



# Prescription Drug Pricing: Scam or Scapegoat?

By Thomas Peter Stossel

February 2016

## KEY POINTS

- *The financial challenges of introducing expensive new “specialty” drugs and abrupt increases in prices charged for some older generic medications have led payers, physicians, and politicians to demand price controls on all drug manufacturers.*
- *This paper reviews the contributions of drugs to improved health and the structural and economic features of drug development responsible for the price increases.*
- *It argues that the principal driver of specialty drug pricing is the hardwired uncertainty of biology and resulting extreme risk of drug development.*
- *Although some pricing practices are arguably antisocial, ideologically and politically motivated misrepresentation of the pharmaceutical industry has obscured the fact that wide application of arbitrary price controls necessarily must impair drug innovation. All health care stakeholders should keep this fact in mind when addressing the stresses incurred by high drug prices.*

America is singular among the nations in that its government does not control prescription medication prices, despite heavily regulating the pharmaceutical industry in many other respects. Drug prices, however, surface from time to time as a topic of political debate. The most recent instance centers largely on the high prices pharmaceutical manufacturers have been asking for a particular class of medications known as “specialty drugs.”

No exact definition for specialty drugs exists, but common usage applies the term to drugs that are expensive; address life-threatening diseases; may be complicated to produce, store, and administer; and often require elaborate patient monitoring. Although drugs and medical devices in general represent a small fraction (about 13 percent) of

total health care expenditures, specialty drug prices temporarily accounted for the sharpest upticks (around 12 percent) in such spending.<sup>1</sup>

The increases reflect not only what companies have charged for new drugs upon regulatory approval and launch of sales, but also steady increases in the prices of some brand specialty drugs that have been on the market for some time.

Public and private insurers, pharmacies, health systems, and patients stuck with unexpectedly high drug bills have complained. Many physicians who prescribe specialty drugs have publicly stated that specialty drug pricing is “out of control” and “unsustainable” and that patients needing specialty drugs suffer financial hardship and may not comply with recommended

treatments because of it.<sup>2</sup> A survey reported that consumers' major health care concern is whether they can afford to pay for their drugs.<sup>3</sup> These concerns are prevalent items reported by the news media.

One exacerbation of the furor over drug prices erupted when a pharmaceutical company named Turing abruptly raised 56-fold the list price of pyrimethamine, an antibiotic used to treat infections in patients with compromised immune systems. Another involved Valeant Pharmaceuticals, a Canadian company, which markedly raised prices of two drugs made by pharmaceutical manufacturers it had acquired that treat heart conditions. Although none of these medicines qualify as a specialty drug—they are very old, no longer patented—the public outrage condemned the entire industry. Congressional hearings ensued, and many public figures including presidential candidates called for medication price controls across the board.<sup>4</sup>

### **Imposition of drug price controls in the US will compromise access to better future therapies, not just for Americans, but also for patients' worldwide.**

Lending energy to criticism of drug pricing are notions that health care is a “right” and should not be treated as a commodity and that imposing high prices on potentially life-saving drugs is immoral.<sup>5</sup> These ideas fuel frequent resort to the “G-word” (greed) in criticisms of the pharmaceutical industry's pricing practices.<sup>6</sup> Former Labor Secretary Robert Reich has compared the pharmaceutical industry to hedge funds, alleging that both are “rotten apples that are costing Americans a bundle.”<sup>7</sup>

Drug pricing discussions involve philosophical questions about society's health priorities and resource allocations for which no easy answers exist. In this article, I propose that misrepresentation of the far less debatable technical aspects drug development has obscured these important fundamentals. The responsibility for this distortion lies with academics, the media, and litigators who have relentlessly demonized

the pharmaceutical industry—pejoratively labeled as “Big Pharma”—over the past 30 years. They have succeeded in degrading its public reputation. I refer to this demonization as the “pharmaphobia” narrative.”<sup>8</sup>

I also explain that the debates have largely ignored a totally unique and very poorly appreciated feature of drug development: the enormous risks inherent in drug development due to the unpredictability of biology. I cannot think of any commercial activity in which the cost of taking a product to market bears so little economic relationship to its development, production, or assessments of present value. Because discerning investors with skin in the game assume that risk, the only way to sustain drug development is prices and sales that are high enough to provide them with sufficient returns.

