ARE WE ADOPTING THE ORPHANS, OR CREATING THEM? MEDICAL ETHICS AND LEGAL JURISPRUDENTIAL GUIDANCE FOR PROPOSED CHANGES TO THE ORPHAN DRUG ACT

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INTRODUCTION

The Orphan Drug Act ("the Act") is the epitome of reaction-based legislation. High-profile cases, the facts of which pull on the heart-strings of even the most stoic among us, spurred both the original enactment and subsequent calls for change. At first, these cases concerned the discovery of potentially life-saving drugs set aside untested for fear that they were not economically viable.[1] Then came the cases of blockbuster orphan drugs, drugs that received the benefits of the Act and were originally approved by the FDA for orphan indications, but whose approval was later expanded to include mass-market indications, leading to billions in sales.[2] More recently, orphan drug prices topping half-a-million dollars annually per patient have pushed the limits of affordability for patients and

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1. Louis Lasagna, *Who Will Adopt the Orphan Drugs*?, 3 REGULATION 27, 28 (1979); *See also,* Judith Randal, *The Orphan Drug Game,* 7(1) THE WILSON QUARTERLY 7, 17 (1983) ("[M]any known remedies for more obscure ailments . . . are 'orphaned' by the economics of the U.S. drug industry."); *A Methadone Alternative?*, 83(11) THE AMERICAN JOURNAL OF NURSING 1529, 1529 (1983) (statement by the Director of the Division of Research at the National Institute of Drug Addictions that LAAM, a methadone alternative, was unlikely to be commercially available despite published studies showing it to be as safe and effective); Peter Huber, *The Old-New Division in Risk Regulation*, 69(6) VA. L. REV. 1025, 1034 n.42 (1983) ("For a novel drug used to treat only a very rare disease, the cost of establishing the drug's safety may exceed the profit that can be earned by marketing it. The manufacturer then has no economic incentive to market the drug . . . .").

2. This issue is sometimes called "orphan drug creep." Michael Drummond & Adrian Towse, *Orphan Drug Policies: A Suitable Case for Treatment*, 15 Eur. J. Health Econ. 335, 336 (2014). *See* Dina Guzovsky, *How a blockbuster drug can become a subsidized 'orphan,'* CNBC (Dec. 2, 2015), http://nbr.com/2015/12/02/how-a-blockbuster-drug-can-become-a-subsidized-orphan/ (describing a study in the *American Journal of Clinical Oncology* which suggests that the Orphan Drug Act has companies "gaming the system to use the law for mainstream drugs"). *See also* Marty Makary, *One Pharma Fix: Limit the 'Orphan Drug' Incentives*, THE WALL STREET JOURNAL (Dec. 20, 2015), http://www.wsj.com/articles/one-pharma-fix-limit-the-orphan-drug-incentives-1450645511 (giving the example of Rituximab, originally submitted as a treatment for a subtype of non-Hodgkin lymphoma, this drug is now the 12th best-selling medication of all time in the U.S.).

insurance companies alike.[3] Now, as an improved understanding of the human genome leads to the dawn of personalized medicine, concerns about rising costs prompt more calls to reform the Act.[4]

For the 30 million Americans living with often untreatable rare diseases and conditions, encouraging pharmaceutical production is a top priority.[5] This is almost one in ten Americans—a staggering percentage of the overall population. Collectively, they are affected with more than 6,800 different rare diseases with different causes and different treatment needs.[6] While pharmaceutical companies and the United States Food and Drug Administration ("FDA") tout the fact that since the Act was passed, between 250 and 400 new treatments have been approved to treat rare diseases,[7] advocates for those with rare conditions argue that this is not nearly enough. Even after accounting for these new treatments, less than 5% of rare diseases have a treatment.[8] Moreover, the number of Americans whose condition is labeled "rare" is expected to rise under the FDA's current interpretation of the Act, because research pharmaceutical

3. Sarah Jane Tribble & Sydney Lupkin, *Sky-High Prices for Orphan Drugs Slam American Families and Insurers*, KAISER HEALTH NEWS (Jan. 17, 2017), http://khn.org/news/sky-high-prices-for-orphan-drugs-slam-american-families-and-insurers/. *See also* Steven Syre, *High prices for drugs to treat rare diseases take a toll*, THE BOSTON GLOBE (May 12, 2015), https://www.bostonglobe.com/business/2015/05/11/high-prices-for-drugs-treat-rare-diseases-take-toll/qrM8s57p3EDQ2TwM5i9s5H/story.html (stating the average price of an orphan drug in 2014 was over $137,000 per patient per year).

4. *See* Ed Silverman, *Tiger in the Fiscal Room: Beware the Increasing Cost and Number of Orphan Drugs*, MANAGED CARE (March 2013) ("There is another reason that such pricing may continue, and that is the promised growth in personalized medicine . . . ."). *See generally* Joseph Guinto, *The High Price of Precision Healthcare*, GENOME MAGAZINE (Jan. 8, 2015), http://genomemag.com/reimbursement/#.VqU30V6DHIU.

5. *Frequently Asked Questions*, GENETIC AND RARE DISEASES INFORMATION CENTER AT THE NATIONAL INSTITUTE OF HEALTH, https://rarediseases.info.nih.gov/about-gard/pages/31/frequently-asked-questions (last visited April 6, 2017) (reporting that between 25 and 30 million Americans are estimated to be affected by rare diseases).

6. *Id.*

7. The reason for this wide range in reported new treatments is unclear. Perhaps the pharmaceutical companies, which tend to report on the high side, wish to show the Act is working and should not be amended, whereas some government agencies, which tend to report on the low end, wish to show the continued problem and need for their agency to receive funding. *Compare* America's BioPharmaceutical Research Companies, *Rare Diseases: A Report on Orphan Drugs in the Pipeline*, MEDICINES IN DEVELOPMENT, at 3 (2013), http://phrma-docs.phrma.org/sites/default/files/pdf/Rare_Diseases_2013.pdf ("more than 400 medicines . . . have been approved to treat rare diseases" between 1983 and 2013), *and Frequently Asked Questions*, *supra* note 5 (reporting that "more than 340 treatments for rare diseases" were approved by the FDA between 1983 and 2008), *with Why TRND Matters*, NATIONAL CENTER FOR ADVANCING TRANSLATIONAL SCIENCES AT THE NATIONAL INSTITUTE OF HEALTH, http://www.ncats.nih.gov/trnd (last visited April 6, 2017) ("only about 250 treatments are available" for rare and neglected diseases).

8. America's BioPharmaceutical Research Companies, *supra* note 7, at 3.

companies are increasingly able to split more common conditions into subsets based on what particular genetic variation caused the disorder.[9]

This Note traces the subtle changes in the underlying purposes of the Act, and evaluates those purposes from the perspectives of medical ethics and legal jurisprudence. Part I begins with the history of the Act discussed not chronologically, but issue by issue, to elucidate the subtle changes in the purpose of the Act through its history. Part II explores the moral and ethical issues presented by the Act to identify eleven guiding principles from medical ethics and legal jurisprudence. Finally, Part III applies these guiding principles to the most common proposed amendments to the Act. It is my hope that through a holistic understanding of the guiding principles which inform the Act from medical and legal perspectives, amendments will no longer be viewed as patches to fix the "problem drugs" gaining national attention, but as opportunities to strengthen the policy goals underlying the Act.

PART I: HISTORY OF THE ORPHAN DRUG ACT

A. What is an Orphan Drug?

Any discussion of the Orphan Drug Act must necessarily begin with an explanation of what an "orphan drug" is. The answer to that question has gradually shifted over the life of the Act. "Orphan drug" has been defined since the passage of the original 1983 Orphan Drug Act ("the 1983 Act") as a treatment for a rare disease or condition (often called an "orphan disease" or "orphan condition").[10] But the 1983 Act was not the origin of the term "orphan drug." Originally, "orphan drug" was a term applied to drugs that no company wanted to sponsor through the FDA's approval process, often in spite of promising preliminary test results.[11] As stated in 1979, "orphan drug cases" arise when "an agent with exciting potential for

9. *See* discussion *infra* Part I(G).

10. The Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049, 2049 (1983) ("The Congress finds that—, (1) there are many diseases and conditions . . . which affect such small numbers of individuals residing in the United States that the diseases and conditions are considered rare in the United States; . . . (3) drugs for these diseases and conditions are commonly referred to as 'orphan drugs'[.]").

11. *A Methadone Alternative?*, *supra* note 1, at 1529 (Statement by the Director of the Division of Research at the National Institute of Drug Addictions that LAAM, a methadone alternative, was unlikely to be commercially available and that LAAM is "[t]ruly an orphan drug" because no private company is interested in it as it is not patentable, and unlikely to be less expensive than the presently used methadone). *See also* Huber, *supra* note 1, at 1034 n.42 ("The 'orphan drug' problem is an instance in which burden of proof alone determines that certain products will not come into the market regardless of their safety.").

treating human disease is blocked through lack of interest on the part of the people and institutions whose commitment is necessary for bringing it to market."[12] By 1983, several drugs had gained national attention as a result of their former "orphan drug" status.[13] Sometimes these drugs were figuratively orphaned, abandoned by their creator and bounced from company to company as an advocate worked to convince anyone to "adopt" the drug through the FDA's testing and approval process.[14] Other times, a drug was orphaned when its primary use became obsolete and the manufacturer halted production despite the drug's secondary benefit as treatment for a rare condition.[15] Prior to 1983, the term "orphan drug" referred to existing drugs which no company would adopt.

