granted if "[n]ecessary studies are impossible or highly impracticable (because, for example, the number of patients is so small or the patients are geographically dispersed)[.]"¹⁵⁷ One important challenge that has persisted with pharmaceutical testing in children under BPCA and PREA is the "relatively small population of potential test subjects."¹⁵⁸ "With children accounting for only 24.6% of the United States population, it is hard to find enough children to participate in studies."¹⁵⁹ In addition, "the size of this country makes it nearly impossible to confine the study to a particular geographic area as children with a specific condition are likely to spread across the country."¹⁶⁰ With only a small number of participants, "studies may not be able to generate statistically reliable information concerning the effectiveness of a drug relative to a control group or a placebo."¹⁶¹ The problem is exacerbated when the subpopulation is narrowed due to the rarity of a disease in children, even if that same disease is widespread in adults. This is one reason it makes sense to exempt orphan drugs from the more stringent pediatric research requirements imposed by PREA.¹⁶² Theoretically, it also may be why drug makers are able to easily secure a waiver or deferral from PREA's clinical study requirements as NORD suggests.¹⁶³

A comparative study conducted by members of the FDA and the European Medicines Agency ("EMA") examined some of the waivers

157. U.S. FOOD & DRUG ADMIN., GUIDANCE FOR INDUSTRY: HOW TO COMPLY WITH THE PEDIATRIC RESEARCH EQUITY ACT; DRAFT GUIDANCE (2005) (citing The Food, Drug, and Cosmetics Act, 21 U.S.C § 505B(a)(4)(A)(i) (1938)).

158. *See* Jerles, *supra* note 42, at 523.

159. *Id.*

160. *Id.*

161. *Id.* (citing INST. OF MED. OF THE NAT'L ACAD., ETHICAL CONDUCT OF CLINICAL RESEARCH INVOLVING CHILDREN 27, 81 (2004)).

162. *See generally* NORD Letter, *supra* note 113.

163. *Id.* at 2.

granted under PREA between 2007 and 2013.¹⁶⁴ Several waivers were granted because the potential pediatric study population was too small.¹⁶⁵ For example, the FDA granted a full PREA waiver to Bracco Diagnostics for CardioGen-82 (rubidium-82), a drug used to treat coronary artery disease.¹⁶⁶ “For the proposed adult indication, [the FDA] considered that the number of pediatric patients with coronary artery disease was too small and granted the waiver based on rarity of the disease, rendering pediatric studies impossible or highly impractical.”¹⁶⁷ Similarly, when considering a PREA waiver for zoledronic acid, the FDA “waived the requirement to conduct pediatric studies in osteoporosis because of the rarity of the disease in the pediatric population.”¹⁶⁸

The FDA-EMA study also compared the number of waivers granted in the United States to those granted in Europe.¹⁶⁹ The data collected provides some insight into the ease with which drug makers can evade PREA’s pediatric testing requirements.¹⁷⁰ Of the products reviewed for waivers by both the EMA and the FDA, the agencies adopted similar opinions about whether or not the waiver should be granted 86% of the time.¹⁷¹ The agencies boasted the value of these parallel outcomes, noting that “[t]his harmonization of scientific opinion is encouraging.”¹⁷² They explain, “while medical research in children is of the utmost importance to facilitate the development of safe and effective medicines for the pediatric population, regulatory agencies need to grant [waivers] from pediatric medical research

164. See generally Gunter F. Egger, et al., *A Comparative Review of Waivers Granted in Pediatric Drug Development by FDA and EMA from 2007-2013*, 50 THERAPEUTIC INNOVATION & REG. SCI. 639, 639–47 (2016).

165. *Id.* at 643.

166. *Id.*; see Letter from U.S. Food & Drug Admin., to Bracco Diagnostics Inc., NDA 19-414/S-012 (July 29, 2010), https://www.accessdata.fda.gov/drugsatfda_docs/appletter/2010/019414s012ltr.pdf.

167. Egger, *supra* note 164, at 643; NORD Letter, *supra* note 113.

168. Egger, *supra* note 164.

169. *Id.* at 640.

170. See *id.*

171. *Id.* at 646.

172. *Id.*

obligations in selected cases . . . to prevent unnecessary clinical research in children, a vulnerable population.”¹⁷³

Notably, the EMA granted 88% of such waivers requested for single active substance products.¹⁷⁴ However, “of the 405 full waiver requests submitted” to the EMA, only 80 (20%) were also reviewed by the FDA during the study period.¹⁷⁵ This variance is largely attributed to the different regulatory structures in the U.S. versus the E.U.¹⁷⁶ Namely, the PREA “loophole” exempts orphan products “from pediatric research requirements in the U.S., whereas they are not exempt from obligations of the Paediatric Regulation in the E.U.”¹⁷⁷ However, the FDA’s new Guidance now brings these varied regulatory structures into closer alignment.