This anomalous nature of drug development, I believe, explains why the American government's hands-off approach has facilitated this country's remarkable drug innovation accomplishments. It also predicts that imposition of drug price controls in the US will compromise access to better future therapies, not just for Americans, but also for patients' worldwide because America is the world's hub of drug innovation.

### **The Specialty Drug Spectrum and the Evolution of Price Criticism**

Almost every specialty drug presents a unique economic scenario based on the condition it treats and the circumstances of its development and use. Three examples illustrate.

The first is Kalydeco, a drug that treats cystic fibrosis, a genetic disease affecting a relatively small numbers of patients. Cystic fibrosis is an “orphan” disease that afflicts about 30,000 people in the United States. Previously, most affected patients experienced progressive lung deterioration and premature death. In 2012, the US Food and Drug Administration (FDA) approved a drug developed by Vertex Pharmaceuticals, named Kalydeco, that slows or

prevents the ravages of the disease in selected patients.

Vertex invoked several reasons to justify pricing Kalydeco at \$294,000 per year. One was the effectiveness of Kalydeco in saving lives and improving quality of life. Another was the fact that patients on the treatment suffered fewer complications requiring expensive medical interventions. Yet another was that the small patient population eligible for treatment mandated a high price to recover the costs of developing the drug. Although some complained about the drug's pricing, payers covered it because the small population of treatment-eligible patients mitigated its economic impact, even though the patients take the drug for their entire, now extended lives.

A second example concerns a therapy for hepatitis C, a far more prevalent, chronic liver disease caused by a family of viruses. In early 2013, the Gilead pharmaceutical company obtained FDA approval of a pill form of Sovaldi, a drug that could *cure* hepatitis C. Gilead set a list price for Sovaldi that would average \$85,000 for a treatment course.

The mainstay of previous hepatitis C therapy involved administration of interferon, an immune system stimulant, in combination with drugs. Interferon causes severe side effects, and the treatment only slows disease progression. In 2011, Vertex and Merck obtained FDA approval of drugs that were more effective in attacking the virus, although they were not curative and still required interferon treatment.

Sovaldi, however, was a game changer. Even though most patients also needed interferon therapy, the potential for a cure and a short (30- to 90-day) course of treatment offset this disadvantage. In October 2014, Gilead received FDA approval for Harvoni, a second antiviral drug that eliminated the interferon requirement altogether and expanded the varieties of hepatitis C amenable to cure. The advent of this powerful competition caused Vertex and Merck to stop marketing their hepatitis C drugs. Gilead priced a Harvoni treatment course at \$95,000.

The introduction of Sovaldi and Harvoni also had game-changing economic consequences. On the positive side, Gilead's cure of a potentially lethal

disease can keep patients economically productive. It can *save* health care costs by shortening the duration of confrontation of hepatitis C patients with medical providers, eliminating expensive complications of hepatitis, such as gastrointestinal bleeding and liver cancer, and obviating the need for liver transplantation that is the only option for the most advanced cases. The average cost of that procedure is \$350,000, and the transplant patients must take immunosuppressive drugs for the rest of their lives to prevent their bodies from rejecting the transplants. From a public health standpoint, eliminating the hepatitis C from individual patients stops its spread. Eventually such treatment could eradicate the disease and its clinical and economic costs. However, the short-term financial stress elicited by the introduction of these drugs has caused payers and politicians to qualify the good news.

An estimated 5 million people in America are infected with hepatitis C. Many infected individuals have no symptoms early on, and the limitations of earlier therapies discouraged aggressive efforts at diagnosis or treating patients who did not have advanced disease. The effectiveness and tolerability of Sovaldi and Harvoni changed this dynamic. Clinicians encouraged their patients known to have hepatitis C to undergo treatment, and Gilead has aggressively promoted diagnostic testing. The resulting upsurge in treatment-eligible patients accounted for a significant fraction of the recent increase in drug expenditures.

