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THE CANCER CURSE: REGULATORY FAILURE BY  
SUCCESS

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*Since the turn of the millennium, a series of regulatory decisions—unrelated in time and design—has shifted the focus of the pharmaceutical industry toward cancer research and treatment. Regulation, of course, is designed to drive public and private behavior, but the sum of these regulatory actions is driving behavior well beyond governmental design. This phenomenon represents a peculiar form of regulatory failure that cannot be sufficiently explained without contemplating a new form of regulatory failure—failure by success.*

*As with any great epic tale, the modern saga is full of celebrities and drama, framed by truly heart-wrenching stories. However, with 89 percent of cancer deaths occurring in those older than 55 and the majority of deaths in those over age 72, this concentration of resources necessarily implicates agonizing and critical social policy decisions, ones that have remained entirely unconsidered.*

*This article examines the regulatory history that led to this shift, ferreting out and connecting the various components for the first time. It explains the way in which this cancer curse falls outside traditional definitions of regulatory failure and should be categorized, instead, as regulatory failure by success. In addition, the article examines selected advantages and disadvantages of unintended regulatory success, along with normative questions regarding whether the cancer moonshot, as it has unfolded, is a desirable goal. In short, when engaging in a*

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*moonshot, it is best to do so with open eyes, given that flying blind is a marvelous way to crash and burn.*

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## I. INTRODUCTION

Since the turn of the millennium, a series of regulatory decisions—unrelated in time and design—has shifted the focus of the pharmaceutical industry toward cancer research and treatment. One can think of this societal focus as a “moonshot” that harkens back to President John F. Kennedy’s pledge to land a man on the moon, in which extraordinary energy and resources are concentrated in pursuit of a single, difficult challenge.

<sup>1</sup>Curiously, these cancer efforts seem to be unintended, or at least not intended in the coordinated, concentrated manner in which they are playing out. For the most part, the programs aimed at cancer have been ad hoc and spread across multiple decades, and they have shifted industry behavior well beyond the stated intent. Other regulations were not at all designed to shift industry behavior in the direction of cancer, and yet they have had such an effect. Driving behavior in one direction inevitably prevents it from taking

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<sup>1</sup> See Alex Davies, *Why “Moon Shot” Has No Place in the 21st Century*, WIRED MAGAZINE (July 19, 2019), <https://www.wired.com/story/apollo-11-moonshot-21st-century/?verso=true>.

other directions, given limitations on time and resources. One cannot drive south at the same time as driving north, just as one cannot invest as many resources into the development of new antibiotics or birth control methods if the predominant focus is on cancer treatment.

Regulation, of course, is designed to drive public and private behavior. With cancer, however, regulation appears to be strongly influencing behavior in an unintended manner. One should think of this circumstance as a peculiar form of regulatory failure, that is, failure by regulatory success. In other words, regulatory efforts have exerted a powerful impact, and yet the combined magnitude and direction were unintended.

Failure by regulatory success is an important form of regulatory failure that is entirely unexplored in the literature. Extensive literature exists in both the legal and economic spheres on how government interference to correct perceived market failures can lead to greater inefficiency,<sup>2</sup> usually analyzing the underlying rationale and potential remedies within the context of a specific industry.<sup>3</sup> While there is sparse literature on generalized causes of regulatory failure (apart from works examining the political, bureaucratic, and administrative landscape that hinders effective functioning of regulatory agencies),<sup>4</sup> prior literature on regulation and regulatory reform points to three commonly identified forms of

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<sup>2</sup> For legal scholarship on government failure, see, e.g., Stephen Breyer, *Analyzing Regulatory Failure: Mismatches, Less Restrictive Alternatives, and Reform*, 92 HARV. L. REV. 547 (1979); Paul S. Dempsey, *Market Failure and Regulatory Failure as Catalysts for Political Change: The Choice between Imperfect Regulation and Imperfect Competition*, 46 WASH. & LEE L. REV. 1 (1989); Barak Orbach, *What is Government Failure*, 30 YALE J. REG. ONLINE 44 (2012). For economic literature on government failure, see, e.g., Mrinal Datta-Chaudhuri, *Market Failure and Government Failure*, 4 J. OF ECON. PERSP. 25 (1990); Clifford Winston, GOVERNMENT FAILURE VERSUS MARKET FAILURE (2006); William R. Keech & Michael C. Munger, *The Anatomy of Government Failure*, 164 PUB. CHOICE 1 (2015).

<sup>3</sup> See, e.g., Stephen Breyer & Paul W. MacAvoy, *The Natural Gas Shortage and the Regulation of Natural Gas Producers*, 86 HARV. L. REV. 941 (1973) (arguing that regulatory policies pursued by the Federal Power Commission in the natural gas industry led to regulatory failure in the form of a shortage); Howard Latin, *Regulatory Failure, Administrative Incentives, and the New Clean Air Act*, 21 ENVTL. L. 1647 (1991) (commenting on the failure of environmental protection programs to achieve their intended regulatory purposes); Kristina P. Doan, *No Child Left Behind Waivers: A Lesson in Federal Flexibility or Regulatory Failure*, 60 ADMIN. L. REV. 211 (2008) (arguing that the granting of waivers for provisions of the No Child Left Behind Act constitutes a regulatory failure).

<sup>4</sup> See, e.g., Richard B. Stewart, *The Reformation of American Administrative Law*, 88 HARV. L. REV. 1667 (1975); JAMES M. LANDIS, REPORT ON REGULATORY AGENCIES TO THE PRESIDENT-ELECT (1960); MARVER H. BERNSTEIN, REGULATING BUSINESS BY INDEPENDENT COMMISSION (1955).

failure: regulatory capture,<sup>5</sup> ineffective design,<sup>6</sup> and regulatory arbitrage.<sup>7</sup> These are by no means exhaustive in accounting for the various causes contributing to regulatory failure, but they serve as the focal points of current scholarship and theoretical framing. This article argues, however, that the regulatory failure underlying the cancer shift does not fit within any of these categories or others that currently exist. There may well be aspects of regulatory capture, ineffective design, and regulatory arbitrage at play within specific regulatory legislation, but the distinctiveness of the cancer phenomenon means that it cannot be sufficiently explained without introducing and exploring a new form of regulatory failure.

Part I of this article traces the history of the realignment toward cancer research and treatment, examining manifestations of this shift. Part II explores the regulatory pathways that have led to or accelerated this movement. These include what the article calls

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<sup>5.</sup> See, e.g., George J. Stigler, *The Theory of Economic Regulation*, 2 BELL J. ECON. & MGMT. SCI. 3 (1971) (introducing the concept of regulatory capture and arguing that “as a rule, regulation is acquired by the industry and is designed and operated primarily for its benefit”); Michael A. Livermore & Richard L. Revesz, *Regulatory Review, Capture, and Agency Inaction*, 101 GEO. L.J. 1337 (2013) (defining regulatory capture as “situations where organized interest groups successfully act to vindicate their goals through government policy at the expense of the public interest”); Sidney A. Shapiro, *The Complexity of Regulatory Capture: Diagnosis, Causality, and Remediation*, 17 ROGER WILLIAMS U. L. REV. 221 (2012) (describing regulatory capture, its causes, and potential solutions); Stewart L. Brown, *Mutual Funds and the Regulatory Capture of the SEC*, 19 U. PA. J. BUS. L. 701 (2017) (describing how the investment management industry is influencing the SEC to maximize profits).

<sup>6.</sup> See, e.g., C. Scott Hemphill, *Paying for Delay: Pharmaceutical Patent Settlement as a Regulatory Design Problem*, 81 N.Y.U. L. REV. 1553 (2006) (examining pharmaceutical patent settlements as a regulatory design problem); Michael J. Bean, *Overcoming Unintended Consequences of Endangered Species Regulation*, 38 IDAHO L. REV. 409 (2002) (illustrating regulatory failure caused by insufficient regulatory design for endangered species). See also Robert E. Litan & Hal J. Singer, *Unintended Consequences of Net Neutrality Regulation*, 5 J. ON TELECOMM. & HIGH TECH. L. 533 (2007) (arguing that there is “much investment at stake in designing the optimal regulatory design framework” for the U.S. broadband industry); Rolf H. Weber et al., *Addressing Systemic Risk: Financial Regulatory Design*, 49 TEX. INT’L L.J. 149 (2014) (describing key areas of consideration when designing financial regulation).

<sup>7.</sup> See, e.g., Victor Fleischer, *Regulatory Arbitrage*, 89 TEX. L. REV. 227 (2010) (defining regulatory arbitrage as a “technique used to avoid taxes, accounting rules, securities disclosure, and other regulatory costs . . . [and exploit] the gap between the economic substance of a transaction and its legal or regulatory treatment”); Kristelia A. Garcia, *Copyright Arbitrage*, 107 CAL. L. REV. 199 (2019) (describing regulatory arbitrage in copyright); Frank Partnoy, *Financial Derivatives and the Costs of Regulatory Arbitrage*, 22 J. CORP. L. 211 (1997) (describing regulatory arbitrage in finance); Rob Frieden, *Regulatory Arbitrage Strategies and Tactics in Telecommunications*, 5 N.C. J.L. & TECH. 227 (2004) (describing regulatory arbitrage in telecommunications); Dan L. Burk, *Perverse Innovation*, 58 WM. & MARY L. REV. 1 (2016) (characterizing regulatory arbitrage as either ontological (“relabeling an activity rather than . . . redesigning or physically altering a product”), technological (circumventing regulation through the “implementation of new procedures, new expertise, and perhaps even new apparatus”), or both).

“positive policies,” which consist of regulatory initiatives that encourage the research and development of cancer therapeutics over other types of drugs. Positive policies include: 1) variations in clinical trial requirements between cancer drugs and other drugs; 2) regulatory property rights and accelerated approval programs such as Orphan Drug and Breakthrough Therapy designations; 3) variations between approvals for lower-priced copies of biologics (cancer drugs are frequently biologics) and lower-priced copies of nonbiologic drugs; and 4) pricing and reimbursement models that favor strategic behavior for drugs such as cancer therapeutics. Relevant regulatory pathways also encompass a lack of “negative policies,” that is, the absence of certain regulatory restraints that exist in various systems outside the United States. These include: 1) requirements that new drugs with new protections show certain levels of superiority or satisfy cost-effectiveness analyses; and 2) coordinated buying systems that reduce strategic behaviors. Part II demonstrates that the effects of these policies, both individually and combined, largely are either unintended or far exceed the drafters’ design. The article will refer to the total effects as the “cancer curse.”

Part III of the article explains the way in which the cancer curse falls outside traditional definitions of regulatory failure and should be categorized, instead, as regulatory failure by success. This part then explores the phenomenon of regulatory failure by success, both in general and in the specific context of cancer. In particular, what are the pros and cons of unintended regulatory success; what are the pros and cons of opacity; and are existing, unintended regulations leading to the desired result? For example, although cancer therapies have achieved important successes for individual patients and certain forms of cancer—such as breast cancer and Hodgkins lymphoma—median improvement in overall survival for new cancer therapies averages as little as 3.43 months.<sup>8</sup>

Part III assumes that society wishes to focus its resources on a cancer moonshot, examining the question from the perspective of whether the accidental byproducts of regulation are efficient and effective. In contrast, Part IV of the article briefly explores, from a normative perspective, whether society should focus its efforts in this manner. It is a tough question indeed. No budget is endless, and no healthcare system can engage in a cancer moonshot without diverting energy from other health goals. With 89 percent of cancer deaths occurring in those older than 55, and the majority of deaths in those over age 72, allocation of resources necessarily involves agonizing decisions.<sup>9</sup> One must contemplate the costs and benefits

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<sup>8</sup> See Sebastian Salas-Vega et al., *Assessment of Overall Survival, Quality of Life, and Safety Benefits Associated with New Cancer Medicines*, 3 JAMA Oncol., 382, 382–90 (2017).

<sup>9</sup> See SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) PROGRAM, NAT’L INSTS. OF HEALTH, CANCER STAT FACTS: CANCER OF ANY SITE (2019),

of focusing on a disease state associated so strongly with age, as well as the costs and benefits of focusing on life-threatening conditions at all rather than, for example, preventing a different disease state that might seriously impact health or mobility. The article sets these questions out in clear terms, not because framing such questions necessarily points the way, but because choices do not improve when we hide them. Shrouding one's legal choices merely "provide[s] camouflage for the failure to resolve issues or to resolve them in a rational manner."<sup>10</sup>

### A. *The Cancer Shift*

Since the turn of the millennium, the pharmaceutical industry in the United States has shifted decidedly toward cancer therapeutics. The shift is manifest both in spending for cancer drugs and in the industry's focus on research and development. Although the trend spans the last two decades, the increase has been particularly pronounced during the last five to ten years. For example, consumer spending on cancer drugs in the United States doubled between 2013 and 2018, exceeding \$56 billion in 2018, and is expected to increase by roughly the same amount by 2023.<sup>11</sup> Cancer drug expenditures in the United States also have increased as a percentage of total U.S. prescription spending, going from 10 percent in 2013 to 17 percent in 2018.<sup>12</sup> Individual cancer therapies are expected to bring in hefty amounts of revenue for companies. For example, Merck's cancer drug Keytruda is expected to earn \$10 billion in annual sales, just five years after its launch in 2014.<sup>13</sup>

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<https://seer.cancer.gov/statfacts/html/all.html>. See generally SURVEILLANCE RESEARCH PROGRAM (2019), [https://seer.cancer.gov/csr/1975\\_2016/sections.html](https://seer.cancer.gov/csr/1975_2016/sections.html); NAT'L CANCER INST., NAT'L INSTS. OF HEALTH, SEER CANCER STATISTICS REVIEW (CSR) 1975–2016.