Today, the term "orphan drug" refers to treatments researched and developed specifically for the treatment of rare diseases and conditions.[16] These treatments are then called "orphan drugs" because they treat an orphan condition. Companies are not adopting orphaned drugs; they are adopting orphaned conditions—conditions not traditionally researched for fear that any treatment would not be economically viable.[17]

B. Why are Drugs Orphaned?

There are two related reasons why pharmaceutical companies are likely to abandon a drug: patent ineligibility and a belief that the drug would not be sufficiently profitable. Patent ineligibility of orphaned drugs is common

12. Lasagna, *supra* note 1, at 28. *See also* Randal, *supra* note 1, at 17 ("[M]any known remedies for more obscure ailments are not being produced. They are 'orphaned' by the economics of the U.S. drug industry.").

13. One example, L-dopa, was orphaned for almost 40 years, from 1930 to 1970. Randal, *supra* note 1. Still today L-dopa is the primary treatment for Parkinson's Disease. Jackie Hunt Christensen, *The Medication Question*, NATIONAL PARKINSON FOUNDATION, http://www.parkinson.org/understanding-parkinsons/newly-diagnosed/medication-question (last visited Jan. 23, 2016).

14. Lasagna, *supra* note 1, at 29 (delineating the extenuating process which Dr. Stephen De Felice undertook to convince any company to bring carnitine, a treatment for heart disease, to market. Other examples in the article include Dopamine (shock, kidney blood flow), triethylene tetramine (lifesaving treatment for Wilson's Disease), and L-5HTP (Parkinsonism)).

15. Randal, *supra* note 1 (giving the example of Mapharsen, a former treatment for syphilis which can cure the rare bladder disorder pyuria).

16. Sara Reardon, *Regulators Adopt More Orphan Drugs*, 508 NATURE 16, 17 (April 3, 2014) (giving the example of Pfizer, which is targeting sickle-cell disease). *See generally* America's BioPharmaceutical Research Companies, *supra* note 7.

17. Some critics believe that pharmaceutical companies are only targeting the sorts of orphan conditions which are most likely to be economically viable. These critics argue that a disproportionate number of new orphan designations are for rare cancers, and that these types of treatments typically command higher prices than other orphan drugs. André Côté & Bernard Keating, *What is Wrong with Orphan Drug Policies?*, 15 VALUE IN HEALTH 1185, 1186 (2012) ("[D]rugs used to treat cancer are, by far, the most profitable.").

in two scenarios. First, imagine that researchers are attempting to find a novel treatment for high blood pressure, a common condition. Generally, researchers will identify a molecular structure within the body that they want the drug to interact with (also called a "target"). The researchers will then identify a large number of chemical compounds that they believe are likely to interact with or bind to that target.[18] Through early testing, researchers will narrow the list of compounds based on specific testing criteria, such as the ability to bind to the target molecular structure.[19] During this process, researchers sometimes observe compounds that do not meet the testing criteria but nevertheless may be useful for some other purpose, such as the treatment of an orphan condition. Particularly in the non-profit and university setting, these compounds may then be disseminated in a scientific publication, a presentation at a research conference, or a thesis, making them ineligible for patent protection.[20]

Second, imagine that a marine researcher discovers that a Caribbean sea sponge contains a compound with the potential to treat cancer.[21] The compound she discovers is a natural product, defined as a compound extracted or isolated from marine organisms, bacteria, fungi, or plants.[22] Unfortunately for the future of her discovery, the patentability of natural products has been questionable since 2013 when the Supreme Court held in *Association for Molecular Pathology v. Myriad Genetics, Inc*.[23] that "a naturally occurring DNA segment is a product of nature and not patent eligible merely because it has been isolated."[24] Regardless of the reason,

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18. *Biopharmaceutical Research & Development*, PhRMA at 4 (2015), http://phrma-docs.phrma.org/sites/default/files/pdf/rd_brochure_022307.pdf.

19. *Id.*

20. *See* 35 U.S.C. § 102(a) ("A person shall be entitled to a patent unless—(1) the claimed invention was patented, *described in a printed publication*, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention . . . .") (emphasis added). In 2012 Congress passed the America Invents Act ("AIA") which provides a limited one-year grace period for disclosures made by the inventor before the effective filing date of the claimed invention. *See* 35 U.S.C. § 102(b)(1).

21. Cytosaur-U® is "a staple for treating leukemia and lymphoma" and was found in a Caribbean sea sponge. *Medicines By Design Chapter 3: Drugs From Nature, Then and Now,* NIGMS, https://publications.nigms.nih.gov/medbydesign/chapter3.html (last updated Oct. 27, 2011).

22. *Natural Products Research—Information for Researchers*, NCCIH (accessed Jan. 18, 2017) https://nccih.nih.gov/grants/naturalproducts.

23. 133 S. Ct. 2107, 2111 (2013).

24. *Id.* The impact of this decision expands beyond orphan drugs. *See* David J. Newman & Gordon M. Cragg, *Natural Products as Sources of New Drugs from 1980 to 2014,* 79(3) J. NAT. PROD. 629, 629 (2016) (From the 1940s to the end of 2014, 49% of the small molecule drugs approved by the FDA were "either natural products or directly derived therefrom."). For examples of what is and is not patentable post-Myriad, *see Subject Matter Eligibility Examples: Life Sciences*, USPTO (May 6, 2016), https://www.uspto.gov/sites/default/files/documents/ieg-may-2016-ex.pdf. For examples of pre-Myriad challenges to obtaining a patent on a natural product, *see* Lasagna, *supra* note 1 (giving the

compounds which are ineligible for patent protection are more likely to be passed over by pharmaceutical companies out of fear that they will not be able to recover the costs associated with drug development and FDA approval before a generic enters the market.[25]

A pharmaceutical company is also likely to forego research on a particular drug if the company simply does not believe the drug will make a profit.[26] In the world of pharmaceutical pricing, to be pursued, a drug must be profitable enough to recover not only the cost its own research and development but also costs incurred in researching and developing other drugs that do not reach the market. Traditionally, these high-profit drugs, called "blockbuster" drugs, have been the financial backbone of the pharmaceutical industry.[27] When the only known use for a particular drug is to treat a rare condition, it is a simple economic decision for the company to direct resources away from the "orphan drug" towards products with higher demand.[28] But there are some cases, like pharmaceuticals for rare and life threatening conditions, where for moral and ethical reasons we may not want economics to dictate the choices of market players.[29]

C. The 1983 Act and the 1984 Amendments

The Orphan Drug Act, as passed in 1983, aimed to create access to treatments for rare conditions where those treatments were not reaching the market because of either economic infeasibility due to a small affected population, or the manufacturer's inability to patent the product. The 1983 Act allowed the "manufacturer or the sponsor of a drug [to] request the Secretary to designate the drug as a drug for a rare disease or condition."[30] "Rare disease or condition" was defined as "any disease or condition

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examples of carnitine, dopamine and L-5HTP as natural product drugs that became orphans in part because of their patent ineligibility).

25. Jamie F. Cardenas-Navia, *Thirty Years of Flawed Incentives: An Empirical and Economic Analysis of Hatch-Waxman Patent-Term Restoration*, 29 BERKELEY TECH. L.J. 1301, 1316–17 (2014) ("[G]enerics tend to dominate the product market immediately after patent protection ends, sometimes capturing up to 90% of the market within their first year or two after entry.").

26. *Id*. at 1307 ("It is estimated that bringing a new pharmaceutical product to market today can cost upwards of $1 billion.").

27. *Id.* at 1316–17 (Noting the reliance of brand name companies on "blockbuster" products, and noting also that this model may be dying as we reach the bottom of the "patent cliff").

28. Lasagna, *supra* note 1.

29. *See* discussion *infra* Part II.

30. The Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049, 2049–50 (1983) ("The Congress finds that . . . it is in the public interest to provide such changes and incentives for the development of orphan drugs.").

which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug."[31] Practically, this provision required drug sponsors to undertake an extensive economic analysis of development costs and expected revenues. Not only was this analysis time-consuming and costly, but also most sponsors were unwilling to reveal the internal financing information required by the analysis. Consequently, one of the major criticisms of the Orphan Drug Act as originally passed was its failure to define "rare disease" in a way that could be readily applied.[32]

Congress responded to these criticisms with a set of amendments passed in 1984.[33] After hearings considering "how [the] FDA and the pharmaceutical industry could ease the administrative burden of proving market conditions by economic data, and to make the process of applying for orphan drug designations easier,"[34] the Act was amended to add an alternative set of requirements for orphan drug designation. Subsequently, instead of showing through lengthy financial disclosures that the drug is not economically viable, the drug sponsor can obtain orphan drug designation by showing a basis for "concluding that the drug is for a disease or condition that is rare in the United States, including . . . (i) [t]he size and other known demographic characteristics of the patient population affected and the source of this information."[35] Additionally, the Act specifically defined "rare disease or condition" as a disease or condition that "affects fewer than 200,000 people in the United States."[36] However, for drugs that target a population exceeding 200,000 people, obtaining an orphan drug designation still requires detailed financial disclosures showing the drug is not economically viable.[37]

The Congressional findings from the 1983 Act explain that the purpose of the Act was to encourage the research and manufacture of drugs for the

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31. *Id.*

32. Martha J. Carter & Alan R. Bennett, *Developments in Orphan Drugs*, 44 FOOD DRUG COSM. L.J. 627, 627 (1989).

33. Pub. L. No. 98-551, 98 Stat. 2815, 2817 (1984).

34. David Duffield Rohde, *The Orphan Drug Act: An Engine of Innovation? At What Cost?,* 55 FOOD & DRUG L.J. 125, 129 (2000) (explaining the early history of Congressional hearings in much greater depth than the present discussion).