Hepatitis C transmission occurs by exposure to virus-containing blood, and the majority of Americans infected with hepatitis C are current or former substance abusers who were infected by contaminated needles. As a result of this demographic—which includes many patients residing in jails—the burden of paying for the medications in the United States has largely fallen to Medicaid rather than to private insurers. A lengthy Senate Finance Committee report issued in December 2015 chronicled the financial burden incurred by public payers and castigated Gilead for having overpriced its drugs.<sup>9</sup>

A third problematic specialty drug-pricing scenario is for new drugs that treat advanced malignant tumors. When I graduated from

medical school nearly 50 years ago, once cancers arising from various body tissues—defined as solid tumors—had spread beyond local sites amenable to surgical removal or bombardment with ionizing radiation, they were incurable with rare exceptions. At that time, a handful of “chemotherapy” drugs could produce remissions of malignancies of the blood (leukemias and lymphomas) that disseminate throughout the body from the start. But these responses were transient, lasting no more than a few weeks, and the medications caused serious side effects.

One advance in the 1960s was the finding that combining these chemotherapy drugs could produce durable remissions and even cures of some leukemias and lymphomas. Hopes that this approaches would work well in many malignancies quickly faded, however, and therapies for most disseminated cancers have by and large evolved incrementally with a few exceptions. Since most of this therapeutic evolution involved adjusting the application, dosing, and timing of old—no longer patent-protected (generic)—drugs, cost was not a major concern. Unsurprisingly, however, this approach has its limits, and only availability of new drugs could promote progress.

### **When drug patents or exclusivity intervals expire, the ability of more than one company to introduce generic drugs can result in significant cost reductions.**

Paralleling the emergence of new cancer drugs has been accrual of a large amount of diagnostic information on the properties of cancers. Malignancies arising in the same organ turn out to have very different biological behaviors and responsiveness to treatments. A consequence of this “personalized” knowledge is that while patients previously thought to have the same type of cancer received identical therapy, now the number of patients eligible for particular medications can be small. This increased selectivity and the fact that in most instances the new treatments provide only minimal life prolongation and therefore duration of sales has

pushed emerging cancer drugs into the high-priced specialty category. Cancer specialists (oncologists) have been among the most vocal objectors to high drug prices and have even attempted to mount a grassroots patient protest.<sup>10</sup>

## **Fundamentals of Drug Development and Pricing**

Since 1962, the FDA has required companies to demonstrate both the effectiveness and the safety of new drugs they develop through “adequate and well-conducted studies.” This stipulation added the considerable cost of performing such trials to the expense of drug development. To help keep drug companies faced with these challenges solvent, Congress superimposed periods of marketing exclusivity, tax breaks, and other protections on top of the intellectual property rights of patented (brand) drugs.

The consequence of these regulations and the adjustments to them is that the innovative pharmaceutical industry sells its FDA-approved products under temporary monopoly status that eliminates price competition. In cases in which a competing product does emerge, prices fall, as in July 2015 when the FDA approved a combination of drugs for hepatitis C manufactured by the firms AbbVie and Bristol Myers-Squibb. To sustain sales of Harvoni, Gilead abruptly lowered its price. When drug patents or exclusivity intervals expire, the ability of more than one company to introduce generic drugs can result in significant cost reductions.

The brand-drug manufacturers’ response to the pricing criticisms has been to cite what they claim is the very high and consistently rising cost of drug approvals by regulators. The most widely referenced source of that information is data compiled by economists Joseph DiMasi and Henry Grabowski. Over several decades, their estimates have risen from hundreds of millions of dollars to the most recent capitalized sum of \$2.6 billion in 2015.<sup>11</sup> If the publicly available annual expenditures of pharmaceutical companies are divided by the number of drugs approved by the FDA, the resulting figures are plausibly close to these economists’ estimates.

An important additional point, however, is that what companies charge for drugs is only one of myriad factors determining actual drug payments. The complex financial ecosystem is riddled with vested interests, the nooks and crannies from which the numerous distracting side-issues arise that obscure what I believe is the central to the pricing issue: the difficulty and expense of drug innovation.

Manufacturers do not *sell* specialty drugs directly to patients, although they *market* to them through direct-to-consumer advertising. Rather, they primarily sell them to pharmacies, directly or predominantly through pharmacy benefit management organizations and other distribution channels. Drug companies may also directly supply physicians in private or hospital-based practices who administer drugs by injection to treat diseases such as cancer. These practices can profit by selling the specialty drugs above their purchase price, and some physicians engaged in this “buy and bill” activity are oncologists who have been so critical of manufacturers’ prices.