<sup>10.</sup> See ROBIN FELDMAN, *THE ROLE OF SCIENCE IN LAW* 193 (Oxford 2009) (discussing the danger when courts lose themselves in the technical aspects of a case); see also *id.* at 28 (citing the discussion of H.L.A. Hart in Brian Bix, *Positively Positivism*, 85 VA. L. REV. 896 (1999) and noting that "the failure to grasp the nettles of our legal quandaries creates chaos in the doctrines").

<sup>11.</sup> See MURRAY AITKEN ET AL., IQVIA INST. FOR HUMAN DATA SCI., *GLOBAL ONCOLOGY TRENDS 2019*, 36 (2019) [hereinafter *IQVIA Report*].

<sup>12.</sup> See *id.* at 39 for cancer drug expenditures in 2013 and 2018. For total US drug expenditures in 2013 and 2018, see Matej Mikulic, *Prescription Drug Expenditure in the United States from 1960 to 2019*, STATISTA (Aug. 9, 2019), <https://www.statista.com/statistics/184914/prescription-drug-expenditures-in-the-us-since-1960/>.

<sup>13.</sup> See Matthew Herper, *Merck's R&D Boss Sees More Promise in His Big Drug and a \$1 Billion Deal*, STAT+ (May 29, 2019), <https://www.statnews.com/2019/05/29/mercks-rd-boss-sees-more-promise-in-his-big-drug-and-a-1-billion-deal/>.

Industry research and development has shifted toward cancer drugs as well. According to a study by the consulting firm IQVIA, the pipeline of cancer drugs in late-stage trials increased by 19 percent in 2018 alone and more than 60 percent from 2013 to the present.<sup>14</sup> Major pharmaceutical houses such as Pfizer, GlaxoSmithKline, and AstraZeneca are reportedly “pivoting to cancer.”<sup>15</sup> In a similar vein, a 2019 company report for drug manufacturer Sanofi described a “pipeline prioritization review” that resulted in accelerating the development of 17 programs—roughly half in oncology.<sup>16</sup> Amidst this robust market, pharmaceutical companies are spending hefty sums to absorb smaller companies with promising cancer products: Merck paid \$1 billion plus a promise of up to \$1.5 billion more to buy Peloton;<sup>17</sup> Novartis bought Endocyte for \$2.1 billion;<sup>18</sup> Gilead purchased Kite Pharma for \$11.9 billion.<sup>19</sup>

As with any great epic tale, the modern saga is full of celebrities and drama, framed by heart-wrenching stories. Legendary Silicon Valley entrepreneur Sean Parker is spending \$250 million of his own money on research for cancer.<sup>20</sup> Vice-President Joe Biden shared with the nation the agonizing loss of his son to brain cancer in

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<sup>14.</sup> See *IQVIA Report*, *supra* note 12, at 2.

<sup>15.</sup> See Dennis Roland, *Cancer-Drug Giant Roche Loses Edge as Rivals Grow*, WALL ST. J. (Apr. 28, 2019), <https://www.wsj.com/articles/cancer-drug-giant-roche-loses-edge-as-rivals-grow-11556449201>. See also Jared Hopkins, *Pfizer Pivots to Cancer Drugs for Growth*, WALL ST. J. (Jan. 27, 2019), <https://www.wsj.com/articles/pfizer-pivots-to-cancer-drugs-for-growth-11548601200>.

<sup>16.</sup> Press Release, Sanofi, Sanofi delivers 2018 business EPS growth of 5.1% at CER (Feb. 7, 2019), <http://www.news.sanofi.us/2019-02-07-Sanofi-delivers-2018-business-EPS-growth-of-5-1-at-CER>.

<sup>17.</sup> Press Release, Merck, Merck to Acquire Peloton Therapeutics, Bolstering Oncology Pipeline (May 21, 2019), <https://investors.merck.com/news/press-release-details/2019/Merck-to-Acquire-Peloton-Therapeutics-Bolstering-Oncology-Pipeline/default.aspx>.

<sup>18.</sup> See Endocyte, Inc., Completion of Acquisition or Disposition of Assets (Form 8-K) (Dec. 17, 2018). See also Press Release, Novartis, Novartis successfully completes acquisition of Endocyte (Dec. 21, 2018), <https://www.novartis.com/news/media-releases/novartis-successfully-completes-acquisition-endocyte>.

<sup>19.</sup> See Gilead Scis., Inc., Entry into a Material Definitive Agreement (Form 8-K) (Aug. 27, 2017). See also Press Release, Gilead, Gilead Completes Acquisition of Kite Pharma, Inc. (Oct. 3, 2017), <https://www.gilead.com/news-and-press/press-room/press-releases/2017/10/gilead-sciences-completes-acquisition-of-kite-pharma-inc>.

<sup>20.</sup> See Rebecca Robins, *Billionaire Sean Parker Is Nerding out on Cancer Research. Science Has Never Seen Anyone Quite like Him.*, STAT+ (July 9, 2019), <https://www.statnews.com/2019/07/09/sean-parker-cancer-research-science/>.

2015,<sup>21</sup> and not too long after, called for “a moonshot in this country to cure cancer.”<sup>22</sup>

In contrast to the cancer industry, certain other pharmaceutical areas are languishing.<sup>23</sup> Numerous academics and commentators have bemoaned the state of research and development in new antibiotic medicines.<sup>24</sup> Despite concerns about the rise of drug-resistant bacteria—including a U.K. report anticipating ten million deaths a year worldwide by 2050<sup>25</sup> and a 2019 United States CDC report documenting nearly three million antibiotic-resistant infections in the country each year and noting that the number of Americans who die from antibiotic-resistant infections is substantially greater than previously estimated<sup>26</sup>—research efforts are declining.<sup>27</sup> A number of major companies have discontinued their antibiotics research programs,<sup>28</sup> while smaller companies in the space have gone bankrupt.<sup>29</sup>

Antibiotics are not the only pharmaceutical arena suffering from a lack of research and funding. Women’s birth control, for example, has received little research attention or innovation.<sup>30</sup> Contraceptive

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21. *Statement on the Passing of Beau Biden*, THE WHITE HOUSE OFFICE OF THE VICE PRESIDENT (2015) (statement of Joe Biden, Vice President).

22. See Dylan Scott, *Joe Biden calls for ‘moonshot’ to cure cancer*, STAT+ (Oct. 21, 2015), <https://www.statnews.com/2015/10/21/joe-biden-calls-for-moonshot-to-cure-cancer/>.

23. See John Lauerma & James Paton, *Miracle Cancer Drugs Are Making Big Pharma Billions. Others Are Getting Left Behind*, BLOOMBERG (Dec. 11, 2019), <https://www.bloomberg.com/news/articles/2019-12-12/miracle-cancer-drugs-are-making-big-pharma-billions-others-are-getting-left-behind> (noting that “the cancer scramble comes at the expense of conditions like multiple sclerosis, psoriasis, asthma” and that U.S. drug revenue from cardiovascular drugs dropped from dominance to 1% over the last two decades).

24. See, e.g., Aaron Kesselheim & Kevin Outterson, *Improving Antibiotic Markets for Long Term Sustainability*, 11 YALE J. HEALTH POL’Y L. & ETHICS 101 (2011); Edward Cox et al., *Needed: Antimicrobial Development*, 380 N. ENGL. J. MED. 783 (2019); Sarah Karlin-Smith & Sarah Oweremohle, *Conservative Thinkers Urge Caution on Gene Therapy*, POLITICO (Apr. 16, 2019), <https://www.politico.com/newsletters/prescription-pulse/2019/04/16/conservative-thinkers-urge-caution-on-gene-therapy-425428>; Laura Harvey, *Tribulations of Trials for Antibacterial Drugs: Interview with Joseph Kuti*, 1 CLINICAL INVESTIGATION 921 (2011).

25. Jim O’Neill, *Tackling Drug-Resistant Infections Globally: Final Report and Recommendations*, REVIEW ON ANTIMICROBIAL RESISTANCE 4 (2016).

26. CENTERS FOR DISEASE CONTROL AND PREVENTION, 2019 AR THREATS REPORT 3 (2019).

27. See James Paton & Naomi Kresge, *Superbugs Win Another Round as Big Pharma Leaves Antibiotics*, BLOOMBERG (July 12, 2018), <https://www.bloomberg.com/news/articles/2018-07-13/superbugs-win-another-round-as-big-pharma-leaves-antibiotics>.

28. *Id.*

29. See Karlin-Smith & Oweremohle, *supra* note 25.

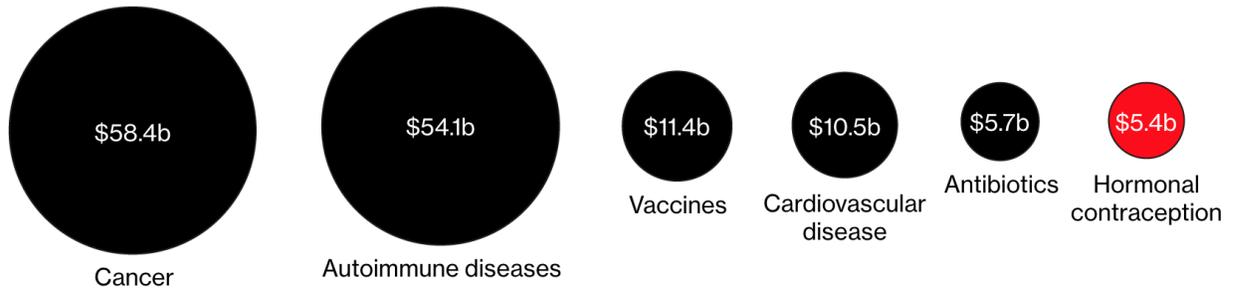
30. See Naomi Kresge & Cynthia Koons, *Better Birth Control Could Exist, But It Wouldn’t Pay for Big Pharma*, BLOOMBERG BUSINESSWEEK (Aug. 8, 2019),

makers spend only two percent of their annual revenue on research and development, and the limited investment has yielded little fruit.

<sup>31</sup>

In short, as the image below demonstrates, cancer is king.

### U.S. Drug Sales for Selected Categories in 2018



Data: IQVIA National Sales Perspectives, Jan. 2019

## II. REGULATORY PATHWAYS LEADING TO THE CANCER SHIFT

The following section analyzes the pathways that have led society to its present focus on cancer treatment and research. Of course, certain U.S. leaders have waxed poetic about the need to address cancer. President Richard Nixon declared a “war on cancer” in the 1970s,<sup>32</sup> and Vice-President Joe Biden announced a “cancer moonshot” in 2017.<sup>33</sup> However, neither appears to be responsible for the tectonic shift. Launched almost 50 years ago, the “war on cancer” can hardly explain the growth in cancer research

<https://www.bloomberg.com/news/articles/2019-08-08/better-birth-control-exists-but-big-pharma-isn-t-interested>.

<sup>31</sup>. See *id.* (“The industry funnels only 2% of annual revenue from contraceptives back into research and development, according to the Gates Foundation.”); cf. Cary P. Gross et al., *The Relation Between Funding by the National Institutes of Health and the Burden of Disease*, 340 *NEW ENG. J. MED.* 1881 (1999) (study showing that NIH spent more on breast cancer research than it would have if the allocation were based on the burden of the disease).

<sup>32</sup>. See Richard Nixon, President of the United States, State of the Union Address (Jan. 22, 1971) (“I will also ask for an appropriation of an extra \$100 million to launch an intensive campaign to find a cure for cancer, and I will ask later for whatever additional funds can effectively be used. The time has come in America when the same kind of concentrated effort that split the atom and took man to the moon should be turned toward conquering this dread disease. Let us make a total national commitment to achieve this goal.”).

<sup>33</sup>. See also OFFICE OF THE VICE PRESIDENT OF THE UNITED STATES, VICE PRESIDENT CANCER MOONSHOT EXECUTIVE REPORT (2016), [https://obamawhitehouse.archives.gov/sites/default/files/docs/finalvp\\_exec\\_report\\_10-17-16final\\_3.pdf](https://obamawhitehouse.archives.gov/sites/default/files/docs/finalvp_exec_report_10-17-16final_3.pdf).

in more recent history.<sup>34</sup> And despite the rhetoric of the “cancer moonshot,” the federal government plans to dedicate a mere \$1.8 billion over 7 years.<sup>35</sup> In comparison, Congress allocated \$6 billion of funding to the National Institutes of Health in 2018 alone, for research on infectious diseases.<sup>36</sup>

It is certainly possible that these political efforts, as distant or limited as they may be, have spurred private development in the field. Perhaps they are reminiscent of King Henry II of England’s utterance in reference to Archbishop Thomas Becket, “[w]ill no one rid me of this turbulent priest?”<sup>37</sup> The utterance was understood by four of his knights as an expression of the sovereign’s desires, which the knights dutifully carried out by assassinating Becket.<sup>38</sup> So too, the flowering of cancer research and treatment efforts, in theory, might be understood as a response to the indirect desires of American sovereigns. Modern industry, however, responds to economic realities; the bully pulpit wields pitiful power in the face of the almighty dollar.<sup>39</sup>

One has to look more deeply to understand what is driving this significant societal shift. The road that has led us to this point seems to have been built by random, mismatched bricks, cobbled together from numerous different regulatory initiatives. This is not to suggest that regulation explains every piece of the structure; other elements undoubtedly provided contributions. Nevertheless, the confluence of incentives created by regulatory initiatives is an essential element.