35. Orphan Drug Act, 21 C.F.R. § 316.10(8) & 316.20(8).

36. *Id.* at § 316.20(8)(i) & 316.20(8). This is the broadest definition of rare disease worldwide. *See infra* note 99.

37. *Id.* at § 316.10(8)(ii). I could find no examples of drugs approved under this section.

treatment of rare diseases and conditions that were not being developed because they were not economically viable.[38] Congress found:

> (4) because so few individuals are affected by any one rare disease or condition, a pharmaceutical company which develops an orphan drug may reasonably expect the drug to generate relatively small sales in comparison to the cost of developing the drug and consequently to incur a financial loss; [and]
>
> (5) there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the applicable Federal laws to reduce the costs of developing such drugs and to provide financial incentives to develop such drugs . . .[39]

The 1983 Act directly reflected this purpose by giving orphan drug designations only to drugs demonstrated to be not economically viable. However, when this method of obtaining orphan drug status proved too onerous, such that pharmaceutical companies were unwilling to undertake the research required to make the showing, the law changed. Now we use a numerical stand-in for the economically viable requirement: under 200,000 Americans affected.

While this change certainly made the incentives of the Act more enticing to pharmaceutical companies, it has also had some limitations. For example, some of the orphaned drugs that gained national attention prior to passage of the Act might still have become orphaned under the changes.[40] Additionally, the 1984 amendments have opened the door for drugs that treat orphan conditions and also have secondary indications for non-orphan conditions.[41] Pharmaceutical companies market and sell these "dual-purpose" drugs to a population larger than is typical for an orphan drug, while also benefiting from the streamlined and less expensive

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

39. *Id.*

40. Lasagna, *supra* note 1 (giving examples of two orphaned drugs which affected populations well in access of 200,000 people, but were orphaned because they were natural products ineligible for patenting). These sorts of drugs are often economically unviable apart from the exclusivity which the Orphan Drug Act can provide. I was unable to find any examples of drugs passed under 21 C.F.R. § 316.10(8)(ii), discussed *supra* note 37. Accordingly there is no authority suggesting that a drug can be claimed to be not economically viable simply because it is unpatentable.

41. See discussion of 'blockbuster' drugs, *infra* at Part III & *passim*. A blockbuster drug is one which generates annual sales in excess of $1 billion. Nafees Malik, *Has the Era of Blockbuster Drugs Come to an End?* 20(12) BIOPHARM INT'L (Dec. 1, 2007), http://www.biopharminternational.com/has-era-blockbuster-drugs-come-end.

process of FDA approval available under the Act.[42] Some critics argue that Congress's purpose in passing the Orphan Drug Act was to defray the costs of creating drugs that are not expected to be profitable, but that companies that take advantage of the Act's incentives while enjoying additional profits from the drug's secondary indication generate windfall profits, contrary to Congress' intention.[43]

D. Incentives

The Orphan Drug Act provides pharmaceutical developers with several incentives, including waiver of the over two-million-dollar new-drug fee, tax incentives, enhanced protection from generic competitors, a faster and less strenuous FDA review process, and, in some cases, grants. More than thirty years later, it remains unclear to what extent each of these provisions has contributed to the uptick in orphan drug production,[44] and, accordingly, Congress has been leery to alter the Act's incentives.[45]

The first and simplest incentive offered to pharmaceutical companies is a waiver of the human drug application fee.[46] This has become a substantial incentive, as the application fee filed with clinical investigation data is set to be $2,038,100 for the 2017 fiscal year.[47] This amount has been increasing rapidly. In 2006, the same application cost only

42. A drug indication is a purpose for which the FDA has approved the drug (also called "labeled indication"). *Approved drug uses,* PUBMED HEALTH (Aug. 20, 2015), http://www.ncbi.nlm.nih.gov/pubmedhealth/approved-drug-uses/. For the purposes of this note, "secondary indication" means that the indication was added *after* an indication for an orphan condition. Off-label use is when the drug is prescribed for a use other than the FDA approved indication.

43. *Id.* The term "windfall profits" typically means large and unexpected profits. In this case, there is some indication that the profits are not unexpected from the perspective of the pharmaceutical companies, but are an unanticipated result of the Act's incentive structure. *See infra* note 109 and accompanying text.

44. Lisa Larrimore Ouellette, *Patent Experimentalism*, 101 VA. L. REV. 65, 93 (2015) ("The number of new orphan drugs per year increased thirteen-fold, but empirical analyses have not disentangled the effects of the different incentives.").

45. *See* President Bush's pocket-veto of a series of amendments in 1990, explaining that the amendments would weaken the incentives at the heart of the Act by diluting the market exclusivity provisions. *Bush Pocket-Vetoes Orphan Drug Measure*, *in* CQ ALMANAC 1990, at 577–79 (46th ed., 1991), *available at* http://library.cqpress.com/cqalmanac/cqal90-1113412.

46. 21 U.S.C. § 379h(a)(1)(F) ("Exception for designated orphan drug or indication:

> A human drug application for a prescription drug product that has been designated as a drug for a rare disease or condition pursuant to section 360bb of this title shall not be subject to a fee under subparagraph (A), unless the human drug application includes an indication for other than a rare disease or condition.").

47. *Prescription Drug User Fee Act (PDUFA)*, U.S. FOOD & DRUG ADMIN. http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ (last updated Dec. 16, 2016).

$767,400.[48] Increases in orphan drug applications, which are exempt from the application fee and constituted nearly half of the new drugs approved in 2015, may be contributing to the rising costs.[49]

Second, the Act offers tax credits for up to 50% of qualified clinical testing expenses.[50] Critics note that this incentive is more helpful for well-established companies than for smaller groups of researchers, who might not incur sufficient tax liability to benefit from this provision.[51]

Third, the Act offers enhanced protection from generic competitors. Once an orphan drug application is filed, the FDA will not approve another application "for such drug for such disease or condition" for seven years,[52] granting the drug's sponsor complete market exclusivity during that time. In contrast, non-orphan drugs generally receive five years of exclusivity after approval. The exclusivity granted to non-orphan drugs protects only against applications for drugs containing the same active moiety.[53] However, the grant of exclusivity to orphan drugs is subject to two limitations: first, where the sponsor is unable to produce "sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug was designated,"[54] and second, where the new drug is more effective or safer than the drug granted exclusivity.[55] I was unable to find proof that either of these scenarios has ever occurred.

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48. Establishment of Prescription Drug User Fee Rates for Fiscal Year 2006, 70 Fed. Reg. 44106 (Aug. 1, 2005).

49. *Novel Drugs Summary 2015*, U.S. FOOD & DRUG ADMIN., http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm474696.htm (last updated Jan. 12, 2016) ("About 47% of the novel drugs approved in 2015 (21 of 45) were approved to treat rare or "orphan" diseases . . . .").

50. 26 U.S.C. § 45C(a) provides, generally, that "the credit determined under this section for the taxable year is an amount equal to 50 percent of the qualified clinical testing expenses for the taxable year." Further, (b)(1)(A) provides that "the term 'qualified clinical testing expenses' means the amounts which are paid or incurred by the taxpayer during the taxable year which would be described in subsection (b) of section 41 if such subsection were applied with the modifications set forth in subparagraph (B).".

51. *Impact of the Orphan Drug Tax Credit on Treatments for Rare Diseases,* BIOTECHNOLOGY INDUS. ORG. & NAT'L ORG. FOR RARE DISORDERS at ii (2015) ("[P]re-market companies without existing drug portfolios would see a smaller decline because they cannot use tax credits until they begin to have tax liability, often not until after their first drug is approved.").

52. 21 U.S.C. § 360cc(a)(2).

53. Renu Lal, *Patents and Exclusivity,* FDA/CDER SBIA CHRONICLES (May 19, 2015), http://www.fda.gov/downloads/drugs/developmentapprovalprocess/smallbusinessassistance/ucm447307.pdf. Active moiety means "[t]he molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance." 21 C.F.R. § 314.108(a) (2016).

54. 21 U.S.C. § 360cc(b)(1).

55. 21 C.F.R. § 316.3(14)(i) "except that if the subsequent drug can be shown to be clinically superior to the first drug, it will not be considered to be the same drug." *See also* 21 C.F.R. § 316.3(3):

Fourth, the Act offers a less strenuous and often faster FDA review process.[56] The FDA has acknowledged that when evaluating rare conditions, some flexibility is often required when evaluating evidence of effectiveness.[57] Because the affected population is small, sponsoring companies may be unable to conduct human studies on as many subjects,[58] and the FDA has explained that "about two-thirds of orphan drugs were approved with one adequate and well-controlled trial with supportive evidence" in comparison to the two or three trials required for mass market drug approval.[59]

Finally, the Act offers grants in some cases.[60] In 2016, the FDA awarded eighteen grants totaling $19 million dollars for the development of drugs intended to treat such rare conditions as sickle cell acute pain, HPV-related oropharyngeal cancer, and malignant glioma.[61] Since 1983, "the Orphan Products Grants Program has provided more than $350

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(3) Clinically superior means that a drug is shown to provide a significant therapeutic advantage over and above that provided by an approved drug (that is otherwise the same drug) in one or more of the following ways:

(i) Greater effectiveness than an approved drug (as assessed by effect on a clinically meaningful endpoint in adequate and well controlled clinical trials) . . .