Historically, the Centers for Medicare and Medicaid Services, the federal drug-financing bureaucracy, have followed what private insurance pays for drugs. During the 2003 congressional debates leading to the establishment of Medicare’s coverage of prescription drugs (Part D), the pharmaceutical industry fought hard to resist allowing the government to “negotiate” prices of the drugs covered by that program or stipulate what drugs it would cover. The industry nominally succeeded, but considerable de facto discounting affects government payments. For example, to have their drugs included in Medicaid’s inventory, manufacturers must participate in a national rebate program that requires them to sell to Medicaid at a rate discounted below what they negotiate with private purchasers. A similar rebate mechanism applies to drug sales to the Veterans Administration, the Defense Department, the Indian Health Service, and the Coast Guard.

Legislation known as “340B” empowers health services providing poorly or unreimbursed care to indigent patients to receive deep discounts on purchased drugs and yet collect market-priced reimbursements from insurers. The

pharmaceutical industry alleges that many health centers that provide relatively little free care exploit this loophole to purchase drugs cheaply and sell them at market prices.<sup>12</sup>

Importantly, merging of health care systems—including insurers, pharmacies, and pharmacy benefit managers—has created major discounting of list prices. These consolidated players have the leverage to demand reduced drug prices in exchange for selecting particular vendors’ drugs and promoting higher sales volumes. The insurance industry, which has also consolidated, has resorted to creating barriers for patients to receive drugs, not covering certain drugs at all, or requiring patients to contribute copays to obtain them.

Additionally, insurers impose an array of “prior-approval” requirements that operationally are rationing schemes. One has been to demand that physicians prescribing hepatitis C drugs document that their patients have an advanced degree of liver damage, necessitating an invasive biopsy procedure with possible side effects. Another is to capitalize on the stigma of addiction by not covering treatment costs unless a patient had been free of substance abuse for a prescribed period of time. Although not applied in the case of hepatitis C therapy, payers have refused to pay for specialty drug treatments until patients fail to respond to older medications, an approach defined as “step therapy.”

Gilead reacted to this resistance by providing free hepatitis C medications to some poor patients, negotiating discounts to government payers, and recruiting prominent liver specialists to object to payment delay or refusal efforts. Insurers linked reducing or removing the prior approval conditions to Gilead’s lowering prices. Gilead refused, and the resulting standoff limited system costs but hampered patients’ access to treatment.

Group purchasing organizations (GPOs) and other distribution outlets created initially to assist hospitals in obtaining drugs at more favorable prices have also consolidated. The resulting monopsony power has enabled these organizations to impose high fees on generic drug makers that combine with low generic-drug profit margins to compromise these companies’ ability to maintain their manufacturing facilities. As a result, the companies can fail FDA inspections

and lack the financial resources to repair the reasons for failure, causing generic drug production to slow or cease. In addition, statutorily mandated low prices for generic drugs discourage companies from incurring the large expenses to obtain FDA approval. The overall result is a lack of generic-drug competition, the problem that enabled the Turing pricing incident.

All of these rebate and discounting activities incentivize upward movements in drug prices initially set by manufacturers.

## Price Control Justifications and Specific Proposals

Not all “price control” proposals represent straightforward imposition of specific prices. Rather, I define “price controls” as maneuvers that directly or indirectly lower drug costs for payers and consumers and that reduce profits for drug manufacturers.

The justification for price controls heavily keys off of the pharmaphobia narrative. At its most extreme, the narrative minimizes the value of industry drug development for improved health<sup>13</sup> and alleges that whatever value it contributes is a result of hijacking government- and charity-sponsored research results.<sup>14</sup> It most vehemently attacks the industry’s marketing activities, claiming that the industry’s pretensions to innovate are invalid because marketing costs exceed research and development expenditures—which is true. Furthermore, it invokes enormous fines paid by most pharmaceutical companies to settle federal prosecutions for what the media reports as illegal marketing as evidence that corporate marketing is corrupt.

It also avers that, based on the Fortune 500 list of net profit figures, the pharmaceutical industry must profiteer, because it is far more “profitable” than all other industries. It claims that some of that profit derives from tweaking existing drugs to generate derivative “me-too” variants of little added benefit or engaging in “pay-to-delay” deals with generic companies that slow the market entry of generics.<sup>15</sup>

Conversely, the pharmaphobia narrative charges that the industry exaggerates the difficulty and

cost of drug development. It disputes the accuracy of the Duke-Tufts cost estimates. It offers up far lower cost estimates.<sup>16</sup>

The pharmaphobia mindset that discounts or denies the value and cost of corporate drug innovation underlies specific price control proposals. The current crop of presidential candidates has called for repealing the statutory ban on Medicare negotiating drug prices and for permitting importation of drugs from foreign countries that control their prices.