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<sup>34.</sup> See The National Cancer Act of 1971, Pub. L. No. 92-218, 85 Stat. 778, 42 U.S.C. 282 § 410(C) (1971) (intended to “amend the Public Health Service Act so as to strengthen the National Cancer Institute in order to more effectively carry out the national effort against cancer” by granting special budgetary authority and \$1.6 billion in federal funding over three years to establish new cancer research centers, local control programs, and an international cancer research data bank among other initiatives). See also Gina Kolata, *Advances Elusive in the Drive to Cure Cancer*, N.Y. TIMES (Apr. 23, 2009), <https://www.nytimes.com/2009/04/24/health/policy/24cancer.html> (“Since the war on cancer began, the National Cancer Institute, the federal government’s main cancer research entity . . . has alone spent \$105 billion.”).

<sup>35.</sup> See 21st Century Cures Act, Pub. L. No. 114-255, 130 Stat. 1033, 1040–41 (2016) (authorizing \$1.8 billion in funding over a 7-year period for the Cancer Moonshot).

<sup>36.</sup> NAT’L INSTS. OF HEALTH, ESTIMATES OF FUNDING FOR VARIOUS RESEARCH, CONDITION, AND DISEASE CATEGORIES (RCDC) 2 (2019).

<sup>37.</sup> THE OXFORD DICTIONARY OF QUOTATIONS 370 (Elizabeth M. Knowles ed., Oxford Univ. Press 1999).

<sup>38.</sup> See MICHAEL STAUNTON, THOMAS BECKET AND HIS BIOGRAPHERS 184–215 (2006).

<sup>39.</sup> See ROBIN FELDMAN, DRUG WARS: HOW BIG PHARMA RAISES PRICES AND KEEPS GENERICS OFF THE MARKET 144 (2017) (suggesting that Congressman Henry Waxman’s imploring the pharmaceutical industry to “cease and desist from inventing new games” appears to have been in vain).

The term “regulatory initiative” encompasses not only actions and policies by regulatory agencies, but also legislative action by Congress.<sup>40</sup> Rounding out the trilogy, judicial decisions interpreting both regulatory and legislative initiatives have contributed along the way.<sup>41</sup>

The following subsections identify six disparate areas of regulatory policy that have contributed to the shift into cancer research and treatment. These initiatives relate to clinical trials, regulatory property and accelerated approval programs; generic approval versus biosimilar approval; pricing and reimbursement models; lack of superiority or cost-effectiveness analyses; and distributed buying systems. These policies can be categorized into “positive policies” and “negative policies.” Positive policies are regulatory initiatives that have the effect, either by accident or design, of encouraging the research and development of cancer therapeutics over other types of drugs. Negative policies reflect the absence of certain regulatory restraints that exist in healthcare systems outside the United States. Negative policies can enhance the effects of the positive policies in two respects. First, the absence in the United States of certain policies that exist abroad allows a supercharged reaction to the positive policy initiatives in this country. Second, the existence of negative policies abroad shifts profit-making activity to the United States, where strategic behaviors remain unchecked.

#### A. Clinical Trials

The approval process for medications in the United States is long and complex. Focused on safety and efficacy, the U.S. Food and Drug Administration (the “FDA”) requires an elaborate application and approval process for new pharmaceuticals.<sup>42</sup> Among other requirements, the process involves three rounds of clinical trials to demonstrate that a drug will be safe and effective, first with animals,

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<sup>40</sup>. For legal scholarship on regulatory statutes, see, e.g., Alfred W. Blumrosen, *Toward Effective Administration of New Regulatory Statutes*, 29 ADMIN. L. REV. 87 (1977); Harry W. Jones, *Legislature-Agency Disagreements Concerning the Construction of Regulatory Statutes*, 36 A.B.A.J. 859 (1950); *Federal Statutes and Regulations*, 126 HARV. L. REV. 347 (2012); *Implying Civil Remedies from Federal Regulatory Statutes*, 77 HARV. L. REV. 285 (1963); *Preemption and Regulatory Efficiency in Federal Energy Statutes*, 103 HARV. L. REV. 1306 (1990).

<sup>41</sup>. For decisions on regulatory interpretation by the Court, see, e.g., *Chevron, U.S.A., Inc. v. NRDC, Inc.*, 467 U.S. 837 (1984); *Lochner v. New York*, 198 U.S. 45 (1905); *Gibbons v. Ogden*, 22 U.S. 1 (1824).

<sup>42</sup>. See U.S. FOOD & DRUG ADMIN., NEW DRUG APPLICATION (NDA) (2019), <https://www.fda.gov/drugs/types-applications/new-drug-application-nda>; U.S. FOOD & DRUG ADMIN., DEVELOPMENT & APPROVAL PROCESS (DRUGS) (2018), <https://www.fda.gov/drugs/development-approval-process-drugs>.

then with healthy volunteers, and finally with patients affected by the targeted disease state or health need.<sup>43</sup>

Clinical trial requirements for the types of drugs typically involved in treating cancer are more favorable than the requirements for certain other types of drugs. Although the favoritism is partially a factor of regulatory initiatives designed to speed approval of cancer therapeutics for desperately ill patients, some of the favoritism is entirely inadvertent.

Clinical trials for antibiotics offer a helpful comparison to the cancer approval pathway. Drug companies have the option to engage either in randomized placebo trials—in which some patients will get an entirely inactive medication and some patients will get the proposed drug—or in so-called “non-inferiority” trials—in which the drug is compared to treatments that already exist on the market.<sup>44</sup> When potential treatments exist, however, patients are unlikely to enroll in a placebo trial. As one researcher explained, “[c]an you imagine a parent wanting to enroll their child in an acute bacterial otitis media trial where there is a chance they could receive placebo?”<sup>45</sup>

Even in the realm of non-inferiority trials, cancer drugs have an easier time than other types of drugs. Regulations allow cancer drug manufacturers to enroll smaller numbers of patients than they do for other types of drugs and allow companies to test the hypothesis that the patient lives longer.<sup>46</sup> This is not to suggest that extending a cancer patient’s life is simple or meaningless, but only that it is easier to demonstrate that “patients don’t die as quickly”<sup>47</sup> than to demonstrate that an infection or other disease state is cured.<sup>48</sup>

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43. *See id.*

44. *See* SUZANNE W. JUNOD, A QUICK GUIDE TO CLINICAL TRIALS 35 (Madhu Davies and Faiz Kerimani eds., 2d ed. 2008) (documenting the history of FDA oversight over clinical drug trials and noting that “[a]lthough several kinds of randomized controlled trial methodologies can be useful to researchers and regulators, ultimately, it was the randomized, double-blinded, placebo controlled experiment which became the standard by which most other experimental methods were judged, and it has often subsequently been referred to as the ‘gold’ standard for clinical trial methodology”). *See also* U.S. FOOD & DRUG ADMIN., PLACEBOS AND BLINDING IN RANDOMIZED CONTROLLED CANCER CLINICAL TRIALS FOR DRUG AND BIOLOGICAL PRODUCTS (2019), <https://www.fda.gov/media/130326/download>.

45. *See* Harvey, *supra* note 25, at 922.

46. *See* Kresge & Koons, *supra* note 31.

47. *Id.* (quoting the head of the NIH’s contraceptive development program).

48. Other clinical trial requirements disfavor antibiotics and other drugs for which existing treatments exist. For example, a new drug intended to target bacteria that is resistant to certain antibiotics would have problems with non-inferiority trials, when the standard of care recommends a combination of drugs. The FDA’s protocols require that the trial exclude organisms resistant to the drug being compared. Designing the trial becomes difficult because one might not be able to determine if the relevant organism is involved. *See* Harvey, *supra* note 25, at 922.

To some extent, this is a factor of the FDA’s regulatory policy allowing “surrogate endpoints” in clinical trials, which are substitutes for actual, clinical results.<sup>49</sup> A surrogate endpoint could be that the size of tumors has been reduced, as opposed to whether the patient is cured or survives longer. When the targeted patient population is likely to be small—as may be the case for cancer therapeutics that target specific forms and variations of cancer—the company may have difficulty collecting sufficient data to show a statistically significant effect. Thus, the FDA permits the use of surrogate endpoints in lieu of clinical outcomes when appropriate.<sup>50</sup> Even with cancers that are more common, surrogate endpoints may be used in a manner that allows the trial to be completed more quickly and a finding of efficacy more likely.

However, drug trials in the bacterial space are more likely to enroll a larger number of subjects. Consequently, surrogate endpoints are less likely to be available. Indeed, the FDA’s recently released list of approved surrogate endpoints is heavy on options designed for cancer drugs.<sup>51</sup> This difference in trial ease incentivizes drug makers to focus on cancer drugs instead of non-cancer drugs. In other words, by recognizing that life is tough for cancer drug manufacturers, the FDA makes life comparatively more difficult for non-cancer drug manufacturers.<sup>52</sup>

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<sup>49.</sup> See NAT’L CANCER INST., NAT’L INSTS. OF HEALTH, NCI DICTIONARY OF CANCER TERMS (2019), <https://www.cancer.gov/publications/dictionaries/cancer-terms>.

<sup>50.</sup> U.S. FOOD & DRUG ADMIN., SURROGATE ENDPOINT RESOURCES FOR DRUG AND BIOLOGIC DEVELOPMENT (2018), <https://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development> (explaining the use of surrogate endpoints in clinical trials). For general discussion on the benefits and risks associated with surrogate endpoints, see, e.g., Jennifer A. Henderson & John J. Smith, *Realizing the Potential for Biomarkers in Imaging: Background and Legal Basis*, 60 FOOD & DRUG L.J. 511 (2005) (highlighting the potential of surrogate endpoints for greater safety and efficacy in comparison to traditional endpoints); Tsung-Ling Lee & Tamra Lysaght, *Adaptive Pathways Regulations for Stem Cells: Accelerating Access to Medicine or Deregulating Access to Markets*, 14 SCRIPTED 81 (2017) (questioning the methodology by which surrogate endpoints are decided); Erika Lietzan, *The Drug Innovation Paradox*, 83 MO. L. REV. 39, 69–70 (2018) (describing the FDA’s conservative approach to surrogate endpoint approval).

<sup>51.</sup> See U.S. FOOD & DRUG ADMIN., TABLE OF SURROGATE ENDPOINTS THAT WERE THE BASIS OF DRUG APPROVAL OR LICENSURE (2019), <https://www.fda.gov/drugs/development-resources/table-surrogate-endpoints-were-basis-drug-approval-or-licensure> (listing surrogate endpoints). See also 21<sup>st</sup> Century Cures Act, *supra* note 36, § 507, at 1088 (prompting FDA release of surrogate endpoint information).

<sup>52.</sup> But see Spencer P. Hey et al., *US Food and Drug Administration Recommendations on the Use of Surrogate Measures as End Points in New Anti-infective Drug Approvals*, JAMA INTERN. MED. (Nov. 11, 2019), <https://jamanetwork.com/journals/jamainternalmedicine/fullarticle/2754093> (finding that “many recent US Food and Drug Administration (FDA) anti-infective drug approvals for acute and/or non-life-threatening diseases have been

Unfortunately, the shift to surrogate endpoints in cancer drugs may not be in the interests of patient outcomes. Retrospective analyses on cancer drug efficacy have cast serious doubt on the reliability of surrogate endpoints, finding that they are weakly correlated with overall survival rates for cancer patients. For example, one study found that out of the 36 cancer drugs approved between 2008 and 2013 using FDA-approved surrogate endpoints, only five drugs were found to increase overall survival for patients; the remaining 31 drugs either failed to improve overall survival or had unknown survival effects.<sup>53</sup>

Even where help for cancer drugs is intended, it is not clear that the intent was to disfavor other drugs. Regulators might be especially eager to accelerate cancer approvals in light of rapidly dying patients (and the resulting pressure from families and patient groups). Nevertheless, they might be entirely unaware that the policy would result in a drastic industry shift away from other drugs. In support of this theory, the author's research failed to uncover any indication that policy makers intended to prompt a shift out of research in non-cancer drugs, such as antibiotics. Moreover, various discussions of governmental initiatives hint that policy makers, caught unaware by the effects of those initiatives, are scrambling to devise a solution.<sup>54</sup> To be successful, however, any initiative would have to counter the combined effects of all of the regulatory initiatives fueling the train.

### B. Regulatory Property & Accelerated Approval Programs

Outside of the clinical trial setting, other specialized programs exist that also have the effect—intentionally or unintentionally—of directing energy toward cancer drugs. These programs provide special regulatory protections or accelerated approvals for new

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based on pivotal trials using surrogate measures as primary end points rather than clinical outcomes”). One should also note that the costs of clinical trials are small compared to overall cost of pharmaceutical R&D.

<sup>53</sup>. Chul Kim & Vinay Prasad, *Cancer Drugs Approved on the Basis of a Surrogate End Point and Subsequent Overall Survival: An Analysis of 5 Years of US Food and Drug Administration Approvals*, 175 JAMA INTERN. MED. 1992, 1992–94 (2015).