(ii) Greater safety in a substantial portion of the target populations, for example, by the elimination of an ingredient or contaminant that is associated with relatively frequent adverse effects . . .

(iii) In unusual cases, where neither greater safety nor greater effectiveness has been shown, a demonstration that the drug otherwise makes a major contribution to patient care.

56. *Rare Diseases: Common Issues in Drug Development; Draft Guidance for Industry; Availability*, 80 Fed. Reg. 49246, 49246 (Aug. 17, 2015) ("FDA acknowledges that certain aspects of drug development that are feasible for common diseases may not be feasible for rare diseases. FDA regulations provide flexibility in applying regulatory standards . . . .").

57. *Id. See also* Frank J. Sasinowski, *FDA Rare Disease Patient Advocacy Day*, NAT'L ORG. FOR RARE DISORDERS (Mar. 1, 2012), http://www.fda.gov/downloads/ForIndustry/ Developing ProductsforRareDiseasesConditions/OOPDNewsArchive/UCM294773.pdf (Finding that 67% of orphan drug approvals between 1983 and June 30, 2010, excluding rare cancers, "resulted from some exercise of FDA flexibility in applying the statutory standard for evidence of effectiveness.").

58. In 2010, program size for orphan drug approvals ranged from 23 to 540 patients. Lawrence J. Lesko, *Introduction: Rare Diseases, Orphan Drugs*, OFFICE OF CLINICAL PHARMACOLOGY: FDA (Mar. 2, 2011), http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeeting Materials/ Drugs/AdvisoryCommitteeforPharmaceuticalScienceandClinicalPharmacology/UCM247635.pdf.

59. Sarah Jane Tribble & Sydney Lupkin, *Drugmakers Manipulate Orphan Drug Rules to Create Prized Monopolies*, KAISER HEALTH NEWS (Jan. 17, 2017), http://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/.

60. 21 U.S.C. § 360ee(c) ("For grants and contracts under subsection (a), there is authorized to be appropriated $30,000,000 for each of fiscal years 2013 through 2017.").

61. Press Release, FDA, FDA awards 18 grants to stimulate product development for rare diseases, (Sept. 21, 2015), http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ ucm463539.htm.

million to fund more than 570 new clinical studies and supported the marketing approval of more than 50 products."[62]

E. Proposed Amendments

Amendments to the Orphan Drug Act are proposed nearly every year. Early amendments were passed in 1984,[63] 1985,[64] and 1988.[65] Then, a 1990 amendment, which would have drastically reshaped the Act's incentives, was passed through both houses before being pocket-vetoed by President George H. W. Bush.[66] In a veto message, President Bush stated: "I believe we must not endanger the success of this program, which is due in large measure to the existence of the 'market exclusivity' provision in the Orphan Drug Act."[67] Since then, Congress has expanded some of the provisions of the Orphan Drug Act, increasing the availability of grant funding to its present amount of $30 million dollars annually[68] and providing priority review for the treatments of rare pediatric diseases.[69] Most recently as part of the 21st Century Cures Act, Congress clarified that grants for orphan conditions can be used to study the natural history of a rare disease as well as the development of therapies, and added an additional provision addressing genetically targeted drugs for rare diseases.[70] Nevertheless, these amendments have left the core of the Orphan Drug Act, including its incentive structure and definition of "orphan drug," unchanged since 1984.

Amendments that are not adopted largely fall into one of three categories: (1) amendments to address perceived abuses of the Act;[71] (2) amendments to further incentivize orphan drug research and enable

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62. *Id.*

63. The 1984 amendment primarily redefined "rare disease or condition." See discussion *supra* at Part I(C).

64. The 1985 amendment primarily extended marketing exclusivity, addressing problems where products were patentable, but expired just before or after marketing approval.

65. The 1988 amendment required orphan drug designation to be obtained before a New Drug Application, marketing approval, or Product License Application could be submitted.

66. *Bush Pocket-Vetoes Orphan Drug Measure*, *supra* note 45.

67. *Id.*

68. 21 U.S.C. § 360ee. This amount is currently set to expire at the end of 2017.

69. 21 U.S.C. § 360ff.

70. 21ST CENTURY CURES ACT, Pub. L. No. 114-255, 130 Stat. 1033 (2016) (amending 21 U.S.C. § 360ee and enacting 21 U.S.C. § 360ff–1). The new law in part defines "genetically targeted drug" as a drug "for the treatment of a rare disease or condition . . . . that is serious or life threatening."

71. *See, e.g.,* The Orphan Drug Program Improvement Act of 2001, H.R. 386, 107th Cong. (2001) (seeking to modify market exclusivity to only the characteristic or feature that rendered the drug clinically superior to a previously approved drug).

discovered treatments to reach patents faster;[72] or (3) amendments to clarify the relationship between the Orphan Drug Act and other laws.[73] It is the proposed amendments falling into the first category that are commonly spurred by national reports of injustice, and which I am characterizing as "reactionary changes."[74] Often, these proposed amendments are the product of public outrage at the next expensive new orphan drug. These criticisms began before the Act with a drug for a rare condition priced at $1,620 annually per patent.[75] Now the most expensive orphan drug commands a price of over $536,000 per patient per year,[76] the average price tag has risen to $111,820,[77] and drug pricing is constantly under media scrutiny.[78]

F. Additional Sticking Point: How is Success Measured?

There are many who consider the Orphan Drug Act a success because more than 400 new drugs and biological products targeted at rare diseases have come to market since its passage.[79] If the determining factor in success is greater research and development in the orphan drug area, then the fact that from 2008 to 2013, one-third of new drug approvals were for orphan drugs, suggests that the Act has been a success.[80]

The Act also has a number of critics who argue that many of the treatments coming to market under the Orphan Drug Act are not the types of treatments Congress meant to incentivize. These critics are concerned that the only orphan conditions targeted by pharmaceutical companies are

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72. *See, e.g.,* Unlocking Lifesaving Treatments for Rare-Diseases Act ("ULTRA") H.R. 3737, 112th Cong. (2011) (working to create an accelerated approval pathway for ultra-rare diseases).

73. *See, e.g.,* Preserving Access to Orphan Drugs Act of 2015, H.R. 3678, 114th Cong. (2015) ("[C]larifying the orphan drug exception to the annual fee on branded prescription pharmaceutical manufacturers and importers . . . .").

74. Consider the news sources, *supra* notes 1–4.

75. Lasagna, *supra* note 1, at 30–31 (giving the example of L-5HTP for Parkinsonism).

76. Marissa Piazzola, *Rx Nation: Top 5 Most Expensive Drugs in the U.S.*, FOXBUSINESS (June 8, 2015) http://www.foxbusiness.com/features/2015/06/08/rx-nation-top-5-most-expensive-drugs-in-us-per-patient-per-year.html (Soliris reportedly costs $536,629 per U.S. patient per year and treats a life-threatening condition that only affects 8,000 Americans. It is also used to treat a second ultra-rare and life-threatening disorder: atypical hemolytic uremic syndrome.).

77. Tribble & Lupkin, *supra* note 3.

78. *See, e.g., supra* notes 2–4.

79. America's BioPharmaceutical Research Companies, *supra* note 7, at 1.

80. *Id.* at 5. That percentage has continued to rise. In 2014, 41% of novel new drugs (17 of 41) were for rare diseases. Jonathan Goldsmith, *Another Tool Helping Developers Navigate the Difficult Road to Approval of Drugs for Rare Diseases*, FDAVOICE (Sept. 15, 2015) http://blogs.fda.gov/fdavoice/index.php/tag/orphan-drug-act/.

those predicted to yield a substantial profit.[81] In support, these critics cite the fact that less than 5% of rare diseases have a treatment, and most new orphan drug designations are targeted only at certain subsets of the rare disease population, like rare cancers.[82] Cancer treatments are known to command high prices and yield high profits.[83] Accordingly, critics believe the Act is doing too much to incentivize the creation of treatments so financially lucrative that no additional incentive was needed.

G. Modern Changes, or, the New Purpose of the Orphan Drug Act?

The number of conditions qualifying for orphan drug status is predicted to continue rising, as scientists identify the specific cells or genetic variations causing each individual's condition.[84] This has allowed pharmaceutical companies to divide more common conditions into smaller subgroups that in turn qualify for incentives under the Act. This is not a theoretical prediction of the future, but a projection based on the current status of the pharmaceutical industry. For example, in 2013, at least 21 different treatments for lymphoma were granted orphan drug designation, even though the condition affects approximately 700,000 people in the United States.[85] These treatments obtained orphan designation because they were directed to a particular subset of individuals with lymphoma.[86] Critics have called the practice of partitioning a condition into subsets "salami-slicing," and argue that allowing this sort of activity thwarts the

81. *Id.* Relatedly, these critics are concerned with perceived loopholes in the Act which enable what they call abuses. These loopholes include alternative indications or off-label use which allow 'Blockbuster' drugs to unnecessarily benefit from the Act's incentives, as well as 'salami slicing' problems, both of which are discussed *infra* at Part II.

82. Côté & Keating, *supra* note 17, at 1186 (five therapeutic classes account for 75% of the orphan drug market: oncology/cancer therapeutics, metabolic disorders, hematology, infectious diseases, and neurological disorders).

83. Carter & Bennett, *supra* note 32, at 631 (recognizing that the Act may over-incentivize production of treatments for rare cancers).