Several states have filed legislation containing such proposals or compelling pharmaceutical companies to provide highly detailed information that the proposers believe will enable officials to cap what they deem excessive prices. Among the parameters to report are research and development costs (including costs paid by public funds), marketing expenditures, and prices charged to different purchasers or intermediaries.<sup>17</sup>

Academic critics insist that the FDA require companies to compare drugs against existing ones and delay or deny approval should the new drug not show clear superiority, thereby reducing the number of regulator-approved high-priced brand drugs. These critics also demand elimination of pay-to-delay and other industry profit-promoting strategies.<sup>18</sup>

Senator Elizabeth Warren (D-MA) has filed legislation to force companies settling federal prosecutions to divert sales revenues to subsidizing medical research supported by the National Institutes of Health (NIH).<sup>19</sup>

Another price control proposal is that drug prices should reflect the medical *value* drugs provide. The proponents of such “value-based pricing” use economic and clinical criteria to define “value.”<sup>20</sup> The prototype of this framework, which is employed by the British National Center for Clinical Health Excellence (NICE), uses the concept of “quality-adjusted life years” (QUALYS) to make cost-effectiveness recommendations for medical treatments including drugs. NICE’s decisions determine what the UK National Health Service (NHS) will pay for, and patients wanting access to drugs rejected by NICE must pay for them out of pocket.

One value-related pricing proposal for cancer drugs consists of a formula, dubbed “the drug abacus.” It incorporates six variables: drug efficacy, drug tolerability, drug novelty, research and development costs for drug introduction, rarity of the diseases a drug treats, and the population burden of those diseases. Additional adjustments include the duration of drug treatment and a drug’s total sales. Application of this formula to marketed drugs has resulted in price recommendations far lower than the prices drug makers actually charge.<sup>21</sup>

Pharmaceutical companies such as Vertex and Gilead have joined the value-pricing bandwagon, since their particular drugs for cystic fibrosis and hepatitis C, respectively, allow them to plead that the high clinical value of their products justifies their high prices. That strategy, however, sets up the critics to contrast such drugs with the marginal survival benefits of new expensive cancer drugs.

A related argument for price controls is that the failure of the American payment system to regulate prices sends “signals” to drug manufacturers that encourage low-value innovation. It calls for reimbursements for drugs—and other medical products—to be “referenced” based on clinical value, such value to be ascertained from “clinical effectiveness research.” Rather than dictating prices per se, this scheme has payers covering only the costs of drugs identified as superior to others by such research.<sup>22</sup>

## Errors of Price Control Justification and Proposals

Contrary to the pharmaphobia narrative and the regulatory imperatives that flow from it, a large body of evidence documents that the introduction of new drugs and devices has been the dominant factor behind a 10-year increase in US longevity, a marked reduction in mortality from cardiovascular diseases and cancer, and improved life quality due to reduced morbidity caused by afflictions such as arthritis.<sup>23</sup> In contrast to the pharmaphobia narrative that discounts this fact, drug development empirically has high value.

Also in error are the critics who deny the DiMasi-Grabowski drug-approval cost figures or the value of drug development accrued by those costs. In my opinion, DiMasi and Grabowski and others have convincingly affirmed their conclusions and rebutted these denials.<sup>24</sup> The major cost driver of drug development is clinical trials, and the average cost of trials is publically available information.

Furthermore, the charge that manufacturers merely exploit government- or charity-sponsored research is false. The preponderance (around 90 percent) of new drugs now arises entirely from private-industry research and development. Corporate investment in such research is more than double that of public sources.<sup>25</sup>

Regarding the complaint that the industry spends more on marketing than research, brand pharmaceutical manufacturers spend far more on research than any other industries—20 percent of all business-funded research and development according to the Congressional Budget Office.<sup>26</sup> Furthermore, marketing is necessary and defensible. Physicians have difficulty learning about new drugs, and only their manufacturers have the best resources to promote efficient education. Drug company marketing, constrained by FDA regulation, is far more rigorously overseen than most other sources of medical information.<sup>27</sup>

**The introduction of new drugs and devices has been the dominant factor behind a 10-year increase in US longevity, a marked reduction in mortality from cardiovascular diseases and cancer, and improved life quality.**

The high “net profits” of drug companies, proffered as evidence of pharmaceutical profiteering are economically meaningless accounting artifacts. They are funds set aside to pay for the majority of drug developments that fail.<sup>28</sup> If the pharmaceutical industry were more profitable than others, investors would flock to it. In fact, the market capitalization of that industry

has lagged behind many others, such as telecommunications, entertainment, and, until recently, energy.