Like the European system, the Guidance eliminates pediatric testing exemptions previously available to certain orphan products under PREA,¹⁷⁸ leaving drug makers with only one option – waivers. Accordingly, the U.S. is likely to see an increase in PREA waiver requests which would mirror the quantity reported in the E.U., and with an 86% similarity index between EMA and FDA decisions, it is fair to predict that the FDA will also mimic the EMA’s outcomes when it comes to granting waivers. Hence, if the FDA matches the EMA’s 88% approval rate of pediatric testing waivers, a substantial number of drugs will now be excused from pediatric testing. Further, under the new Guidance, these drugs will no longer receive any of the ODA benefits used to entice manufacturers to engage in such testing despite an exemption.

2. *The Prohibitive Effect on Small Bio-Pharma Companies*

Aevi, a small genomic development company, contends that “without orphan designation[s], the development of novel drugs and biologics in children is much more difficult and in many cases, practically impossible” because “[c]linical trials in pediatric

173. *Id.* at 646

174. *Id.* at 642.

175. *Id.* at 644.

176. *Id.* at 645.

177. *Id.*

178. *See generally* GUIDANCE, *supra* note 8.

populations, especially orphan populations are often difficult and arduous.”¹⁷⁹ Aevi explains that most of the companies engaged in the production of pediatric orphan drugs are small-scale organizations that “can benefit greatly from the incentives provided by orphan drug designation.”¹⁸⁰ Specifically, Aevi explains that the seven years of regulatory exclusivity the ODA offers has been crucial to the development of older drugs that have a limited patent life for new pediatric indications.¹⁸¹

Small-to-medium-sized companies require exclusivity to provide stockholders with a guarantee that competitors cannot infringe upon its products.”¹⁸² Although “diseases affecting 200,000 Americans are ‘rare’ under the law, they may represent sizeable – even hugely profitable – markets for small companies.”¹⁸³ In addition, orphan designations under the ODA are based solely on U.S. disease populations.¹⁸⁴ Because the ODA “does not account for the potential profits on international sales,” its incentives become even more enticing for companies both small and large.¹⁸⁵ The proof of profitability for orphan drug manufacturers benefiting from the ODA’s financial

179. Aevi Letter, *supra* note 9, at 1.

180. *Id.*; see also Suzanne Shelley, *Orphan Drug Commercialization is Maturing*, PHARMACEUTICAL COMMERCE (Sept. 1, 2016), <http://pharmaceuticalcommerce.com/brand-marketing-communications/orphan-drug-commercialization-maturing> (noting “many of the companies pursuing orphan drugs have been smaller companies”). *But see* Joseph Burns, *Orphan Drugs: Way Too Many, Way Too Expensive*, MANAGED CARE: DRUG MANAGEMENT (June 4, 2017), <https://www.managedcaremag.com/archives/2017/6/orphan-drugs-way-too-many-way-too-expensive> (“When the orphan drug legislation was passed, small pharmaceutical companies and universities were developing medications for rare diseases Right now, all the largest pharmaceutical companies are involved in the research and development of orphan drugs.”).

181. See Aevi Letter, *supra* note 9. See also Annette K. Kwok, et al., *Incentives to Repurpose Existing Drugs for Orphan Indications*, 6 ACS MED. CHEMISTRY LETTERS 828, 828 (2015) (explaining the value of incentives for repurposing existing drugs for orphan indications).

182. Bohrer, *supra* note 74, at 381 n.74 (citing John Henkel, ORPHAN DRUG PRODUCTS: NEW HOPE FOR PEOPLE WITH RARE DISORDERS, FDA SPECIAL REPORT ON NEW DRUG DEVELOPMENT IN THE UNITED STATES (1995)).

183. *Id.* at 381.

184. *Id.*

185. *Id.*

incentives has been crucial in establishing the industry.”¹⁸⁶ He explains, “[the ODA] suddenly created a business model that said you can go after these incredibly rare diseases and survive.”¹⁸⁷

The Guidance threatens to minimize access to ODA incentives for pediatric subpopulations, which have been fundamental to the sustainability of small businesses. It is also important to note that some of the Tax Bill’s favorable corporate benefits do not flow to small-scale companies. For example, pharmaceutical giants that keep substantial revenues overseas can reap the benefits of the Bill’s low repatriation rate.¹⁸⁸ Additionally, to the extent that a profitable company’s effective tax rate is lowered by the new corporate tax, their financial yields could increase.¹⁸⁹ This is not so for small companies that have not yet become profitable and do not hold cash overseas.¹⁹⁰ Hence, while large-scale corporations are able to hedge their loss in orphan tax credits against their gains from other provisions, small-scale companies only feel the burden of losing an important incentive. It is unclear whether this loss will be enough to push small players out of the orphan drug market completely, but it is certainly enough to generate concern.