84. Note the 2003 completion of the Human Genome mapping project. Reardon, *supra* note 16. This area of study is called pharmoacogenomics. David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?* 31 AM. J. LAW & MED. 365, 365 (2005) (noting "Drug applicants will include true orphan drugs along with 'Trojan' applicants that seek to co-opt the benefits for drugs that should not qualify as orphans.").

85. Reardon, *supra* note 16, at 16 (noting that lymphoma affects nearly 700,000 people in the United States, but "has been sliced into several dozen subgroups," resulting in FDA grants of orphan-drug designations to specific lymphoma treatments at least 21 times).

86. *Id.* Critics complain that this sort of situation (1) prioritizes a treatment for a subset of those with the condition over a treatment for those with the condition as a whole, and (2) may incentivize later secondary indications or off-label use for all of the other individuals affected by the condition (meaning the original drug should not have qualified for the incentives of the Act at all).

real purpose of the Act.[87] In contrast, pharmaceutical companies point out that the use of pharmacogenetics (commonly termed "personalized medicine") allows them to create drugs that target inherited genetic markers and are not only more effective, but also less likely to cause adverse reactions.[88] Though the FDA requires "scientifically plausible evidence for the uniqueness of a disease," critics claim that this is not a high bar given recent scientific advances.[89]

Although we continue to see an increasing number of orphan drug designations, it is important to note that the incentives generated by the Act have not changed. In fact, repeated attempts at amendment have failed, indicating that the status quo is likely to remain.[90] Yet if the incentives have not changed, then why are so many new orphan drugs hitting the market? Critics have pointed to two possibilities: (1) certain orphan drugs are now economically viable to produce under the Act's provisions, and (2) it is increasingly difficult to improve upon treatments for more common diseases.

Pharmaceutical companies have seen that at least some treatments for orphan conditions are economically viable, and it now makes financial sense to pursue them. At least so far, insurance companies have been willing to pay the high prices pharmaceutical companies charge to recoup sunk costs.[91] Additionally, orphan drugs are often not a cure, but a treatment that patients must undertake for the rest of their lives. Over a thirty-year span, pharmaceutical companies have also developed a sense

87. *Id. See also* Loughnot, *supra* note 84, at 374 ("In the past, this salami slicing has been based on distinctions regarding medical classifications. Pharmacogenomics might allow drug sponsors to nudge salami slicing from the arena of medical judgment towards the arena of scientific fact."); Gary A. Pulsinelli, *The Orphan Drug Act: What's Right with It*, 15 SANTA CLARA HIGH TECH. L.J. 299, 315 (1999) ("If a company is successful with this approach, it may acquire multiple approvals for the same drug for treating what are essentially facets of the same disease and obtain market exclusivity for a drug that is not really an orphan. This process abuses the principles of the Act.").

88. America's BioPharmaceutical Research Companies, *supra* note 7, at 6; *Biopharmaceutical Research & Development*, *supra* note 18, at 3.

89. Reardon, *supra* note 16 (discussing what sorts of subgroups get a designation despite their differences from the extremely rare genetic diseases which spurred the creation of the Act in the first place). *See also* Orphan Drug Regulations, 78 Fed. Reg. 35117 (June 12, 2013) (codified at 21 C.F.R. 316) (discussing the FDA's definition of "orphan subset" as an alternative to the "medically plausible" language previously used and stating that the phrase "'medically plausible' has been misinterpreted by sponsors to mean any medically recognizable or clinically distinguishable subset of persons with a particular disease or condition . . . [which] if accepted by FDA, could result in artificially narrow subsets for the purpose of orphan-drug designation.").

90. *See* discussion of enacted and proposed amendments *infra* at I(C) & (E).

91. Tribble & Lupkin, *supra* note 3 (citing Dr. Steve Miller, chief medical officer for Express Scripts as stating: "We have very little negotiating power because the pharmaceutical company can set the price and we have to be a price acceptors.").

for which treatments are more likely to allow costs to be recovered. For example, as previously mentioned, cancer treatments command some of the highest prices among pharmaceuticals. There is also some evidence that companies favor treatments expected to have a profitable secondary indication. A recent study from John Hopkins University School of Medicine reports a pattern of pharmaceutical companies taking advantage of the incentives of the Orphan Drug Act, only to later market the drug for broader off-label use, resulting in large profits.[92] This study also supports critics who believe that the incentives of the Act are effectively different from what Congress intended because, while there have been no amendments, pharmaceutical companies have been better able to exploit weaknesses in the incentive structure of the Act.

Those well attuned to the business models of the pharmaceutical industry know that the twentieth century was full of "blockbuster drugs," but in the modern era it has become increasingly difficult for pharmaceutical companies to create improvements to already existing products for common diseases and conditions.[93] In contrast, in the orphan drug world, there are often no competing treatment options.[94] The orphan drug market is growing at almost double the rate of the overall prescription drug market, and orphan drugs have a median retail cost 13.8 times higher than non-orphan drugs.[95] Moreover, eight orphan drugs hit the blockbuster level in 2014,[96] and seven of the top ten best-selling drugs in 2015 had at least one orphan designation.[97] These realities suggests that pharmaceutical companies are increasingly incorporating orphan drugs into their business plans.

H. International Considerations

After the United States adopted the 1983 Orphan drug Act, Japan, Australia, the EU, and the UK passed similar acts.[98] While each country

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92. *'Orphan Drug' Loophole Needs Closing, Johns Hopkins Researchers Say,* JOHNS HOPKINS MED. (Nov. 19, 2015), http://www.hopkinsmedicine.org/news/media/releases/orphan_drug_loophole_needs_closing_johns_hopkins_researchers_say (interviewing the researchers who conducted the study: Michael G. Daniel et al., *The Orphan Drug Act: Restoring the Mission to Rare Diseases*, AM. J. CLIN. ONCOL. (Nov. 17, 2015) [Epub ahead of print]).

93. Cardenas-Navia, *supra* note 25.

94. *Id.* at 1317.

95. *Orphan Drug Report 2015*, EVALUATEPHARMA 6, 8 (Oct. 2015), http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD15.pdf.

96. *Id.* at 11.

97. Tribble & Lupkin, *supra* note 59.

98. Christopher McCabe, Karl Claxton & Aki Tsuchiya, *Orphan drugs and the NHS: should we value rarity?*, 331 BMJ 1016, 1017 (2005).

(or group of countries) passed its own particularized version of the Act,[99] each country focused on creating incentives for the production of treatments for rare conditions through limited market exclusivity, eased drug testing processes, and financial incentives. In recent years, however, differences in reimbursement policies for drug funding have resulted in dissimilar environments for pharmaceutical companies.[100] For example, in Europe, recent policies have increased uncertainty about which treatments will be reimbursed, particularly in countries where health care is primarily publicly financed.[101] In the United States, on the other hand, orphan drugs have become an increasingly large part of the pharmaceutical market.[102]

PART II: JUSTIFICATIONS

To determine the best course of action regarding the Orphan Drug Act going forward, it is necessary to look critically at when, and to what extent, the incentives of the Act can be justified. This Note draws on perspectives from the medical and legal communities to identify principles from which amendments to the Act may be evaluated. In Part III, commonly proposed amendments will be evaluated in light of these principles.

A. The Greatest Good Approach: A Classic Utilitarian Perspective

Classical utilitarianism advocates for "the greatest good for the greatest number."[103] But the question of how to apply this deceptively simple principle has produced a surprising amount of debate. Most of the debate circles around two questions: how do we define the "good" that we want to maximize, and how do we deal with minority needs and perspectives?

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99. Laws passed in each country vary in how they define "rare" condition, set terms of exclusivity, and whether they allow later review of orphan status. For example, while in the U.S. a rare condition affects 6.4 individuals per 10,000 and guaranteed market exclusivity is 7 years, in the EU a rare condition is one which affects less than 5 individuals per 10,000 and market exclusivity is 10 years. Drummond & Towse, *supra* note 2, at 335. The U.S. definition of "rare" is the most generous in the world, with Japan, Australia and the UK requiring a prevalence of 4, 1.1, and 0.18 individuals affected per 10,000 respectively. *Id.*

100. *See* Drummond & Towse, *supra* note 2, at 335.

101. *Id.*

102. Reardon, *supra* note 16 (noting that in 2013 more than one-third of all new drugs approved by the FDA were orphan designated drugs).

103. This phrase was coined by the founder of utilitarianism, Jeremy Bentham. *See* John Black, Nigar Hashimzade & Gareth Myles, *"utilitarianism"*, A DICTIONARY OF ECONOMICS, (3d ed.) http://oxfordindex.oup.com/view/10.1093/acref/9780199237043.013.3277 (last visited Jan. 20, 2017).

This note discusses utilitarianism as it applies to "public health" and contrasts that perspective with legal utilitarianism as characterized by the classic works of Jeremy Bentham and John Stuart Mill. The following discussion applies the utilitarian philosophy to answer two questions: (1) what does this philosophy say about the principles underlying the Orphan Drug Act, and (2) what should amendments to the Act achieve?

1. The Medical Utilitarian Perspective: Public Health

The Orphan Drug Act must first be understood in context as but one piece within the broad domain of public health. One of the most "influential contemporary definitions" of public health, proposed by The Institute of Medicine, is: "[p]ublic health is what we, as a society, do collectively to assure the conditions for people to be healthy."[104] The word "conditions" is of particular importance in this definition. Public health is primarily concerned with prevention, and envisions public conditions in which the public is sick less, spends less on healthcare, and is better prepared for natural disasters.[105] Typical public health policies include vaccinations, worker safety standards, child nutrition programs, and seatbelts.[106] Nevertheless, it is impossible to eliminate every threat to each individual's health,[107] and the goal is not to attempt to do so. Even though any one orphan condition is rare, orphan conditions afflict 10% of the total American population, a significant figure from a public health perspective.