Recommendations to prohibit statutorily all corporate profit-sustaining strategies, such as patent extending and “pay-to-delay” negotiations between brand and generic companies address only one aspect of these strategies: that they slow introduction of generic drugs. The recommenders fail to acknowledge that sustaining profitability of the companies exercising these maneuvers benefits both brand *and* generic drug development.

Senator Warren’s proposed legislation that would punish firms settling prosecutions for allegedly illegal marketing misunderstands that these settlements are manifestations of a federal extortion racket, not smoking guns for corporate corruption. Physicians often and rightly prescribe FDA-approved products “off label” for unapproved indications. Prosecutors deform the definition of a “false claim”—billing the government for unperformed services—to allege that devious corporate marketing that physicians cannot resist coerced them to prescribe off label. However, the prosecutions based on these implausible allegations never go to trial because conviction for one indictment confers a penalty called “debarment.” A debarred company cannot sell any of its drugs to the government, the major purchaser of them. Given the enormous adverse financial consequences of a conviction, the companies always settle.<sup>29</sup>

Finally, those calling for importation of cheaper drugs from abroad have offered no specific suggestions as to how such reimportation would operate. Presumably we would need to create a bureaucracy—and pay it—to determine patient eligibility for the purchases and manage the transfers of drugs and finances. The drug companies’ patient assistance programs, which are already in place and often operate in collaboration with nonprofits dedicated to specific diseases, seem far more efficient and sensible, and they lack the drug-quality concerns associated with reimported products. In addition, the FDA has consistently resisted reimportation because it lacks the bandwidth to police the quality of such drugs.

Turning to value-based pricing proposals, the criteria recommended for assessing value depend on pooled outcome data, and regulators rely on these data to determine whether a drug is effective or safe enough to warrant regulatory approval. These averages often hide enormous variations in responses of individual patients.

Another problem is that arbitrary value determinations can be highly subjective. For example, in cancer treatment for which value-based pricing schemes have been most enthusiastically recommended, one proposal is that regulators approve only therapies that add an average of three months or more of life prolongation.<sup>30</sup> This approach is a very blunt instrument: how can one estimate the value of a few months to an eight-year-old otherwise healthy child, a frail 80-year-old, a person whose affairs are in order and wants to enter hospice palliative care, or someone who desperately wants to see a grandson graduate from college or attend a daughter’s wedding?

Of particular concern is that “novelty,” one of the “abacus” cancer drug pricing criteria, is an extremely poor benchmark for value. It reflects academics’ obsession with novelty for novelty’s sake and a failure to recognize that most innovation is incremental. The criticism of follow-on (“me too”) drugs, which can be just as expensive to develop as first-in-class variants, is a manifestation of this failure.

The subjectivity of value-based pricing is also an open invitation to inflict politics on the price-determining process and increase lobbying of the bureaucrats who assign such value.

## Why Price Controls Must Impair Drug Innovation

Based on the DiMasi-Grabowski figures, the average capitalized cost of obtaining a drug approval by the FDA has risen 100-fold since the enactment of the Kefauver Amendments.<sup>31</sup> More stringent FDA requirements and the greater difficulty and expense of completing clinical trials have contributed to this increase. But such stringency, difficulty, and expense have not increased by 100-fold. Rather, I posit that the principal reason for the markedly increased costs

of drug approval is that small changes in regulatory burden have a disproportionate effect because of *the high failure rate* of drug development. This failure rate in part informs the DiMasi-Grabowski drug approval cost estimates, although in my view these economists do not highlight fact enough. Instead, they emphasize cost of capital effects.