<sup>54</sup>. See 21st Century Cures Act, *supra* note 36, § 3041-3044, at 1111–14 (outlining a regulatory pathway for antibiotics intended to treat serious and rare pathogens among other measures to combat antibiotic resistance); Food and Drug Administration Safety and Innovation Act, Pub. L. No. 112-144, § 801, 126 Stat. 993 (2012) (introducing 21 U.S.C. § 505E which extends the exclusivity period for new qualified infectious disease products); Strategies To Address Antibiotic Resistance Act, S. 2304, 116th Cong. (2019); Cox et al., *supra* note 25; Paton & Kresge, *supra* note 28 (noting new government initiatives in antibiotics in the U.S. and India); Seema Verma, *Aligning Payment And Prevention To Drive Antibiotic Innovation For Medicare Beneficiaries*, HEALTH AFF. BLOG (Aug. 2, 2019), <https://www.healthaffairs.org/doi/10.1377/hblog20190802.505113/full/> (outlining the U.S. Centers for Medicare and Medicaid Services' “multi-pronged strategy for stimulating access to antibiotic innovation”).

drugs. By far, the most powerful of these is Orphan Drug designation, intended for drugs that treat rare diseases that affect small populations.<sup>55</sup>

Orphan Drug designation brings a host of benefits, including a more cooperative relationship with the FDA during the approval process, a 25 percent tax credit for the cost of clinical trials, and direct grants from the FDA to support clinical trials.<sup>56</sup> Treasury Department estimates suggest that the Orphan Drug designation tax credit will provide \$43 billion in tax credits between 2019 and 2028.<sup>57</sup>

Discussing the approval process for orphan drugs, a former head of the FDA's Office of Orphan Products Development commented that "[t]he FDA is more flexible in evaluating rare diseases" and that "about half of them get through with just one pivotal clinical trial. Not so for common diseases."<sup>58</sup> More valuable than all of these benefits, however, is a seven-year marketing right. During the seven-year period, the FDA will not grant any other company approval to market the same drug for the same orphan designation. Marketing rights such as these are known as "regulatory rights" or "regulatory property," in contrast to the more well-known system of patent rights.<sup>59</sup> A company whose drug enjoys an orphan designation can exclude other drug makers from the market, even if the drug's patents have expired or are held invalid. In addition, the Orphan Drug marketing right can be tacked onto other regulatory rights or patents to extend the period of protection.<sup>60</sup>

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<sup>55.</sup> See 21 U.S.C. §§ 360aa-360ee. Although the original Orphan Drug Act was passed into law in 1982, the program did not gain traction until amendments to the Act in 1984. See Robin Feldman, *Regulatory Property: The New IP*, 40 COLUM. J.L. & ARTS 53, 66–67 (2016) (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, 375 (2005) (explaining why drug companies were reluctant to take advantage of Orphan Drug designations prior to the Hatch-Waxman amendments)); see also Health Promotion and Disease Prevention Amendments of 1984, Pub. L. No. 98-551, § 4(a)-(b), 98 Stat. 2815, 2817 (1984).

<sup>56.</sup> See David Loughnot, *Potential Interactions of the Orphan Drug Act and Pharmacogenomics: A Flood of Orphan Drugs and Abuses?* 31 AM. J.L. & MED. 365, 368–69 (2005); Orphan Drug Act, Pub. L. No. 97-414, §§ 4-5, 96 Stat. 2049, 2053–57 (1983).

<sup>57.</sup> OFFICE OF TAX ANALYSIS, U.S. DEP'T OF THE TREAS., TAX EXPENDITURE ESTIMATES FOR FISCAL YEAR 2020 25 (2018).

<sup>58.</sup> See Sarah J. Tribble & Sydney Lupkin, *Drugmakers Manipulate Orphan Drug Rules to Create Prized Monopolies*, KAISER HEALTH NEWS (Jan. 17, 2017), <https://khn.org/news/drugmakers-manipulate-orphan-drug-rules-to-create-prized-monopolies/> (quoting Dr. Tim Coté).

<sup>59.</sup> For a description of these rights, see generally Feldman, *supra* note 56. See also *id.* at App. A (containing a cheat sheet of more than a dozen regulatory rights).

<sup>60.</sup> See *id.* at 64. One study suggests that the seven-year marketing right may have little real-world effect, given the 20-year length of patent terms. See Ameet Sarpatwari et al., *Evaluating the Impact of the Orphan Drug Act's Seven-Year Market*

Drugs can obtain Orphan Drug designation by demonstrating that the drug would treat a disease that affects fewer than 200,000 people in the U.S. or for which there is no reasonable expectation that sales would recover costs.<sup>61</sup> The 200,000-person threshold was not a carefully considered limit based on objective scientific or economic principles. Rather, Congress chose the number to ensure that the program would apply to two particular drugs, neither of which was a cancer drug.<sup>62</sup>

The Orphan Drug program has been a poster child for dramatic rhetoric since the passage of the original Act. The Congressional hearings, in a truly strange moment in the annals of Congressional debates, featured a Hollywood star re-enacting a heart-wrenching television dramatization.<sup>63</sup> That rhetoric continues to this day, with industry sources using language that sounds as if the diseases in question are neighborhood mafia dons. Rare diseases are “tragically killing and brutalizing mostly children,” comments one industry representative.<sup>64</sup> “Dead children . . . people are willing to pay a lot to prevent that,” comments a former Director of the FDA’s Orphan Drug Products Development Office.<sup>65</sup>

In the last decade, the Orphan Drug Act has been wildly successful, although perhaps it is better described as an uncontrolled wildfire. For example, more than 40 percent of the drug approvals by the FDA in 2014 were for orphan drugs.<sup>66</sup>

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*Exclusivity Period*, 37 HEALTH AFF. 5 (2018). One can think of a drug’s protection as an arsenal of weapons, however, that a company can draw on as needed. The greater the arsenal, the greater the chance of winning the war. This may be particularly true if the company’s patents may be vulnerable to being overturned.

<sup>61.</sup> See 21 U.S.C. § 360bb(a)(2) (1997).

<sup>62.</sup> See OFFICE OF INSPECTOR GEN., DEP’T OF HEALTH & HUMAN SERVS., THE ORPHAN DRUG ACT: IMPLEMENTATION AND IMPACT 4 (May 2001), <https://perma.cc/8PFF-L5KW> (noting that the 200,000 figure was intended to cover a drug for narcolepsy and a drug for multiple sclerosis).

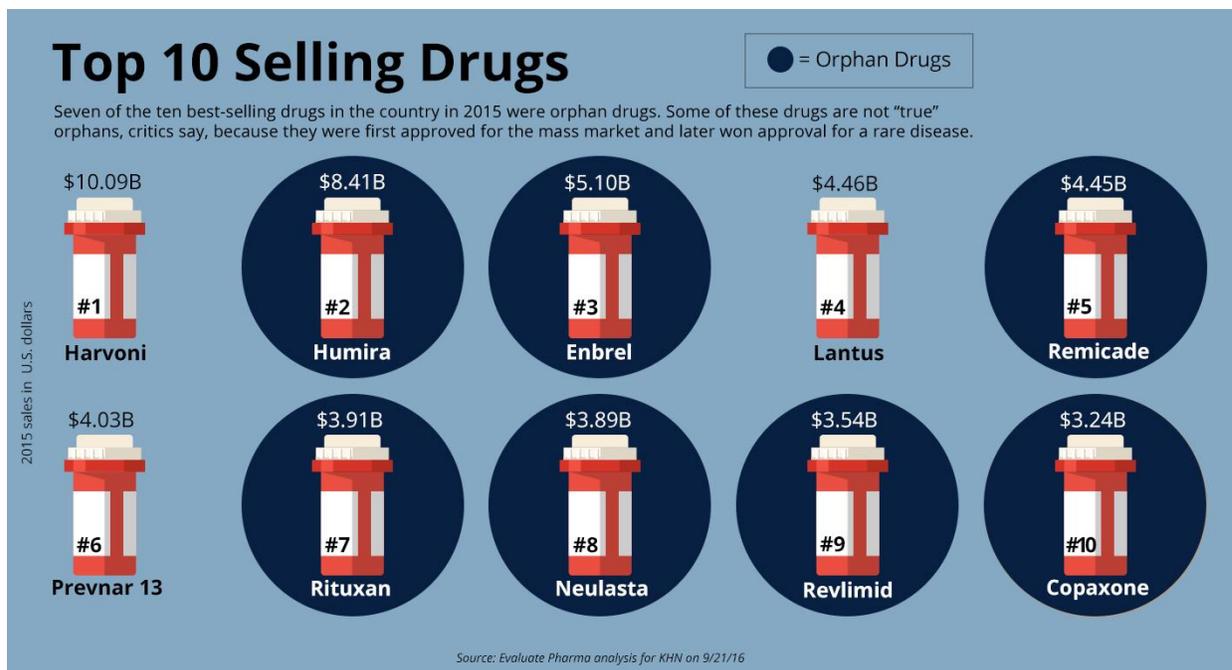
<sup>63.</sup> *Health and the Environment Miscellaneous—Part 2: Hearing on Orphan Drugs—H.R. 1663 Before the Subcomm. on Health and the Envtl of the Comm. on Energy and Commerce*, 97th Cong. 11-12 (1981) (statement of Jack Klugman, Actor).

<sup>64.</sup> See Tribble & Lupkin, *supra* note 59 (quoting Jim Greenwood, President of the Biotechnology Industry Organization and former U.S. Representative).

<sup>65.</sup> See *id.* (quoting Dr. Tim Coté).

<sup>66.</sup> See Michael G. Daniel et al., *The Orphan Drug Act: Restoring the Mission to Rare Diseases*, 39 AM. J. CLIN. ONCOL. 210 (2016); OFFICE OF GENERIC DRUGS, CTR. FOR DRUG EVALUATION & RES., 2015 ANNUAL REPORT: ENSURING SAFE, EFFECTIVE AND AFFORDABLE MEDICINES FOR THE AMERICAN PUBLIC 10 (2015), <https://perma.cc/R7P9-4YYD>.

The Act also has led to public outcry, when drugs that have orphan designations are used to treat other non-orphan indications, resulting in tiny population benefits combined with large population revenues. For example, Suboxone, a blockbuster drug that is used to treat opioid addiction, received an Orphan Drug designation,<sup>67</sup> as did Humira, the blockbuster drug that treats various inflammatory disorders such as rheumatoid arthritis, which holds at least five Orphan Drug indications.<sup>68</sup> In fact, one pharmaceutical data source concludes that out of the ten drugs with the highest annual sales revenue in 2015, seven were orphan drugs.<sup>69</sup> By 2020, sales of drugs with orphan status are expected to garner \$176 billion in annual sales, constituting twice the growth rate of the overall prescription drug market.<sup>70</sup>



Orphan drugs also play a prominent and increasing role in the strategic behavior known as “evergreening,” in which companies try to extend the protections surrounding their drugs.<sup>71</sup> A study of all

67. OFFICE OF ORPHAN PRODS. DEV., U.S. FOOD & DRUG ADMIN., ORPHAN DRUG DESIGNATIONS AND APPROVALS DATABASE (2018), [https://www.accessdata.fda.gov/scripts/opdlisting/opd/detailedIndex.cfm?cfg\\_ridkey=79093](https://www.accessdata.fda.gov/scripts/opdlisting/opd/detailedIndex.cfm?cfg_ridkey=79093).

68. See Tribble & Lupkin, *supra* note 59.

69. See *id.*

70. Daniel et al., *supra* note 67, at 211.

71. See Robin Feldman, *May Your Drug Price Be Evergreen*, 5 J.L. & BIOSCI. 590, 636 (2018); Robert A. Bohrer & John T. Prince, *Tale of Two Proteins: The FDA's Uncertain Interpretation of the Orphan Drug Act*, 12 HARV. J.L. & TECH. 365 (1999).

non-biologic drugs on the market between 2005 and 2015 found that the number of drug makers engaging in the evergreening tactic of piling on patents doubled during the period;<sup>72</sup> the number of drugs with an added orphan drug exclusivity tripled during the same study period.<sup>73</sup> Another study concluded that one-third of orphan drug approvals were “either for repurposed mass market drugs or drugs that received multiple orphan approvals.”<sup>74</sup>

Of course, repurposing drugs can have benefits to patients, such as providing a track record of safety.<sup>75</sup> The question, however, is not whether repurposing can be helpful to patients but whether a repurposed drug is appropriate for the societal benefits being conferred and whether the resulting market movement is desirable as a matter of public policy.

Evergreening is a particularly powerful strategy in the Orphan Drug space because the reward is so great. An extra patent here or there might be weak or might fall when challenged in court. An Orphan Drug award stands firm, however, and it survives even if patents are invalidated. Moreover, Orphan Drug marketing rights are self-executing in that the drug company need not go to court to enforce it. The FDA enforces it on behalf of the company by declining to approve their competitors.

Although the 200,000 patient threshold may not have been chosen with cancer drugs in mind, cancer drugs have found a particularly happy home in the program. Thanks in part to advances in personalized medicine and genomics, cancer treatments can be described in terms of small, targeted populations so that treating each of those populations can lead to multiple Orphan Drug designations for the same drug.<sup>76</sup> For example, even though lymphoma affects 700,000 Americans, at least twenty-one different treatments for lymphoma won Orphan Drug designations in 2013 because pharmaceutical companies were able to categorize—with FDA approval—various forms of lymphoma afflicting different populations.<sup>77</sup>

This practice of “salami slicing” diseases into smaller, targeted subsets for the sake of gaming the Orphan Drug Act and its

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<sup>72.</sup> See Feldman, *supra* note 72.

<sup>73.</sup> See *id.* at 626.

<sup>74.</sup> See Tribble & Lupkin, *supra* note 59 (Kaiser Health News is not associated with the Kaiser Permanente health maintenance organization).