Facilitating the availability of treatments for such a large portion of the population is consistent with the goal of "creating conditions for people to be healthy." However, those 10% are affected by thousands of different conditions, and creating individual treatments for each one requires extensive resources.[108] If the Orphan Drug Act enables treatments for only a small portion of these rare conditions, and at a high cost, it becomes harder to justify the preference for orphan drugs under the public health rationale. Justifying this preference becomes even more difficult if, as a

104. PUBLIC HEALTH LAW & ETHICS 2 (Lawrence O. Gostin ed., 2d ed. 2010).

105. *Fact Sheet: What is Public Health?*, AM. PUB. HEALTH ASS'N, http://apha.org/~/media/files/pdf/factsheets/whatisph.ashx. (last visited Jan. 20, 2017).

106. *What is Public Health?*, AM. PUB. HEALTH ASS'N, http://apha.org/what-is-public-health (last visited Jan. 20, 2017).

107. PUBLIC HEALTH LAW & ETHICS, *supra* note 104, at 3. "The IOM definition also makes clear that even the most organized and socially conscious society cannot guarantee complete physical and mental well-being.".

108. *See Frequently Asked Questions*, *supra* note 5. Some treatments may be approved for multiple rare conditions, but even added together these represent a small portion of the population.

number of sources suggest, the Act is effectively incentivizing only certain categories of rare conditions, such as rare cancers.[109]

i. Can the Traditional Role of Public Health be Applied to Orphan Conditions?

Public health policy is primarily concerned with conditions that affect the public as a whole. Thus, to apply the traditional framework of public health to the Orphan Drug Act, a statue necessarily targeted at individual small population groups, is unconventional Two main premises buttress the global health regime. First, there exist collective health goods that individuals cannot obtain acting alone and second, "collective entities (e.g., governments and communities) take responsibility for healthy populations."[110]

To apply these premises to the Orphan Drug Act, first we must ask whether treatments for orphan conditions can qualify as "collective goods." Generally, public health advocates use the term "collective goods" to refer to goods indiscriminately valued by everyone, like "environmental protection, hygiene and sanitation, clean air and surface water, uncontaminated food and drinking water . . . ."[111] On their own, individuals can only make so much progress towards reaching each of these health "goods," and it is only through a collective effort that they can be ultimately realized. Drugs for rare conditions are not indiscriminately valued by everyone, because they primarily benefit only those afflicted by the rare conditions. Nevertheless, they are a collective good to the extent that they are difficult to acquire without collective effort; an individual with a rare and untreatable condition cannot generally fund the needed research acting alone. The policy behind "collective health goods," that "there is a great deal that individuals cannot do to secure their health, and therefore these individuals need to organize and collaborate on building infrastructure and developing shared resources,"[112] applies squarely to orphan conditions. Shared resources and collaboration are the only means by which treatments can be developed, as the financial means and knowledge to do so is generally beyond the individuals affected.

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109. Carter & Bennett, *supra* note 32, at 631 (recognizing that the Act may over-incentivize production of treatments for rare cancers).

110. PUBLIC HEALTH LAW & ETHICS, *supra* note 104, at 3.

111. *Id.*

112. *Id.*

Second, we must ask whether the global health mandate that "collective entities" take responsibility for healthy populations applies to the health of those with rare conditions. Certainly those with rare conditions are a substantial part of the population at almost 1 in 10 Americans. Additionally, if public health is providing the conditions for people to be healthy, a world in which a higher proportion of diseases are treatable will certainly enable more people to be healthy. Under the U.S. Constitution, while you have a right to education, you do not have a comparable right to healthcare.[113] The Supreme Court has held that there is "no affirmative right to governmental aid, even where such aid may be necessary to secure life . . . ."[114] Nevertheless, Congress exercised its permissive ability to provide government funding and incentives for the treatment of rare diseases through the Orphan Drug Act, determining that it was in the public interest to do so.[115] Thus the question is: which public health principles should guide amendments to the Act?

ii. Why is the Act Controversial from a Public Health Perspective?

Unlike most health policies enacted by Congress, the Orphan Drug Act does not compel individuals or companies to act.[116] Consequently, the Orphan Drug Act is a relatively uncontroversial policy from a public health perspective.[117] However, critics suggest that the Act improperly distort the relative importance of different public health concerns, violating "[a] principle aim of public health [which] is to achieve the greatest health benefits for the greatest number of people."[118] By definition, the Act is focused only on the health benefits of small groups of people who might otherwise be overlooked. This criticism goes to the policy consideration already mentioned: incentives of the Act ought to

113. Dean M. Harris, CONTEMPORARY ISSUES IN HEALTHCARE LAW & ETHICS 261 (4th Ed. 2014).

114. DeShaney v. Winnebago Cnty Dep't of Soc. Serv., 489 U.S. 189, 196 (1989).

115. *See* Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049, 2049 (1983) (codified in scattered sections of 15, 21, 26, 35, 42 & 95 U.S.C) ("The Congress finds that. . . it is in the public interest to provide such changes and incentives for the development of orphan drugs.").

116. Compare e.g., seatbelt laws, vaccination laws, coverage requirements for insurers, worker safety laws, etc. These problems and many others are more likely to invoke due process concerns. *See generally*, Kathleen Hoke, *Due Process and Public Health*, NETWORK FOR PUB. HEALTH L., http://apha.org/~/media/files/pdf/factsheets/due_process_and_public_health_factsheet.ashx (last visited Jan. 20, 2017).

117. PUBLIC HEALTH LAW & ETHICS, *supra* note 104, at 10 (generally discussing the controversial public health policies which involve personal and economic liberties).

118. *Id.* at 14.

encourage the creation of treatments for as many individuals affected with orphan conditions as possible.

The Act is also criticized from a public health perspective because outcomes generated by the Act's provisions do not always align with the public health view of which values should be maximized for the common good. "[P]ublic health . . . draws from the traditions of consequentialism, which judges the rightness of an action by the consequences, effects, or outcomes that it produces."[119] For example, a proponent of public health might say that researchers should focus more attention and resources to developing treatments for life-threatening or seriously debilitating conditions, because such conditions generally create the greatest societal burden.[120] Alternatively, a proponent of public health might advocate for a calculation "maximizing health benefits in terms of a single index, combining life expectancy and health related quality of life, such as quality adjusted life years or disability adjusted life years[.]"[121] Such a calculation would ensure that the most individuals receive the most beneficial outcomes. While public health proponents will disagree as to what outcomes should ultimately be maximized, they nevertheless would agree that the choice of which treatments to pursue should not be based solely on economic considerations.

Accordingly, the public health perspective provides three guiding principles: the Act should incentivize the creation of treatments for a wide swath of those affected with orphan conditions, we should critically consider which outcomes are being maximized under the current incentives of the Act, and, generally, we should be aware that profit considerations might distort the ultimate effect of the Act.

2. The legal utilitarian perspective

Under the legal utilitarian approach, the question is not whether the Act creates utility,[122] but rather whether the current version of the Act creates

119. *Id.*

120. Drummond & Towse, *supra* note 2, at 335, 339 (discussing European law which applies only to rare diseases that are life-threatening or seriously debilitating).

121. C. A. Gericke, A. Riesberg & R. Busse, *Ethical Issues in Funding Orphan Drug Research and Development*, 31 J. MED. ETHICS 164 (2005) (giving examples of ways in which European countries have considered evaluating and comparing orphan conditions).

122. *See The History of Utilitarianism*, STANFORD ENCYCLOPEDIA OF PHILOSOPHY (Sep. 22, 2014), http://plato.stanford.edu/entries/utilitarianism-history/ (Noting Bentham's view of "the principle of utility as the standard of action on the part of governments. . . ."). At its core the Orphan Drug Act has the utilitarian purpose of promoting happiness through health for those whose conditions would be treated, as well as the friends and family of the patient. Moreover, the purpose of the

the most utility for the most people. This discussion identifies the principles that guide legal utilitarians in considering amendments to the Act.

First, it is necessary to define utility and to evaluate whether the Act creates utility. The classic utilitarian, Jeremy Bentham, proposed that utility means increasing pleasure and decreasing pain.[123] The Act increases happiness for those whose conditions are now treatable with no resulting unhappiness except, perhaps, to those who believe government could have better spent their tax dollars. Therefore, under Bentham's view, the Act creates utility. Whether it creates the most utility for the most people is less clear.

Though the Act creates utility, utilitarians may still criticize the Act for failing to maximize utility.[124] The utilitarian's criticisms take several forms. First, the Act tends to weigh the good of a few more highly than the good of many. This criticism does not refer to the fact that those with rare conditions are the only ones who directly benefit from the provisions of the Act. Instead, weighing the good of a few over the good of many is a criticism the Act's critics call "salami-slicing," or targeting a small subset of a larger group in order to obtain an orphan indication.[125] The legal utilitarian would argue that resources should go towards the entire group affected by the condition with few exceptions. For example, a utilitarian might not object to allocating funds to an affected population of limited size when treatment options already exist for that population but are not effective for a certain subset, or when the benefit of the new treatment is quantifiably greater for that subset.[126] Additionally, all else equal, the legal utilitarian would object to the Act's two-tiered path to obtaining orphan designation, where conditions that affect more than 200,000 Americans

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treatments is to reduce pain, including the patients pain caused by the condition, the pain of not having any hope of treatment, and sometimes the pain of visible deformities or lost abilities.