The failure frequency is a matter of public record. Across all disease indications, 9 of 10 drug development projects that go into clinical trials crash,<sup>32</sup> but in drug candidates for disseminated solid tumors, it has recently been 17 of 18.<sup>33</sup> By analogy, a 10 percent reduction in the size of the goal in a low-scoring game like hockey or soccer would diminish scoring by far more than that amount. A key concern, therefore, is that we may be approaching a point at which drug development ceases to be cost-effective. Some analysts suggest we are close to it.<sup>34</sup>

Unfortunately, the low success rate of drug development is not intuitively obvious in the context of modern technology, which has delivered spectacular improvements in transportation and communication. Unlike the man-made engineering capabilities that enabled these achievements, drug development suffers the severe limitation that it must obey obscure laws of biology that nature—not we—created. A prime reason for the high failure frequency is nature’s built-in variability that enables us to withstand assaults by microorganisms that can adapt with far greater speed to their environments than we can. Those life forms figured out long ago how to attack many, if not most, of the component molecules of our bodies. If human biology were more predictable than it is, assaults by these microbes would have eliminated our species long ago.

The downside of this protective diversity explains why drugs that seem to work well in the laboratory or in inbred experimental animals are found to be ineffective or unsafe when tested in human clinical trials involving a sufficient number of subjects. Only such trials can identify unacceptable side effects or reveal that an apparently effective drug tested in small numbers of individuals was a statistical fluke. Perversely, such safety and efficacy often become manifest

only in very large and very expensive late-stage trials.

The low success rate of drug development affects the entire world, yet only America addresses it by enabling its drug developers to operate without price controls. The rest of the world therefore freeloads off of American innovation.

The idiosyncrasies of drug development and its high failure rate expose the futility of legislation intended to enforce “transparency” in an attempt to fix drug prices by trying to assess what particular companies spent to move particular drugs to market. A prime illustration of this futility is the recent Senate report concerning Gilead’s pricing of its hepatitis C drugs.<sup>35</sup> The report repeatedly refers to Gilead’s failure to provide specific expense information despite agreeing to cooperate with the Senate investigation. This complaint misses the point that the incremental, nonlinear, and nearly random progress leading to approvable drugs hardly lends itself to precise accounting for the

**Unlike the man-made engineering capabilities that enabled these achievements, drug development suffers the severe limitation that it must obey obscure laws of biology that nature—not we—created.**

myriad steps in that development, especially to politicians with no drug development experience.

Sovaldi and Harvoni evolved from precursor compounds Gilead obtained by purchasing Pharmasset, a pharmaceutical company, for \$11 billion. Gilead bought Pharmasset because its own pipeline of potential hepatitis C drugs did not appear promising. Despite this setback, the efforts Gilead had expended to advance its knowhow in antiviral therapy that led to Sovaldi and Harvoni are arguably legitimate expenses to include in the later successful drug development. In purchasing Pharmasset, Gilead gambled that the drug assets it was acquiring would lead to such success. Financial analysts did not agree, and Gilead transiently lost a third of its investment value.<sup>36</sup>

This background also contradicts the idea proposed by the reference-based pricing proposers that companies deliberately develop poor drugs because the reimbursement system “signals” that they can get paid to do so. Faced with a huge failure rate, why would any rational person gamble with a hand that has no chance of overcoming it? This signal theory resonates with misguided ideas proposed by some of the oncologist critics in an article published in *The Mayo Clinic Proceedings* that, if only our intentions were better, we would develop better drugs: “Innovation in cancer research is not stifled by curbing profits and by increasing affordability. It is the result of creative minds and cancer researchers driven by societal and humanistic missions.”<sup>37</sup>

Analyses by historians and sociologists of science reveal the falsity of that statement. They document how solving practical problems are rarely motivations of leading researchers. Rather, they predominantly work to discover elegant solutions for scientific puzzles, impress influential peers, and gain credit for priority of discoveries.<sup>38</sup>

Another conceit underlying reference-based pricing is that “big data” will deliver sufficient knowledge in real time to inform “comparative effectiveness” on which to base referencing. The limitations of drawing conclusions from averages regarding effectiveness and safety results obtained from randomized controlled clinical trials performed to achieve regulatory approval are far worse once drugs are on the market. Patient heterogeneity, comorbidities, and many other parameters drug developers try to avoid in premarket testing will conspire with far less stringent monitoring to confound comparative effectiveness research.