<sup>75.</sup> See Feldman, *supra* note 72, at 637; Tribble & Lupkin, *supra* note 59 (citing FDA Director of Orphan Drug Products Development Dr. Gayatri Rao, who also suggested that such repurposing may be driving up prices in a surprising manner).

<sup>76.</sup> For a description of how these factors play out in the pharmaceutical market, see *IQVIA Report*, *supra* note 13, at 47.

<sup>77.</sup> LYDIA RAW, *ARE WE ADOPTING THE ORPHANS, OR CREATING THEM? MEDICAL ETHICS AND LEGAL JURISPRUDENTIAL GUIDANCE FOR PROPOSED CHANGES TO THE ORPHAN DRUG ACT*, 9 WASH. U. JURIS. REV. 295, 308 (2017).

exclusivity designation has been roundly criticized in the press and academic literature.<sup>78</sup> Nevertheless, the match between the salami slicing opportunities for cancer drugs and the generous benefits available through Orphan Drug designations has led to a veritable tidal wave of oncology orphan drugs, once again helping to drive development into the cancer space. Of all drug launches in various therapy areas in 2018, oncology had the greatest number; three-quarters of those oncology launches were orphan drugs.<sup>79</sup> The economic implications are enormous. The Orphan Drug market today is growing nearly twice as fast as the total prescription market, with global sales topping \$178 billion dollars.<sup>80</sup>

Other accelerated regulatory approval programs favor cancer therapeutics. These include an accelerated approval pathway for so called “breakthrough” drugs and the “fast-track” program.<sup>81</sup> Both are designed for serious or life-threatening conditions, for which cancer therapeutics seem to fit the bill.<sup>82</sup> Half of the drugs between 2014 and 2016 that received breakthrough pathway designation were cancer drugs.<sup>83</sup>

In a similar vein, the FDA’s “expanded access” program, sometimes called “compassionate care,” allows patients to access drugs that have not been approved and do not meet clinical trial eligibility requirements when alternative therapies are unavailable.<sup>84</sup>

The FDA approves around 99 percent of requests for compassionate care access, according to separate analyses by the FDA and the non-partisan Government Accountability Office (GAO).<sup>85</sup> Of the 5,061 approved expanded access requests between

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<sup>78.</sup> See Feldman, *supra* note 56, at 79–80; Feldman, *supra* note 72, at 625; Tribble & Lupkin, *supra* note 59; Daniel et al., *supra* note 67.

<sup>79.</sup> IQVIA Report, *supra* note 13, at 5; see also Thomas J. Hwang et al., *Efficacy, Safety, and Regulatory Approval of Food and Drug Administration–Designated Breakthrough and Nonbreakthrough Cancer Medicines*, 36 J. CLIN. ONCOL. 1805, 1806 (2018) (of the 58 new cancer drugs approved between 2012 and 2017, 72 percent had Orphan Drug designations).

<sup>80.</sup> See Raw, *supra* note 78; see also EVALUATEPHARMA, ORPHAN DRUG REPORT 2015 6 (2015).

<sup>81.</sup> U.S. FOOD & DRUG ADMIN., FREQUENTLY ASKED QUESTIONS: BREAKTHROUGH THERAPIES (June 28, 2019), <https://www.fda.gov/regulatory-information/food-and-drug-administration-safety-and-innovation-act-fdasia/frequently-asked-questions-breakthrough-therapies>.

<sup>82.</sup> See *id.*

<sup>83.</sup> See Jonathan J. Darrow et al., *The FDA Breakthrough-Drug Designation—Four Years of Experience*, 378 NEW ENGL. J. MED. 1444, 1444–45 (2018).

<sup>84.</sup> See U.S. FOOD AND DRUG ADMIN., EXPANDED ACCESS (May 2019), <https://www.fda.gov/news-events/public-health-focus/expanded-access>; see also U.S. FOOD AND DRUG ADMIN., EXPANDED ACCESS PROGRAM REPORT (May 2018), <https://www.fda.gov/media/119971/download>.

<sup>85.</sup> See U.S. GOV’T ACCOUNTABILITY OFFICE, GAO-17-564, INVESTIGATIONAL NEW DRUGS: FDA HAS TAKEN STEPS TO IMPROVE THE EXPANDED ACCESS PROGRAM BUT SHOULD FURTHER CLARIFY HOW ADVERSE EVENTS DATA ARE USED (2017); see also Alison Bateman-House, *To Speed Access to*

2012 and 2015, 20 percent involved cancer drugs, second only to anti-infective treatments, which constituted 25.6 percent of approved requests.<sup>86</sup>

### C. *Generic Approval Compared to Biosimilar Approval*

Small-molecule drugs, or non-biologics, differ from biologics not only in how they are synthesized, but also in how they are approved and regulated. With the right chemical ingredients, non-biologics can be easily synthesized in a laboratory, and thus, their resulting chemical structures are relatively simple.<sup>87</sup> Non-biologics are called small-molecule drugs because they are made up of fewer atoms and are less complex in shape.<sup>88</sup> They may be composed of only a few dozen atoms and can be drawn in a two-dimensional sketch. In contrast, the chemical makeup of biologics, which are synthesized in living organisms such as cells, bacteria, and animal tissues,<sup>89</sup> can include multiple compounds folded together, with each compound made up of thousands to millions of atoms.<sup>90</sup> Biologics also cannot be drawn in a simple two-dimensional sketch. Finally, their complexity means that they cannot be easily synthesized through chemical reactions in a laboratory.<sup>91</sup>

One well-known biologic is insulin, which can be harvested from pigs and used to treat patients with Type 1 diabetes.<sup>92</sup> Given that biologics are synthesized in living organisms, the resulting chemical makeup of two biosimilars is never exactly the same, and there are valid concerns for ensuring biologic equivalence and safety.<sup>93</sup> Thus, the approval process for and regulatory pathway of biologics cannot be as simple and streamlined as that of non-biologics. The article will use the terms “biologic drugs” and “non-biologic drugs” to simplify the topic for those without a scientific background.

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*Compassionate Use, Look Beyond the FDA*, HEALTH AFF. BLOG (Aug. 10, 2017), <https://www.healthaffairs.org/doi/10.1377/hblog20170810.061480/full/>.

<sup>86.</sup> *See id.*

<sup>87.</sup> *See* Feldman, *supra* note 56, at 82.

<sup>88.</sup> *See* Robert N. Sahr, *The Biologics Price Competition and Innovation Act: Innovation Must Come Before Price Competition*, B.C. INTELL. PROP. & TECH. F. 1, 2 (2009).

<sup>89.</sup> *See id.* (citing Benjamin Leader et al., *Protein Therapeutics: A Summary and Pharmacological Classification*, 7 NATURE REV. DRUG DISCOVERY 21, 22 (2008)).

<sup>90.</sup> *See* Benjamin Leader et al., *Protein Therapeutics: A Summary and Pharmacological Classification*, 7 NATURE REV. DRUG DISCOVERY 21, 22 (2008).

<sup>91.</sup> *See id.* at 33.

<sup>92.</sup> *See* Richard Dolinar et al., *A Guide to Follow-On Biologics and Biosimilars with a Focus on Insulin*, 24 ENDOCRINE PRACTICE 195 (2018).

<sup>93.</sup> *See* Bryan A. Liang, *Regulating Follow-On Biologics*, 44 HARV. J. ON LEGIS. 363, 370 (2007) (citing Simon D. Roger, *Biosimilars: How Similar or Dissimilar Are They?* 11 NEPHROLOGY 341, 342 (2006)).

Copies of non-biologic drugs are called generics; copies of biologic drugs are called biosimilars and interchangeable.<sup>94</sup> For both types of follow-on drugs, Congress has created pathways designed to ensure rapid entry of lower-priced copies of the brand drug, once patent and non-patent protections expire. These pathways allow follow-on drugs to use the safety and efficacy data developed by the original drug maker. The follow-on generic drug maker need only show that its drug is sufficiently equivalent to the original drug—that is, a generic drug maker must show bioequivalence. In contrast, a biologic follow-on drug maker must meet the higher standards of biosimilarity or interchangeability.

The pathway for rapid entry of generics is known as the Hatch-Waxman system;<sup>95</sup> the biologic pathway is known by the more complex acronym, BPCIA (the Biologic Price Competition and Innovation Act, hereinafter the “Biologics Act”).<sup>96</sup>

The Biologics Act provides greater protection for branded biologic drugs than Hatch-Waxman provides for branded non-biologic drugs. For example, under Hatch-Waxman, branded drugs receive either a four or five-year period in which generic companies cannot use their safety and efficacy data, regardless of whether patents are in force.<sup>97</sup> Under the Biologics Act, biologic drugs can receive 12 years of data protection.<sup>98</sup>

The structures of the two pathways also provide relatively greater opportunities for biologics companies to engage in strategic behaviors that delay the entry of follow-on drugs and ensure that follow-ons have difficulty gaining traction when they do get to market. Under Hatch-Waxman, brand drugs generally must list all of their patent and regulatory rights in the Orange Book, an FDA publication that is freely available.<sup>99</sup> Biologics are listed in the FDA’s Purple Book, which provides far less information to the public and competitors.<sup>100</sup> For example, in contrast to small-molecule drug

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<sup>94.</sup> See U.S. FOOD & DRUG ADMIN., GENERIC DRUGS: QUESTIONS & ANSWERS (2018), <https://www.fda.gov/drugs/questions-answers/generic-drugs-questions-answers>; U.S. FOOD & DRUG ADMIN., BIOSIMILAR AND INTERCHANGEABLE PRODUCTS (2017), <https://www.fda.gov/drugs/biosimilars/biosimilar-and-interchangeable-products>.

<sup>95.</sup> Drug Price Competition and Patent Term Restoration Act, Pub. L. No. 98-417, 98 Stat. 1585 (1984) [hereinafter *Hatch-Waxman Act*].

<sup>96.</sup> Biologics Price Competition and Innovation Act of 2009, Pub. L. No. 111-148, 124 Stat. 119 (2009) [hereinafter *Biologics Act*].

<sup>97.</sup> See *Hatch-Waxman Act*, *supra* note 96.

<sup>98.</sup> See *Biologics Act*, *supra* note 97.

<sup>99.</sup> U.S. FOOD AND DRUG ADMIN., ORANGE BOOK: APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS (2019), <https://www.accessdata.fda.gov/scripts/cder/ob/index.cfm> (last visited Dec. 13, 2019).

<sup>100.</sup> CTR. FOR BIOLOGICS EVALUATION AND RES., U.S. FOOD AND DRUG ADMIN., CBER LIST OF LICENSED BIOLOGICAL PRODUCTS (2019), <https://www.fda.gov/media/89426/download> (last visited Dec. 16, 2019).

makers, biologics companies are not required to list all relevant patents and non-patent exclusivities in the Purple book at the time of a drug's approval or when the protection is obtained.<sup>101</sup> In addition, under the Hatch-Waxman system, the generic drug maker is in the driver's seat and can choose to challenge all of the brand drug's rights at once. With the Biologics Act, the brand company controls the challenge process and can decide to assert whichever rights it chooses in whatever order it chooses, potentially across a series of legal battles.<sup>102</sup> And of course, those rights are not conveniently listed upfront.

In short, brand drugs in the Hatch-Waxman system must put all of their cards on the table; brand drugs in the Biologics system can hide their hands, playing cat-and-mouse games with follow-on drug companies. This distinction is crucial, because cancer drugs are frequently biologics. Thus, the greater protections available under the Biologics Act further encourage companies to pursue opportunities in the cancer space.

#### D. Pricing and Reimbursement Models

Perhaps the strongest impetus for cancer therapeutics lies with the simple economics of the available pricing and reimbursement models. To put it bluntly, the big money is in cancer, and it is big indeed. Although a variety of factors are at play, several regulatory processes provide key contributions.

Pricing in the healthcare system is, simply put, not rational.<sup>103</sup> My life and my health are likely to be infinitely valuable to me, in a way that other things I could spend my money on may not be. This phenomenon is enhanced by the fact that a significant portion of healthcare costs are borne by third parties, such as health insurance companies or the government, rather than by the patient. One is always likely to spend more when someone else is footing the bill and even more so when one's life is at stake.<sup>104</sup>

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<sup>101.</sup> See Evert Uy Tu & Jeffrey A. Wolfson, *FDA Throws the (Purple) Book at Biosimilars—Purple v. Orange*, HAYNESBOONE (2014), <http://www.haynesboone.com/~media/files/alert%20pdfs/fdapurplebookvorangebook.ashx>.

<sup>102.</sup> For related cases involving biologics, see, e.g., *Amgen Inc. v. Hospira, Inc.*, 866 F.3d 1355 (Fed. Cir. 2017); *Amgen Inc. v. Apotex Inc.*, 827 F.3d 1052 (Fed. Cir. 2016); *Sandoz Inc. v. Amgen Inc.*, 773 F.3d 1274 (Fed. Cir. 2014).

<sup>103.</sup> See John G. Curran, *The New York Pharmaceutical Cost Transparency Act: How a Narrow View of the Prescription Drug Pricing Puzzle Renders a Well-Intentioned Bill Irrational*, 82 BROOK. L. REV. 315 (2016); Erin C. Fuse Brown, *Irrational Hospital Pricing*, 14 HOUS. J. HEALTH L. & POL'Y 11 (2014).

<sup>104.</sup> See TOM A. COBURN & JOHN HART, *THE DEBT BOMB: A BOLD PLAN TO STOP WASHINGTON FROM BANKRUPTING AMERICA* 130–33 (2013) (positing that “spending other people’s money on yourself” is one of the reasons why government spending doesn’t work very well and is rarely efficient).