123. JEREMY BENTHAM, AN INTRODUCTION TO THE PRINCIPLES OF MORALS AND LEGISLATION Ch I (II) (1781), *available at* http://www.utilitarianism.com/jeremy-bentham/index.html ("By the principle of utility is meant that principle which approves or disapproves of every action whatsoever according to the tendency it appears to have to augment or diminish the happiness of the party whose interest is in question: or, what is the same thing in other words to promote or to oppose that happiness. I say of every action whatsoever, and therefore not only of every action of a private individual, but of every measure of government.").

124. For purposes of this section, I assume that the Orphan Drug Act and the incentives it creates are justified, and consider only this criticism.

125. Loughnot, *supra* note 84, at 366–67 (giving examples of ways which a subdividing diseases can result in exploitations of the Act's incentives).

126. In some cases, orphan drugs are prescribed more broadly for all of those affected by the rare condition. *Id.* at 371 (giving the example of Epogen, which was approved only for anemia associated with the orphan condition end-stage renal disease, but was then prescribed broadly off-label).

are subject to more stringent standards than those affecting less than 200,000 Americans, even though the latter has the potential to yield greater utility by affecting a larger population.[127] This was one of the consequences of the 1984 amendments.[128]

A second utilitarian criticism of the Act emerges from the broader definition of utility embraced by Bentham's student, John Stewart Mill. Bentham believed that no pleasure was inherently greater than another, putting base sensual pleasures on the same level as pleasures derived from accomplishments of skill, the arts, benevolence, or time spent with friends and family.[129] His student expanded the definition of utility to encompass a broader range of pleasures.[130] Mill further posited that pleasures can naturally be differentiated and stated: "[i]t is quite compatible with the principle of utility to recognize the fact, that some kinds of pleasure are more desirable and more valuable than others."[131] Mill argued that those pleasures we must wait longer to realize are more valuable than others, including "the mere pleasures of the moment."[132]

Accordingly, the Act may be criticized for failing to differentiate between greater and lesser pleasures. In other words, all rare conditions are incentivized equally, regardless of their severity or the ability of the treatment to relieve pain.[133] The problem of how to differentiate between pleasures is generally one which legal utilitarians, Mill included, have failed to address in a satisfactory manner.[134] In fact, Mill's own method was one of the hardest to apply, as it appears that he would have required a poll of those who have experienced both pleasures, stating that we can easily decide between "two pleasures, if there be one to which all or almost all who have experience of both give a decided preference, irrespective of any feeling of moral obligation to prefer it, that is the more desirable pleasure."[135] The Act is an example of how difficult applying

127. In reality other concerns, such as the severity of the condition, would also be considered.

128. *See supra* Part I(C).

129. *Id.* at Ch V(II-III) ("Bentham, recall, had held that there were no qualitative differences between pleasures, only quantitative ones.").

130. JOHN STUART MILL, UTILITARIANISM Ch. 2 (1863), *available at* http://www.utilitarianism.com/mill2.htm.

131. *Id.*

132. *Id.*

133. Moreover, the correct answer for Mill was not to simply value the condition which affect the most people more, as he stated: ("It would be absurd that while, in estimating all other things, quality is considered as well as quantity, the estimation of pleasures should be supposed to depend on quantity alone."). *Id.*

134. Bhardwaj, Kiran, *Higher and Lower Pleasures and our Moral Psychology,* 1 RES COGITANS 126, 127 (2010).

135. *Id.*

Mill's proposed method can be, as it is likely that no human has ever experienced the two rare conditions we wish to compare. A modern variation on Mill's idea of comparing pleasures is the use of medical indexes that differentiate between conditions based on life expectancy, debilitating effects, and pain.[136] By using such indices, a legal utilitarian can consider the quality of the utility created by new orphan drugs in addition to the quantity of individuals affected.

Legal utilitarians would also be concerned that so few changes have been made to the Act, despite many proposals. Broadly stated, utilitarianism is a form of consequentialism, which is largely concerned with the results of an action.[137] Accordingly, utilitarians are willing to consider the outcomes of the Act and enact changes which create greater utility given Congress's goals. This is specifically demonstrated by Bentham's original view of utilitarianism, which directly tied whether an act is right or wrong to the results of the act.[138] Thus, the major changes in the climate of the pharmaceutical industry since 1983 are good cause to reconsider whether the current results of the Act are truly creating the greatest utility.[139]

Accordingly, the legal utilitarian viewpoint provides three guiding principles: the Act should weigh the good of a few over the good of many only if there is a sound reason for doing so, the Act should differentiate between greater and lesser pleasures, and Congress should readily consider amendments in light of a changing pharmaceutical climate.

B. Individual Rights Based Approaches

Perspectives focused on individual rights, in contrast to the utilitarian approaches just discussed, prioritize individual needs. The individual rights based analog to a public health perspective is medical ethics, which prioritizes the personal health of individuals. However, it is difficult to identify a personal legal analog to utilitarianism. Generally, the law consists of rights, obligations, and duties, but under this Act, action is

136. Gericke, Riesberg & Busse, *supra* note 121.

137. *The History of Utilitarianism*, *supra* note 122.

138. BENTHAM, *supra* note 123 at Ch I (II) ("Nature has placed mankind under the governance of two sovereign masters, *pain* and *pleasure*. It is for them alone to point out what we ought to do, as well as to determine what we shall do. On the one hand the standard of right and wrong, on the other the chain of causes and effects, are fastened to their throne.").

139. *Id.*

permissive, not mandated.[140] The Act places no obligation on any private actor to do anything, nor does it give rights to anyone afflicted with an orphan disease or condition. Nevertheless, the exclusivity granted under the Act is comparable to the exclusivity given to inventors under patent law, and the justifications for granting market exclusivity for new drugs mirrors many of the justifications for giving exclusive patent rights to inventors.[141] Accordingly, this note considers individual rights in the context of medical ethics and intellectual property to answer the questions: (1) what do this philosophies say about the principles underlying the Orphan Drug Act, and (2) what should amendments to the Act achieve?

1. The Medical Ethics Approach

Three concepts in medical ethics have particular relevance when considering the policies of the Orphan Drug Act: beneficence, non-abandonment, and scientific progress. Beneficence broadly includes "all forms of action intended to benefit other persons [or] to contribute to their welfare." Embedded within this is the requirement that "agents take positive steps to help others, not merely to refrain from harmful acts, or to treat individuals autonomously."[142] The Act, which encourages the production of treatments to help those who cannot help themselves, is thus a prime example of beneficence. Acclaimed biomedical ethics philosophers Beauchamp and Childress, advocate a form of beneficence where "agents balance benefits, risks, and costs."[143] In other words, Beauchamp and Childress recognize that there are limits to how we improve welfare. In terms of the Act, this means that production of a drug that may save a life might come before one that merely improves a person's standard of living given the same costs.[144]

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140. PUBLIC HEALTH LAW & ETHICS, *supra* note 104, at 10. ("Rather than using ethical discourse. . . the law uses the language of duties, powers, and rights.").

141. Interestingly, the utilitarian theories discussed above have commonly been applied to the patent system generally. *See* Emma Perot, *Maximizing Utility: Applying Utilitarian Theory to International Patent Law*, 5 KING'S STUDENT L. REV. 58, 59 (2014) ("It will be argued that utilitarianism, despite its criticisms, is the most suitable ethical theory to apply [to International Patent Law]. . . ."). *See also* David S. Olson, *Taking the Utilitarian Basis for Patent Law Seriously: The Case for Restricting Patentable Subject Matter*, 82 TEMP. L. REV. 181, 182-183 (2009); Patrick Croskery, *Institutional Utilitarianism and Intellectual Property*, 68 CHI.-KENT L. REV. 631 (1992–93).

142. Gericke, Riesberg & Busse, *supra* note 121, at 166.

143. *Id.*

144. While in the United States this sort of balancing test has never truly been applied in any context, some guidance can be taken from the policies of countries with a comparable Orphan Drug Act, but where government insurance is common and the government has decided for financial reasons to not cover some of the incentivized orphan drugs. *See* D.A. Hughes, B. Tunnage & S.T. Yeo, *Drugs*

Non-abandonment is an idea originally proposed by Landman and Henley, and states that individuals with a need for highly specialized medical care should not be abandoned when creating policies for resource allocation.[145] At its heart, the Act is a policy to "counteract distributive injustice caused by market incentives."[146] Proponents of non-abandonment justify the theory through "caring externalities," or the idea that "individuals derive utility from the satisfaction of providing help to those in need."[147] There is also some evidence that the public generally agrees with this policy, though not when the money could more cost-effectively improve the health of a larger number of people.[148]

Scientific advancement is the idea that research into rare diseases is important because it develops the overall knowledge base of researchers.[149] By funding medical research now, we are able to provide hope that in the future all rare conditions will have a treatment.[150] However, reaching this goal will take much longer if parties do not share research, because competing groups will duplicate the same research, wasting time and money. Currently, collaboration efforts are primarily headed by the Genetic and Rare Diseases Information Center, a department under the National Institute of Health's National Center for Advancing Translational Sciences.[151]

Accordingly, the three guiding principles from an individualistic medical perspective are: while we will take active positive steps to help those with rare conditions, we may value the pursuit of some treatments over the pursuit of others because of costs, benefits, and risks; under the policy of non-abandonment, we should seek to pursue treatments for untreatable conditions over those which are simply rare; and in the interest

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for Exceptionally Rare Diseases: Do They Deserve Special Status for Funding?, 98 Q. J. Med. 829, 830 (2005).