Ultimately, big pharma has been awarded a lower corporate tax rate and reduced costs for bringing cash back into the U.S. This translates to more cash in corporate pockets with no incentive to direct those yields where they are most needed – the orphan drug market.¹⁹¹ In fact, there is a direct disincentive for manufacturers to engage in these markets of great need due to the reduced orphan tax credit and more rigid pediatric testing requirements. Meanwhile, big pharma continues to operate without transparency, and free from requirements to keep

186. Johnson, *supra* note 124.

187. *Id.*

188. See Brennan, *supra* note 100; see also @bradloncar, *supra* note 104.

189. John Engle, *How Tax Reform Will Impact Development Biotech*, SEEKING ALPHA (Dec. 18, 2017, 8:06 AM), <https://seekingalpha.com/article/4132460-tax-reform-will-impact-developmental-biotech> (“Dropping the corporate tax rate . . . will be a boon for all case flow positive businesses, but it may have some negative impacts on development-stage businesses that are currently burning capital in order to develop new products. Such is the case in much of biotech, in which a large number of development-stage companies make significant annual losses.”).

190. *Id.*

191. Jennifer Huron, *35 Ways to Celebrate the 35th Anniversary of NORD*, NORD (Mar. 5, 2018), <https://rarediseases.org/35-ways-celebrate-35th-anniversary-nord> (noting that 95% of the 7,000 rare diseases still have no treatment).

2019]

ROBBING THE CRADLE

421

profits within a reasonable range or to pass savings on to consumers. Hence, exorbitant orphan drug pricing remains unchanged and pharmaceutical giants prevail with greater profitability. Meanwhile, children with rare diseases suffer as the overall value of developing treatments for their conditions has been diminished.

CONCLUSION

Since its 1983 enactment, the ODA has been monumental in spurring the development and accessibility of treatments for rare disorders. The same is true for the impact that BPCA and PREA have had on the research and development of drugs for pediatric indications. However, industry exploitation of ODA benefits, as well as strategic uses of the PREA-ODA “loophole,” run contrary to the legislative intent behind these provisions. Big pharma is reigning in huge profits by gaming the systems intended to benefit vulnerable patient populations. In an effort to curb these industry abuses, the administration has used the Tax Bill to reduce the orphan tax credit, and the FDA issued the Guidance to eliminate drug sponsors’ eligibility to receive ODA benefits for some pediatric subpopulations.

However, these joint efforts fail to address pervasive concerns related to the ODA. For example, although the Guidance prevents pediatric orphan designations for diseases commonly manifested in adults, it does not address “salami slicing” practices. In other words, drug manufacturers can continue to harvest ODA incentives by introducing a drug under its rare indication then catapulting it to a blockbuster through off-label and subsequently approved indications. This allows for continued abuse of the ODA on a large scale, while deterring engagement in pediatric subpopulations – where research is arguably most needed.

In addition, the Tax Bill’s reduced orphan tax credit does not address the problems attributed to a lack of price transparency and price-gouging in the orphan market. In fact, the bill’s favorable corporate tax rate and repatriation provision allow greater profitability for large companies in the mass market. Meanwhile, it removes incentives from small-players who rely heavily on the rare disease sector. Although the Tax Bill and PREA Guidance were introduced, at least in part, to curb abuses of the ODA and the PREA “loophole,” there

is no indication that these efforts actually advance the interests of pediatric orphan drug consumers (i.e. children with rare disease).

Unfortunately, the combined effect of these administrative efforts exemplifies the type of lopsided government action that inadvertently advances the interests of drug makers while failing to consider the disparate impacts on patients. The joint measures threaten to, yet again, tip the scales in favor of drug makers. Reducing tax credits and forcing drug makers to engage in more extensive pediatric research for rare diseases might reduce big pharma's profits, however, it will not reduce patients' costs or make more treatments available to them. Ultimately, the Tax Bill, coupled with the FDA Guidance, reduces engagement in the pediatric orphan drug market while permitting bio-pharma firms to price-gouge orphan drug consumers and operate free of transparency or profit limitations. In the end, the only groups that stand to lose are children suffering from rare diseases.