Moreover, the pricing models for pharmaceuticals are increasingly moving away from the cost-based approach historically used with most goods and towards a value-based approach. Specifically, the traditional economic approach to the pricing of goods involves a cost-plus method, in which companies set prices by calculating the costs of production, including the costs of research and development, plus an amount of profit.<sup>105</sup> In contrast, value-based pricing is based on the customer's perception of the value of the product.<sup>106</sup> And as described above, the value of life itself can be infinitely high to a patient.

Untethered from calculations related to production costs, drug companies have begun basing pricing models on other aspects, such as the added quantity and quality of a patient's life from the benefit of the drug or the value of other healthcare expenditures that could be avoided.<sup>107</sup> These pricing mechanisms have helped fuel, or at the very least helped justify, enormous price tags for cancer therapeutics. For example, Novartis's Car-T cancer drug Kymriah costs \$475,000 for a one-time treatment, with estimated totals, including hospitalization and other costs, of \$800,000 to \$1.5 million.<sup>108</sup> The recent decision by the U.S. Centers for Medicare and Medicaid Services to cover Car-T therapies and to reimburse up to 65 percent<sup>109</sup> reflects steps towards general acceptance of these pricing models.

Other regulatory rules favor spending for cancer drugs. For example, Medicare designates six protected classes of drugs, for which health plans must provide coverage for all or substantially all class-member drugs.<sup>110</sup> One of those classes, "antineoplastics," covers many chemotherapy drugs, although it is only one of the six. Other Medicare rules favor highly expensive drugs, such as cancer therapeutics, because high-priced drugs push the patient more

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<sup>105</sup> See also Ward Hanson, *The Dynamics of Cost-Plus Pricing*, 13 *MANAGERIAL AND DECISION ECON.* 149 (1992).

<sup>106</sup> See generally Louis P. Garrison & Adrian Towse, *Value-Based Pricing and Reimbursement in Personalised Healthcare: Introduction to the Basic Health Economics*, 7 *J. PERSONALIZED MED.* 10 (2017).

<sup>107</sup> See Robin Feldman, *The Perils of Value-Based Pricing for Prescription Drugs*, *WASH. POST* (Apr. 11, 2019), <https://www.washingtonpost.com/outlook/2019/04/11/perils-value-based-pricing-prescription-drugs>.

<sup>108</sup> See Allison Inzerro, *CMS Says It Will Cover CAR-T for Medicare Beneficiaries Nationwide*, *AJMC* (Aug. 7, 2019), <https://www.ajmc.com/newsroom/cms-says-it-will-cover-car-t-for-medicare-beneficiaries-nationwide>.

<sup>109</sup> CMS Principles of Reasonable Cost Reimbursement; Payment For End-Stage Renal Disease Services; Prospectively Determined Payment Rates For Skilled Nursing Facilities; Payment For Acute Kidney Injury Dialysis, 42 C.F.R. § 413 (2018).

<sup>110</sup> See Modernizing Part D and Medicare Advantage To Lower Drug Prices and Reduce Out-of-Pocket Expenses, 84 *Fed. Reg.* 23,832 (May 23, 2019) (to be codified at 42 C.F.R. pts. 422-423).

quickly to the monetary threshold at which the government, as opposed to the health plan, picks up most of the patient's costs for all drugs.<sup>111</sup> Specifically, when Medicare patients reach what is known as the "catastrophic" level, the government steps in to pick up 80% of the cost, while the health plan pays only 15% of the cost.<sup>112</sup>

All of these pricing and reimbursement aspects enhance the shift into cancer therapeutics. When so much money is available, other drug target opportunities pale in comparison. And indeed, that is the case for the example mentioned above with the lack of research dollars going into antibiotics.<sup>113</sup> As one commentator noted, the problem for antibiotics is not just the challenges of the research, but how little a company can sell the product for in comparison to expensive cancer drugs, particularly when an antibiotic will be given for a few days or weeks versus cancer drugs that will be administered for months.<sup>114</sup> One might also wonder whether the perception of the disease, and our past success in the field, affects the pricing calculus. We expect antibiotics to cure us, and we are unlikely to accept a few more months of life as an acceptable outcome for a bacterial infection treatment.

The brightest news in the antibiotics space is that the FDA recently approved a nonprofit organization's application for a new antibiotic to treat drug-resistant tuberculosis.<sup>115</sup> While the new treatment could make great strides in combating this deadly disease,

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<sup>111.</sup> See *Medicare Part D – Direct and Indirect Remuneration (DIR)*, CTR. FOR MEDICARE & MEDICAID SERVS. (Jan. 19, 2017), [www.cms.gov/newsroom/fact-sheets/medicare-part-d-direct-and-indirect-remuneration-dir](http://www.cms.gov/newsroom/fact-sheets/medicare-part-d-direct-and-indirect-remuneration-dir) (explaining "the final three phases of the part D benefit: the initial coverage phase, the coverage gap, and the catastrophic phase. High priced drugs [...] shift more and more of the drug spend into the catastrophic phase"); *An Overview of the Medicare Part D Prescription Drug Benefit*, KFF (Oct. 12, 2018), <https://www.kff.org/medicare/fact-sheet/an-overview-of-the-medicare-part-d-prescription-drug-benefit/> ("For total drug costs above the catastrophic threshold, Medicare pays 80%, plans pay 15%.").

<sup>112.</sup> See *id.*

<sup>113.</sup> See generally, *supra* note 25–29 and accompanying text.

<sup>114.</sup> See Paton & Kresge, *supra* note 28; see also James Gallagher, *Take Over Pharma to Create New Medicines, Says Top Adviser*, BBC NEWS (Mar. 27, 2019), <https://www.bbc.com/news/health-47719269> (noting that there is simply not enough money to be made in antibiotics, given that any new drug has to be cheap and used rarely to minimize the risk of resistance); cf. Kresge & Koons, *supra* note 31 (noting in the context of limited innovation in women's birth control that "[i]n the era of \$20 billion blockbusters such as the arthritis drug Humira and \$2 million-a-patient gene therapies to treat rare diseases, the pharmaceutical industry doesn't see a big payoff in rolling out products that don't have record-breaking potential").

<sup>115.</sup> Press Release, U.S. Food & Drug Admin., FDA Approves New Drug for Treatment-Resistant Forms of Tuberculosis that Affects the Lungs (Aug. 14, 2019), <https://www.fda.gov/news-events/press-announcements/fda-approves-new-drug-treatment-resistant-forms-tuberculosis-affects-lungs>.

the fact that the new drug came from a nonprofit organization serves to underscore that commercial incentives are failing in the antibiotic space.<sup>116</sup> The economic value is in cancer.

### *E. Negative Policies in Contrast to Positive Policies*

The subsections above identify various positive regulatory policies in the United States that have encouraged the remarkable shift toward cancer therapeutics. In contrast, negative policies reflect the lack of a particular regulatory restraint that might exert counter-pressure on the shift. In particular, the United States lacks two sets of regulatory policies that exist in the healthcare systems of other nations.

First, the U.S. drug regulatory systems for granting approval and rights lack a systematic approach for considering issues such as the cost-benefit analysis of a new drug or its clear superiority over other treatments. In granting patent rights, the U.S. Patent and Trademark Office does not ask whether the drug is better or more cost-effective than other available treatments. The question is whether the drug is different.<sup>117</sup>

In granting approval for drugs, the FDA also does not ask whether a new drug is cost-effective in comparison to other treatments. Rather, it asks whether the drug is safe and effective. Furthermore, until recently, the FDA did not even ask whether drugs applying for Orphan Drug status were clinically superior to existing drugs on the market. A statutory amendment in 2018 overturned court rulings and established that the Orphan Drug designations can be made only for drugs that are clinically superior to the previously approved drugs.<sup>118</sup> Even that change, however,

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<sup>116.</sup> See Betsy McKay, *FDA Approves New Pill for Drug-Resistant TB*, WALL ST. J. (Aug. 14, 2019), <https://www.wsj.com/articles/fda-approves-new-pill-for-drug-resistant-tb-11565822369> (“Unusually, the drug was developed by a not-for-profit.”).

<sup>117.</sup> For an example of a case where plaintiff sued defendant for infringement of patents related to composition of a cancer drug, see *Aventis Pharma S.A. v. Hospira, Inc.*, 675 F.3d 1324 (2012).

<sup>118.</sup> The courts interpreted the Orphan Drug Act as not requiring such a showing, ruling against the FDA in two cases. See *Depomed, Inc. v. U.S. Dep’t of Health & Human Servs.*, 66 F. Supp. 3d 217 (D.D.C. 2014); *Eagle Pharms., Inc. v. Azar*, U.S. Dist. LEXIS 101735 (D.C. Cir. 2018). However, a recent statutory amendment in 2018 overturned the court’s rulings and clarified that the “FDA will not recognize orphan-drug exclusive approval if the sponsor fails to demonstrate upon approval that the drug is clinically superior to the previously approved drug.” 21 C.F.R. § 316.34(c) (2018). See Angela Drew & William Stoltman, *Orphan Exclusivity for ‘Same Drug’: What Has Changed Since FDARA 2017/PDUFA VI?* Camargo Blog (Aug. 8, 2018), <https://camargopharma.com/resources/blog/orphan-exclusivity-for-same-drug-what-has-changed-since-fdara-2017-pdufa-vi>. Along the same lines,

does not provide for an analysis of whether any improvement is cost-effective. In other words, one could still receive Orphan Drug designation for a drug that brings a very small improvement at a very high price tag.<sup>119</sup>

In contrast, the United Kingdom's National Institute for Health and Care Excellence performs health technology assessments to establish the cost-effectiveness of new medicines which determines whether a drug is approved for public reimbursement.<sup>120</sup> Other countries including Australia, New Zealand, and Canada have followed suit, considering cost-effectiveness when appraising drugs for use in their publicly funded healthcare systems.<sup>121</sup> The Canadian government estimates that new rules, allowing the federal drug price regulator to consider the cost-effectiveness of new medicines before allowing them into the nation's healthcare system,<sup>122</sup> will save Canada's patients, employers, insurers, and state and federal governments a total of \$10 billion over the next decade.<sup>123</sup>

A second negative policy involves the lack of coordinated buying structures. Other countries, such as Canada and European nations, have national healthcare systems that coordinate buying and limit

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companies who receive regulatory rights by virtue of testing their drug in children do not have to show that the test was successful. See Feldman, *supra* note 56, at 86–87.

<sup>119</sup>. Scholars disagree over whether and the extent to which the Affordable Care Act expressly forbids the use of cost-effectiveness calculations in health insurance. Compare Barry R. Furrow, *Cost Control and the Affordable Care Act: CRAMPing Our Health Care Appetite*, 13 NEVADA L.J. 822 (2013) with Elizabeth Weeks Leonard, *Death Panels and the Rhetoric of Rationing*, 13 NEVADA L.J. 872 (2013). For an in-depth, nuanced analysis of the question, see Govind Persad, *Priority-Setting, Cost-Effectiveness, and the Affordable Care Act*, 41 AM. J.L. & MED. 119, 129 (2015) (arguing that the Affordable Care Act does place substantial limitations on the use of traditional cost-effectiveness analysis and fails to remove certain limitations created by other laws, but is not invariably hostile to the use of cost-effectiveness, if employed in a way that avoids considering prohibited factors); see also Govind Persad et al., *Principles for Allocation of Scarce Medical Interventions*, 373 THE LANCET 423 (Jan. 31, 2009).

<sup>120</sup>. See William K. Evans & Claire de Oliveira, *Evaluating Cost-Effectiveness: An Essential Part of New Cancer Drug Approvals*, 12 J. THORACIC ONCOL. 1461 (2017); Rumona Dickson et al., *EMA and NICE Appraisal Processes for Cancer Drugs: Current Status and Uncertainties*, 16 APPL. HEALTH ECON. & HEALTH POL'Y 429 (2018).

<sup>121</sup>. See Evans & Oliveira, *supra* note 121.

<sup>122</sup>. Allison Martell, *Exclusive: Canada Told Drugmakers It Would Limit Scope of Some New Price Rules*, REUTERS (May 29, 2019), <https://www.reuters.com/article/us-canada-pharmaceuticals-pricing-exclus/exclusive-canada-told-drugmakers-it-would-limit-scope-of-some-new-price-rules-idUSKCN1SZ2HM>.

<sup>123</sup>. *Canada Announces Regulations to Cut Price of Prescription Drugs*, THE GUARDIAN (Aug. 9, 2019), <https://www.theguardian.com/world/2019/aug/09/canada-prescription-drugs-cut-cost>.

pricing.<sup>124</sup> Given historic reluctance from companies to enter into healthcare systems that have features resembling price controls, the United States has resisted adopting such an approach.<sup>125</sup>

These negative policies are enhancing the effects of the positive policies in two ways. First, the absence of negative policies helps facilitate an overheated reaction to the positive policy initiatives, given the lack of counter-pressure that could theoretically be exerted. Second, the existence of certain policies abroad, combined with the lack of those policies at home, may have an effect on pricing in both arenas. When other nations enact policies that put downward pressure on pricing, U.S. consumers can end up, in essence, helping lower prices abroad. For example, it may be easier to accede to European demands for lower prices when substantial profits can be reaped in the U.S. This is not to suggest that drug companies are losing money abroad; rather the notion is simply that bargaining becomes easier when the party on the other side of the table can compensate in another market.