145. Gericke, Riesberg & Busse, *supra* note 121, at 166.

146. *Id.*

147. *Id.*

148. Hughes, Tunnage & Yeo, *supra* note 144, at 833. *See also* Drummond & Towse, *supra* note 2, at 335, 337 (surveys in Europe indicating the publics opinion that individuals have a right to treatment, regardless of the rarity of their condition, but also noting that in some surveys there was a lack of support for a special funding status for rare disease treatments).

149. Gericke, Riesberg & Busse, *supra* note 121, at 166 ("Funding medical science in general has been considered as fulfilling a moral obligation of beneficence for existing patients who are given hope that treatments might be developed to cure them, and as a societal commitment to provide potential benefits for future generations.").

150. *Id.*

151. *See About GARD*, UNITED STATES DEPARTMENT OF HEALTH & HUMAN SERVICES, https://rarediseases.info.nih.gov/ (last visited Feb. 6, 2015).

of scientific discovery we will create policies that encourage the collaborative sharing of information regarding rare conditions.

2. The legal approach

The Orphan Drug Act provides, among other incentives, seven years of exclusivity, giving it some similarities to patent law.[152] Through patents, an inventor receives limited market exclusivity in exchange for revealing the secrets of her invention in a publicly available patent application.[153] The theory is that absent the right to exclude, the inventor could not recoup sunk costs, and therefore would lack economic incentive to invent,[154] or, if she did create, she might attempt to keep the knowledge of her discovery a secret to prevent competition.[155] To determine whether exclusivity incentives should be altered, Congress should consider whether "there is a market failure present." In other words, it is important to determine, whether absent the Orphan Drug Act, too little innovation would occur because of economic considerations.[156]

To make this determination, three questions are relevant: (1) "Would this type of innovation occur at sufficient levels without a patent grant? (2) Would granting a patent right for this type of innovation cause more loss to society than gain?" and "(3) If society would not benefit from granting patentability to the particular type of innovation, can sufficiently clear lines be drawn between this subject matter and other subject matter that does need the protection of patentability?"[157] These three questions can be applied to the Orphan Drug Act in order to determine what guiding principles patent law provides for considering amendments to the Act.

When the Act was passed, Congress addressed the first question: whether anyone would create orphan drugs absent the Act's incentives. Congress stated, "because so few individuals are affected by any one rare disease or condition . . . there is reason to believe that some promising orphan drugs will not be developed unless changes are made in the

152. Patent law grants inventors exclusive rights to make, use, offer to sell, or sell their patented invention during the term of the patent, which is currently 20 years from the date the patent application was filed. 35 U.S.C. § 271(a); 35 U.S.C. 154(a)(2).

153. Olson, *supra* note 141.

154. *Id.* at 182–83.

155. In the pharmaceutical context, regulations and required FDA disclosures make keeping aspects of the drug's composition a secret practically impossible. Compare, for example, the secret formula of Coca-Cola®.

156. Olson, *supra* note 141 at 184.

157. *Id.*

applicable Federal laws . . . ."[158] News reports and literature published before the Act's implementation further support these statements.[159] The principle established from this first question is that, to the extent possible, we should incentivize the creation of only drugs for rare diseases that would not be developed in the absence of the Act.

The second question, whether granting exclusivity for this type of innovation causes more loss to society than gain, is much harder to apply to the unique case of the Orphan Drug Act. There is no clear loss to society when exclusivity is given in exchange for research and development of a treatment for an orphan condition. In the patent arena, one of the concerns is that the exclusivity provided by patent law will allow prices to go unchecked, which may then place a treatment beyond the price point of some consumers.[160] At least in the United States, orphan drugs have been accessible even to those who cannot afford them through the intervention of non-profits and the benevolence of pharmaceutical companies who often give the drug away for free to those who cannot afford it.[161]

The third question, whether sufficiently clear lines can be drawn between this subject matter and other subject matter that does need the protection of patentability, is particularly relevant. Even if developing treatments for certain conditions should be incentivized, but the treatment of other conditions should not be, the distinction is irrelevant if we are unable to draw a clear line between the two. In the context of the Act, the cost of excluding conditions that are truly not economical to produce otherwise is high. More than 95% of rare conditions have no treatment, and without incentives, treatments for these conditions are unlikely to be developed. This possibility suggests that where a clear line cannot be drawn, the tendency should be towards over-inclusiveness.

Thus a comparison to patent law reveals the following guiding principles: incentives should be limited to those treatments which would not otherwise be developed, but since that distinction may not be clear, we should be careful to draw either a clear line or an over-encompassing one.

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

159. *See, e.g. Lasagna,* supra note 1.

160. This is a concern when developing countries are involved, and the benefit to the pharmaceutical company must be balanced with the health value achieved as a function of which how many of the affected individuals can financially access the treatment. *See* Perot, *supra* note 141, at 68.

161. Suzanne Shelley, *The Business of Orphan Drugs is Booming,* PHARMACEUTICAL COMMERCE (Aug. 26, 2015), http://pharmaceuticalcommerce.com/brand-marketing-communications/ the-business-of-orphan-drugs-is-booming/ (discussing Patient Assistance Programs (PAPs) which allow patients access to free or low cost medications).

III. PROBLEMS AND PROPOSALS

The Orphan Drug Act has been criticized from many perspectives. While some of those criticisms are intrinsic to the idea of providing large financial incentives to research conditions affecting a small number of individuals, some may be remedied by amending the incentive structure of the Act. The following is an example of how the previous discussion of utilitarian and individual rights perspectives in the medical and legal communities might guide consideration of the most commonly proposed change. The hope is that through this example, other common criticisms, such as the existence of a "blockbuster" loophole, and the potential for "salami-slicing," will also be discussed in terms of guiding principles from different relevant perspectives.

A. Redefining Orphan Condition

The most common proposed amendment to the Orphan Drug Act is a definition of orphan condition that encompasses more than rarity.[162] Advocates for this type of amendment believe the core purpose of the Act is to encourage research and development of drugs *that would not otherwise be created*.[163] They argue that while the defining feature of an "orphan disease" is rarity, there are strong policy reasons for adding additional criteria such as severity, other existing therapy options, and potential for improved life quality.[164]

There are important historical reasons for why this proposed change has been unable to gain traction. In the 1984 Amendments, Congress implicitly rejected the claim that the Orphan Drug Act was intended to stimulate only the production of drugs not economically viable.[165] Originally, the Act applied only to drugs expected to be economically unviable,[166] but in 1984 Congress amended the Act, allowing proof that the orphan condition affects less than 200,000 Americans as a stand-in.[167] At the very least, Congress found that the extensive financial data required

162. *See e.g.* Reardon, *supra* note 16; Côté & Keating, *supra* at 17; Carter & Bennett, *supra* note 32.

163. Gericke, Riesberg & Busse, *supra* note 121.

164. *Id.*

165. See discussion *supra* at Part I(C).

166. The Orphan Drug Act, Pub. L. No. 97-414, 96 Stat. 2049 (1983) ("Rare disease or condition" was defined as "any disease or condition which occurs so infrequently in the United States that there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug.").

167. Pub. L. No. 98-551, 98 Stat. 2815, 2817 (1984).

to evaluate economic viability was too great of a deterrence to the development of needed treatments for rare conditions.

However, almost every guiding principle favors an amendment to the definition of "orphan drug." From the legal utilitarian viewpoint, we understand that in light of the rapidly changing pharmaceutical climate, evaluating whether the Act creates the most utility means considering whether the Act is incentivizing the production of new treatments as originally intended. Public health principles also weigh in favor of amendment because under the current Act, all "rare" conditions are weighted equally though studies suggest that pharmaceutical companies are actively pursuing only limited subsets of rare treatments. The guiding principles underlying three of the four perspectives suggest that differentiation based on more than rarity is justified, because quality concerns should be considered as well as quantity, the wrong outcomes are being maximized, or because of a cost, benefit, and risk analysis.

Weighing against an amendment to the definition of "orphan drug" is the concern that a new definition would exclude rare conditions that are not economically viable to produce apart from the incentives of the Act. This concern is reflected by the guiding principle that if a clear line cannot be drawn, an over-inclusive line should be used instead. Further, while the guiding policies considered suggest that the definition of "orphan drug" could be amended to better conform with the intention of the Act, they do not consider the potential consequences of disrupting the stability of the Act over the last thirty years.

IV. CONCLUSION

For over thirty years, The Orphan Drug Act has represented hope to millions of Americans, and incentivized the discovery and development of treatments for rare diseases. Despite major advancements in the pharmacological industry and nearly yearly calls for amendment, however, the core incentive structure of the Act has remained unchanged since 1984. Critics have demonstrated that the incentive structure of the Act has encouraged research into certain categories of rare conditions over others based on economic considerations, rather than considerations of need or condition severity. Further, recent data has suggested that long-discussed "loopholes" in the Act have resulted in "blockbuster orphans" and "salami-slicing" conditions that take advantage of the incentive structure for conditions affecting more than 200,000 Americans. I have proposed that part of the reason that proposed changes to the Act have been unsuccessful is that the proposed changes are reactionary—concerned

primarily with alleviating high-profile perceived injustices in the application of the Act's incentives. Alternatively, I have developed a series of eleven guiding principles from an examination of four normative stances in the legal and medical community, and have demonstrated that these principles can be used to weigh proposed amendments. It is time to fix the Orphan Drug Act, and give *all* thirty million Americans affected with rare conditions hope.