Although these issues have the potential to affect all pharmaceuticals, they may play a particular role in the shift toward cancer drugs. To the extent that the ability to charge high prices pushes the industry toward cancer drugs, negative policies resulting in a lack of restraints on those economics can create an echo effect, enhancing the attractiveness of drugs that can be marketed at superheated prices.

Together, these positive and negative policies have helped to tilt the pharmaceutical industry sharply in the direction of cancer drugs. In some cases, the policies were not particularly aimed at incentivizing research into cancer therapeutics. In other cases, the policies were intended to do so, but were not necessarily designed to produce such a dramatic shift. In no cases were these policies contemplated as a coordinated or coherent whole, in which the sum total of the effect can be said to have been intentional.

### III. REGULATORY FAILURE BY SUCCESS

As described in Part II, a variety of regulatory programs operate to encourage the industry shift toward cancer therapeutics.

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<sup>124.</sup> See, e.g., U.S. GOV'T ACCOUNTABILITY OFFICE, GAO/HEHS-94-30, PRESCRIPTION DRUGS: SPENDING CONTROLS IN FOUR EUROPEAN COUNTRIES (1994).

<sup>125.</sup> See Steven R. Salbu, *Aids and Drug Pricing: In Search of a Policy*, 71 WASH. U.L.Q. 691, 697 (1993) notes 47-49 and accompanying text (suggested price controls for AZT (AIDS drug) during the Clinton administration in 1993 were met with staunch resistance and pushback from drug companies).

One can describe this phenomenon as a form of regulatory failure—specifically, regulatory failure by success.

#### A. Existing Theories of Regulatory Failure

As described in the opening of this article, prior literature on regulation and regulatory reform focuses on three commonly identified forms of failure: regulatory capture, ineffective design, and regulatory arbitrage. Regulatory capture occurs when regulatory agencies are dominated by the industries they are designed to regulate, inevitably leading to the promotion of industry-specific interests at the expense of the public interest.<sup>126</sup> Ineffective regulatory design allows firms to circumvent regulation by exploiting regulatory loopholes, causing unintended consequences even if the regulation is successful to an extent.<sup>127</sup> Regulatory arbitrage, while commonly discussed in the context of companies taking advantage of jurisdictional differences to benefit from a more lenient regulatory regime, generally refers to any regulatory manipulation leading to the “avoidance of laws in ways that evade the law’s intent or purpose but do not actually constitute unlawful behavior.”<sup>128</sup>

Aspects of regulatory capture, ineffective design, and regulatory arbitrage operate within the cancer curse phenomenon.

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<sup>126.</sup> See Stigler, *supra* note 6, at 3 (introducing the concept of regulatory capture and arguing that “as a rule, regulation is acquired by the industry and is designed and operated primarily for its benefit”). See also Livermore & Revesz, *supra* note 6, at 1340 (defining regulatory capture as “situations where organized interest groups successfully act to vindicate their goals through government policy at the expense of the public interest”); Shapiro, *supra* note 6 (describing regulatory capture, its causes, and potential solutions); Brown, *supra* note 6 (describing how the investment management industry is influencing the SEC to maximize profits).

<sup>127.</sup> See, e.g., Hemphill, *supra* note 7 (examining pharmaceutical patent settlements as a regulatory design problem); Bean, *supra* note 7 (illustrating regulatory failure caused by insufficient regulatory design for endangered species). See also Litan & Singer, *supra* note 7, at 535 (2007) (arguing that there is “much investment at stake in designing the optimal regulatory framework” for the U.S. broadband industry); Weber et al., *supra* note 7 (describing key areas of consideration when designing financial regulation).

<sup>128.</sup> See Ronald Turner, *Reactions of the Regulated: A Federal Labor Law Example*, 17 LAB. LAW. 479, 479 (2002). See also LEO KATZ, ILL-GOTTEN GAINS: EVASION, BLACKMAIL, FRAUD, AND KINDRED PUZZLES OF THE LAW 4 (1996) (coining the term “avoision”); Garcia, *supra* note 8 (describing regulatory arbitrage in copyright); Fleischer, *supra* note 8 (defining regulatory arbitrage as a “technique used to avoid taxes, accounting rules, securities disclosure, and other regulatory costs . . . exploits the gap between the economic substance of a transaction and its legal or regulatory treatment”); Partnoy, *supra* note 8 (describing regulatory arbitrage in finance); Frieden, *supra* note 8 (describing regulatory arbitrage in telecommunications); Burk, *supra* note 8 (characterizing regulatory arbitrage as either ontological (“relabeling an activity rather than . . . redesigning or physically altering a product”), technological (circumventing regulation through the “implementation of new procedures, new expertise, and perhaps even new apparatus”), or both).

For example, industry capture undoubtedly played a role in the FDA's tolerance of salami slicing behaviors.<sup>129</sup> In discussing repurposing behaviors such as salami slicing, one press article noted the following exchange with Dr. Gayatri Rao, director of the FDA's Office of Orphan Drug Products Development:

“‘We always talked about how we permit the second bite of the apple, third bite of the apple, as one small way to incentivize repurposing,’ Rao said, noting that industry and patient groups have been pressing the FDA for even stronger incentives. ‘Now, all of [a] sudden, it seems like, wow, this practice may be driving up prices.’”<sup>130</sup>

In fact, one might reasonably ask whether the entire effect across all of these regulatory programs is best characterized as the silent hand of industry, carefully moving the pieces of the chess board into place. That would be a story of industry capture, carefully lobbying and moving each agency and each initiative across decades. It would require an extraordinary level of patience, plotting, and brilliant strategic coordination. The pharmaceutical industry certainly boasts a powerful lobbying record, spending \$167 million on lobbying in 2017, \$169 million in 2018, and employing nearly 800 lobbyists.<sup>131</sup> However, a story of such pure genius would be a tough act to pull off. Human beings are fallible, legislative and regulatory environments are quixotic, and manipulation of the body politic in such a sustained and comprehensive manner would be challenging. More likely, the story is one of opportunistic behavior—an industry adept at taking advantage of the hidden incentives tucked within various regulatory regimes, undoubtedly combined with some clever lobbying along the way. This characterization would come closer to

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<sup>129.</sup> See JOHN MASON, CITIZENS FOR RESPONSIBILITY AND ETHICS IN WASHINGTON, A BITTER PILL: HOW BIG PHARMA LOBBIES TO KEEP PRESCRIPTION DRUG PRICES HIGH 8–9 (2018) (noting that specific industry groups and drug companies reported lobbying for orphan drug legislation related to orphan drug designations and the extension of exclusivity periods for old drugs if approved for new uses in orphan diseases).

<sup>130.</sup> See Tribble & Lupkin, *supra* note 59.

<sup>131.</sup> See CTR. FOR RESPONSIVE POL., INDUSTRY PROFILE: PHARMACEUTICAL MANUFACTURING, 2017 (2017), <https://www.opensecrets.org/lobby/induscode.php?id=H4300&year=2017>; CTR. FOR RESPONSIVE POL., INDUSTRY PROFILE: PHARMACEUTICAL MANUFACTURING, 2018 (2018), <https://www.opensecrets.org/lobby/induscode.php?id=H4300&year=2018>; CTR. FOR RESPONSIVE POL., PHARMACEUTICAL MANUFACTURING: LOBBYING, 2019 (2019), <https://www.opensecrets.org/industries/lobbying.php?cycle=2020&ind=H4300>. See also Nick Florko & Lev Facher, *How Pharma, Under Attack from All Sides, Keeps Winning in Washington*, STAT+ (July 16, 2019), <https://www.statnews.com/2019/07/16/pharma-still-winning/>; Feldman, *supra* note 55 (tracing the history of more than a dozen major regulatory rights to Congressional terms in which the industry had to accept an initiative it opposed).

ineffective regulatory design or regulatory arbitrage, in which either a particular regulatory scheme allows for the exploitation of loopholes for firms to circumvent the regulation, perhaps with unintended consequences, or manipulation leading to outright avoidance of the regulation by legal means.

Nevertheless, industry capture of regulatory agencies cannot provide a full explanation of the shift to cancer. The pharmaceutical industry is not monolithic. As such, although an agency focus on cancer might benefit some players, it would not benefit others. Moreover, there is no reason to believe that companies with cancer drugs have greater political power than others. In short, industry capture cannot begin to answer the question of why research and treatment focus has shifted so sharply towards cancer.

*B. The Need for a Regulatory Failure Theory Based on Success*

One can certainly observe strains of ineffective regulatory design and regulatory arbitrage in evergreening behavior, with its ability to avoid the end of protection or to evade the impact of the system for rapid approval of follow-on drugs. Neither ineffective design nor regulatory arbitrage, however, can capture a full and accurate picture of the regulatory failure at issue. In fact, the regulations have not so much failed as they have succeeded. In some cases, they have succeeded well beyond expectations—for example, speeding approvals of cancer drugs at the expense of disincentivizing non-cancer drugs.<sup>132</sup> In other cases, they have succeeded in ways unanticipated—for example, advancing cancer drugs specifically, rather than drugs for rare and small population diseases in general.<sup>133</sup> A more accurate description of this regulatory outcome must be based on a vision of success rather than failure, albeit a level and extent of success that may not match the expectations of the regulatory design.

The larger question concerns what one might learn from an observation of regulatory failure by success, either in relation to cancer therapeutics or in the abstract. Specifically, one should contemplate whether it is problematic that the regulatory outcome transpired in a manner unintended in scope or direction. In the case of cancer therapeutics, one can identify three potential areas of exploration, two of which relate largely to unintended direction and one of which relates to unintended scope.

The inquiry should begin from the perspective that regulatory initiatives have created a form of cancer moonshot but done so indirectly. Rather than making a conscious effort to focus society's resources in the direction of cancer drugs, we have unwittingly

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<sup>132.</sup> See *supra* Part II.A & Part II.B.

<sup>133.</sup> See *id.*

arrived at this juncture. Is the fact that society is indirectly engaging in a cancer moonshot problematic? One could conceivably argue in either direction for each of three areas of potential concern: unintended consequences; lack of transparency; and failure to reach the goal.

First, one could argue that activity without thought can lead to unintended and unpleasant consequences.<sup>134</sup> As prior literature has described, unintended regulatory consequences can occur even when society aims at a particular goal, and thought and intention are no guarantee of avoiding unintended consequences.<sup>135</sup> Good intentions may yield less than good results.<sup>136</sup> The likelihood of unpleasant consequences might even be greater with accidental goals.

Unintended regulatory direction, however, can have advantages. Amidst constant lobbying and legislative logrolling, government can easily bungle its regulatory agenda. Approaching a goal by indirect means—for example, an indirect moonshot—might protect against the type of diversion that can occur in normal governmental processes. From this perspective, one could argue that opacity in governance might be a positive attribute.<sup>137</sup> Parties can

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<sup>134.</sup> Cf. Roscoe Pound, *Mechanical Jurisprudence*, 8 COLUM. L. REV. 605, 606–14 (1908) (arguing that when longstanding legal doctrines are unexamined and applied mechanically, they ultimately fail to respond appropriately to the human condition).

<sup>135.</sup> See, e.g., Cass R. Sunstein, *Political Equality and Unintended Consequences*, 94 COLUM. L. REV. 1390 (1994) (outlining some of the harmful but unintended consequences of campaign finance regulation); Samuel Issacharoff & George Loewenstein, *Unintended Consequences of Mandatory Disclosure*, 73 TEX. L. REV. 753 (1995) (concluding that mandatory disclosure will have the opposite of its intended effect); Burk, *supra* note 8 (suggesting that unintended innovation arising from the exploitation regulatory loopholes may be socially beneficial); Bean, *supra* note 7, at 414 (arguing that “to improve the current condition of many endangered or threatened species, it is insufficient simply to prohibit harmful activities” and prohibitory regulation alone creates unintended consequences that are detrimental); Litan & Singer, *supra* note 7, at 572 (suggesting that one of the unintended consequences of net neutrality regulation would be to “undermine the incentive of access providers and content providers to invest in new technologies”).

<sup>136.</sup> See ROBIN FELDMAN, *DRUGS, MONEY, AND SECRET HANDSHAKES: THE UNSTOPPABLE GROWTH OF PRESCRIPTION DRUG PRICES* 87 (2019) (describing provisions of the Affordable Care Act that were intended to control the price of drugs for seniors but have had significantly different results); HORST SIEBERT, *RULES FOR THE GLOBAL ECONOMY* 164 (2016) (citing Howard Davies, *The Future of Financial Regulation*, 9 WORLD ECON. 11 (2008) and noting that “new regulations, introduced with the best of intentions, may have hidden incentive effects which may represent new moral hazards so that the institutional arrangement is not improved”).

<sup>137.</sup> For legal scholarship on the limits of transparency and disclosure in government and regulation, see also Joanna Shepherd, *Is More Information Always Better? Mandatory Disclosure Regulations in the Prescription Drug Market*, 99 CORNELL L. REV. ONLINE 1 (2013); Caroline Bradley, *Transparency is the New Opacity: Constructing*

neither capture nor manipulate what is unseen.<sup>138</sup> The problems with such an approach, however, are numerous and substantial. The notion that unexamined and unintended governance might be advantageous undermines the entire rationale for governance.<sup>139</sup> And it certainly undermines historic priorities of open government. Moreover, the possibility that a direction could even be truly unintentional and entirely hidden in the modern world defies common sense. Someone's goals will be operating; some parties will recognize the mechanisms at work.<sup>140</sup> It would be unrealistic to think that goals could be attained without any leakage.

The question of leakage leads to the third potential problem, and one that seems more than abstract in the case of cancer drugs. Specifically, are we succeeding at the cancer moonshot? Are we getting the type of innovation one might desire in treating cancer, even if it is not the innovation contemplated with the different regulatory initiatives? Along these lines, the scholar Dan Burk has argued that anticipating and allowing companies to practice avoision, "a type of formal compliance, or at least an ostensible change in behavior, but . . . not necessarily the type of compliance the regulator might have anticipated,"<sup>141</sup> can be a positive for society, if appropriate innovation results.<sup>142</sup> Perhaps the failure by success we are experiencing is a good thing.

At the moment, it appears that these regulatory programs are incentivizing a lot of activity with minimal effects on extending the quality and quantity of life in many cases. Although cancer

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*Financial Regulation after the Crisis*, 1 AM. U. BUS. L. REV. 7 (2011); Mark Fenster, *The Opacity of Transparency*, 91 IOWA L. REV. 885 (2006).

<sup>138.</sup> *But see* LIAM WREN-LEWIS, EMERGING ISSUES IN COMPETITION, COLLUSION, AND REGULATION OF NETWORK INDUSTRIES 159 (Antonio Estache ed. 2011) (suggesting that "making the regulator's workings transparent to the government and citizens is likely to reduce the risk of capture").

<sup>139.</sup> *See also* John Locke, TWO TREATISES OF GOVERNMENT § 123 (Peter Laslett, ed., Cambridge Univ. Press 1988) (1690) (positing that government exists so that man can avoid the state of war that often occurs in the state of nature).

<sup>140.</sup> *See also* GLENN BLACKMON, INCENTIVE REGULATION AND THE REGULATION OF INCENTIVES 9 (describing the hidden action problem stemming from the information asymmetry that exists between the regulator and regulated firm which creates "the opportunity for the [regulated] firm to improve its economic payoffs by engaging in unobserved, socially expensive behavior, or 'abuse.'").

<sup>141.</sup> *See* Burk, *supra* note 8, at 11; *see also* Katz, *supra* note 129, at 4 (coining the term "avoision").

<sup>142.</sup> *See* Burk, *supra* note 8, at 1–12. This discussion occurs against a backdrop of regulatory literature debating the extent to which regulatory penalties may be more effective than regulatory rewards in incentivizing innovation. *See, e.g.*, Ian Ayres & Amy Kapczynski, *Innovation Sticks: The Limited Case for Penalizing Failures to Innovate*, 82 U. CHI. L. REV. 1781, 1781 (2015). For arguments related to whether patents or regulatory prizes best stimulate innovation, *see* Daniel J. Hemel & Lisa L. Ouellette, *Beyond the Patents-Prizes Debate*, 92 TEX. L. REV. 303 (2013), and sources cited therein.

therapeutics have yielded important progress for some patients and certain types of cancers—such as breast cancer and Hodgkins lymphoma—progress on the whole is disappointing. Adjusting for the aging of the population, the overall death rate from cancer has fallen only five percent since 1950, and some attribute the decline in cancer mortality since the 1990s to lifestyle changes such as a decline in smoking.<sup>143</sup> Many cancer drugs, including extremely expensive therapeutics, do no more than extend life for limited periods of time, if at all. One recent study, for example, found that cancer drug trials wildly exaggerate their success in extending patient survival, and that the average cancer drug extends life only marginally. Of the 53 new cancer drugs approved between 2003 and 2013 by the FDA, a third did not improve overall survival at all relative to preexisting treatments, and nearly another third only improved overall survival by three months or less. Average improvement in overall survival with these “novel” medications was as little as 3.43 months.<sup>144</sup>

Another study looking at new cancer drugs for solid tumors found similar results, with a median overall survival of 2.1 months.<sup>145</sup>

In addition, current clinical trial processes for oncological therapies are coming under fire for repeatedly testing an approach even after it has failed multiple times.<sup>146</sup> Clinical trials often involve patients with advanced-stage cancers, desperately hoping for a chance at recovery, and some commentators have argued that industry is “duplicating harm to patients” when it replicates studies that lower one’s overall survival rate.<sup>147</sup> When one’s life or the life of a loved one is threatened, any extension is deeply meaningful. From a societal perspective, however, one might hope for something more.

In addition, in the rush to speed cancer drugs through approval, the FDA may be using measures that are poor predictors of clinical success. As scholarship has noted, surrogate measures such as the ones the FDA is relying on have not shown a strong correlation with clinical outcomes in cancer.<sup>148</sup>

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<sup>143.</sup> See John Horgan, *Sorry, But So Far War on Cancer Has Been a Bust*, SCI. AM.: CROSS-CHECK (May 21, 2014), <https://blogs.scientificamerican.com/cross-check/sorry-but-so-far-war-on-cancer-has-been-a-bust/>.

<sup>144.</sup> SALAS-VEGA ET AL., *SUPRA* NOTE 9, AT 382–90.

<sup>145.</sup> See Tito Fojo et al., *Unintended Consequences of Expensive Cancer Therapeutics—The Pursuit of Marginal Indications and a Me-Too Mentality that Stifles Innovation and Creativity: The John Conley Lecture*, 140 JAMA OTOLARYNGOLOGY-HEAD & NECK SURGERY 1225, 1225 (2014). See also Sham Mailankody & Vinay Prasad, *Overall Survival in Cancer Drug Trials as a New Surrogate End Point for Overall Survival in the Real World*, 3 JAMA ONCOL. 889, 889–90 (2017).

<sup>146.</sup> See Gail McIntyre, *Enough With the Me-Too Drugs. New Treatments Should Be Worthy of the People Who Invest Their Lives in Clinical Trials*, STAT+ (Sept. 4, 2019), <https://www.statnews.com/2019/09/04/me-too-drugs-cancer-clinical-trials/>.

<sup>147.</sup> *Id.*

<sup>148.</sup> See Darrow et al., *supra* note 84, at 1449.

One could argue that society will only achieve the big leaps in cancer treatment if it takes baby steps. One cannot know if that will be the case in some far distant future. For the moment, however, we seem to be incentivizing very little in the way of “giant leap[s] for mankind.”<sup>149</sup> That, in the end, is the ultimate danger of an accidental moonshot: it may incentivize a flurry of activity but not an actual moon landing.

#### IV. NORMATIVE PERSPECTIVE—DO WE WANT A CANCER MOONSHOT?

The prior section operated under the assumption that society wishes to focus its resources on a cancer moonshot, examining the question from the perspective of whether unintended regulation is an efficient and effective choice. In contrast, one might also consider the normative perspective of whether society should, indeed, focus its efforts in the manner.

The question is challenging, and even its contemplation risks plunging the reader into deeply uncomfortable territory. It requires one to choose among different categories of lives and among the suffering that might be alleviated or the joy conferred. Is extending the life of an adult, for example, of greater value than preventing a child from being crippled?

Focusing on cancer therapeutics also involves decisions about the timing of healthcare spending. Specifically, should the priority be the end-stages of life or when there is the possibility of many years of life. For the most part, we try to avoid that issue in healthcare public policy, but it is brought to the forefront with the shift to cancer. Despite rhetoric that evokes children either suffering from cancer or watching their parents suffer—a trope that this article has employed as well—cancer deaths are concentrated in the old rather than the young. In fact, the majority of people who die from cancer are over the age of 72, and almost 90 percent are older than 55.<sup>150</sup> Focusing research and treatment efforts on this cohort necessarily involves de-emphasizing research and treatment efforts for those at a younger age, as well as for those in the same age range who suffer from Alzheimer’s, heart disease, and other non-cancer ailments. No budget is endless, and by moving aggressively into the cancer realm,

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<sup>149.</sup> The quote is attributed to astronaut Neil Armstrong upon being the first person to walk on Earth’s moon. See Natalie Wolchover, “*One Small Step for Man*”: Was Neil Armstrong Misquoted? SPACE.COM (Aug. 27, 2012), <https://www.space.com/17307-neil-armstrong-one-small-step-quote.html> (discussing whether the first part of Armstrong’s quote was “one small step for man” or “one small step for a man”).

<sup>150.</sup> See SURVEILLANCE, EPIDEMIOLOGY, AND END RESULTS (SEER) PROGRAM, *supra* note 10.

we may be leaving other healthcare needs behind. These are excruciatingly difficult choices.

The choices we make do not improve, however, by virtue of being ignored. As previously noted in the context of courts that wrap their decisions in scientific jargon, shrouding one's legal choices merely "provide[s] camouflage for the failure to resolve issues or to resolve them in a rational manner."<sup>151</sup>

Moreover, the law constantly engages in this type of weighing and balancing, whether implicitly or explicitly. Extensive legal and philosophical explorations exist in the literature. In particular, classic jurisprudential analyses grounded in ethical universalism, the most commonly applied modern form of utilitarianism, evaluate courses of action based on the overall balance of good over bad results for the community as a whole.<sup>152</sup> In the context of health care, such analyses necessarily require comparing the value of different lives.<sup>153</sup> In addition, disparate doctrinal arenas including torts and insurance law measure the value of a life, explicitly considering a person's likely remaining life span, their earning capacity, and the presence of a partner or other family members. The healthcare system itself is no stranger to such weighing and balancing, with the notion of triage occupying a central role in the delivery of any modern healthcare system. An extensive discussion of this literature is outside the scope of this

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<sup>151</sup>. See Feldman, *supra* note 11, at 193 (discussing the danger when courts lose themselves in the technical aspects of a case); see also *id.* at 28 (citing the discussion of H.L.A. Hart in Brian Bix, *Positively Positivism*, 85 VA. L. REV. 896 (1999) and noting that "the failure to grasp the nettles of our legal quandaries creates chaos in the doctrines").

<sup>152</sup>. See ROBIN FELDMAN, *RETHINKING PATENT RIGHTS* 76–77 (Harvard 2012) (comparing consequentialist theories—which are based on evaluating the effects of one's actions—with non-consequentialist or rights-based theories—which hold that actions can be judged regardless of the outcomes—and further comparing the differences between ethical egoism—in which individuals choose their actions to maximize their personal good—with ethical universalism or utilitarianism—in which actions should be chosen to maximize the good for the community as a whole. For classic literature on law and moral philosophy, see *UTILITARIANISM AND BEYOND* 3–4 (Amartya Sen & Bernard Williams, eds., Cambridge Univ. Press 2001); RONALD DWORKIN, *TAKING RIGHTS SERIOUSLY* 234 (1977); ROBERT NOZICK, *ANARCHY, STATE, AND UTOPIA* 28–29 (1974); WILLIAM K. FRANKENA, *ETHICS* (2d ed. 1973); see also SAMUEL SCHEFFLER, *THE REJECTION OF CONSEQUENTIALISM: A PHILOSOPHICAL INVESTIGATION OF THE CONSIDERATIONS UNDERLYING RIVAL MORAL CONCEPTIONS* 1 (1982). For a discussion comparing and contrasting literature in the fields of "bioethics" and "health and human rights," see David Benatar, *Bioethics and Health and Human Rights: A Critical View*, 32 J. MED. ETHICS 17 (2006); see also JONATHAN BARON, *AGAINST BIOETHICS* (MIT Press 2006).

<sup>153</sup>. See, e.g., JOHN HARRIS, *THE VALUE OF LIFE: AN INTRODUCTION TO MEDICAL ETHICS* (1985); JOHN RAWLS, *A THEORY OF JUSTICE* (1971); JONATHAN GLOVER, *CAUSING DEATHS AND SAVING LIVES* (1977); see also *ENCYCLOPEDIA OF BIOETHICS* (Stephen G. Post et al. eds., 3d ed. 2004).

article, and beyond the point as well. The point is simply to note that throughout legal history, law and legal literature have grappled with issues that force society to consider head-on the value of life in varying circumstances. Although the terrain is difficult, one need not assume that law is incapable or ill-equipped to engage in the inquiry. In this case, the unexamined choice to tilt sharply in the direction of cancer research and treatment imposes costs on society that may become intolerable over time.

## V. CONCLUSION

As this article demonstrates, disparate regulatory initiatives, individually and on the whole, have shifted the healthcare industry's focus strongly in the direction of cancer research and treatment. From exploration dollars to approvals to national expenditures, cancer occupies an increasingly significant portion of national time and resources. These initiatives occur both as a result of positive policies and as a result of negative policies. They include policies related to clinical trials, accelerated approvals, generics versus biosimilars, pricing and reimbursement models, and a dearth of requirements for cost-benefit analyses.

We have not reached this point by coordinated design. Rather, many of the regulatory initiatives either were not intended to focus on cancer or have resulted in behavioral shifts far beyond what was contemplated. The cancer phenomenon can be described as a form of regulatory failure. Although this regulatory failure contains elements of previously identified failure forms—such as industry capture, improper design, and regulatory arbitrage—none of the current theories of regulatory failure can fully capture the cancer phenomenon. Rather, this form of regulatory failure is best defined as failure by success. Society has succeeded in a concentrated focus, either outside the intent or beyond the magnitude of actions contemplated. There may be certain advantages to accidental regulatory focus, including avoiding industry capture and governmental diversion. Nevertheless, the costs of accidental focus significantly outweigh the benefits, including the potential for failing to reach even the target at which one aims accidentally.

When engaging in a moonshot, it is best to do so with open eyes, given that flying blind is a great way to crash and burn. The greatest risk is not simply that our moonshot will fail, but that the nation's public health needs will be left in the dust.