Sustained investment, not lofty intentions, is the only antidote for the high drug development failure rate. The pharmaceutical business must provide sufficient returns to attract such investment. A confirmation of this reality is that former presidential candidate Bill Clinton’s threat to impose drug price controls in 1992 caused a 52.3 percent drop in market-adjusted stock prices—an amount greater than the entire capitalization of the biotechnology industry at the time—as the S&P in general rose by 8.1 percent.

Pharmaceutical company stocks did not recover until nearly a year later when the price control threats abated.<sup>39</sup> The current presidential candidates’ pronouncements about drug prices have spurred a similar investment flight.<sup>40</sup>

The Senate Finance Committee report concerning Gilead’s hepatitis C drugs did not seem to recognize this reality:

Gilead’s own documents and correspondence show its pricing strategy was focused on maximizing revenue—even as the company’s analysis showed a lower price would allow more patients to be treated.<sup>41</sup>

Gilead’s careful analysis leading to the pricing of its drugs—minutely documented in the Senate report—was directed at ensuring the ability of the company to sustain its innovation activities. The more profitable drug companies are, the more capability they may possess to take more shots at the elusive goal of successful drug development.<sup>42</sup> The fact that Gilead’s pricing strategy resulted in fewer hepatitis C treatments in the short term was because of payers’ prior-approval obstructionism—an outcome the company predicted.

Furthermore, the pricing criticisms ignore that what any company charges for its drugs is only one part of an extensive innovation *system*. The drug pricing and profitability debates tend to blur the fact that the drug industry is incredibly diverse, ranging from merged behemoths to struggling startups. For example, the biotechnology industry currently consists of only seven highly profitable companies, and as a whole it barely breaks even.<sup>43</sup> Vertex Pharmaceuticals, the company that sells the cystic fibrosis drug Kalydeco, has been profitable for one year of its 26-year existence.<sup>44</sup> Biotechnology investment has always been of particularly high risk. Thanks to pent up demand from the resolution of the recent recession, investment in that sector has been relatively brisk, although the history of such investment reveals high volatility and long downturns.<sup>45</sup>

If, as is often claimed, the cutting edge of innovation resides in small companies desperately scratching for investment to stay afloat and ultimately dependent on selling

technologies to or being purchased by larger companies to have their drugs actually achieve regulatory approval, price controls would disproportionately harm these small innovators and the patients their products might benefit.

## Conclusions and Policy Implications

I have argued that the premium pricing of specialty drugs is a rational response to the dreary economic risks of developing such drugs and that, on balance, the resultant profits provide us with more and better products that maintain the trajectory of improving health value. I have also predicted that price control schemes will curtail the investment essential to achieve that end.

We certainly want patients to have access to health care in general and good medications in particular without experiencing financial ruin. But a reflexive default to the emotionally satisfying measure of simply punishing drug firms in hopes that the punishment can improve outcomes will, as summarized here, have adverse systemic consequences.

That conclusion, however, does not mean that a “Just say no!” approach to drug price controls is in itself a satisfactory policy solution. The stresses imposed by drug price increases have substantive consequences for payers, caregivers, and patients. Although I disagree with the idea that health care—including provision of medications—is a right, I cannot argue that sustaining the profitability of drug companies to promote medical innovation is a categorical imperative either. In theory, the introduction of ever more expensive specialty drugs, however beneficial medically, could be financially catastrophic, and whether competition could mitigate this is uncertain.

As a physician, however, who has witnessed great improvements in health care thanks to drug and medical device innovation and who confronts patients with serious unmet medical needs, I can only advocate for innovation as a personal preference and hope that we can make the benefits outweigh the risks.

Although I have defended the pharmaceutical industry, I can hardly place it on a pedestal. The industry’s passivity in the face of the pharmaphobia narrative has allowed what should be a balanced, serious (if not easily resolved), deliberative exercise to deteriorate into a witch hunt. Companies’ refusals to comment for news stories publicizing patients’ problems are clearly unhelpful in informing the public about the risks they face or debunking the significance of drug costs.<sup>46</sup> In addition, the drug makers could be more forthright about their “net profits.” Presumably, they have not done so out of concern that it would spook their investors. Instead, they tend to tout their profits, the promise scientific advances present, and the value of their products, thereby inflaming the profiteering charges and inflaming the oncologist critics who find the value of expensive drugs overrated. Since investors have already demonstrated skepticism compared with earlier years regarding returns from the pharmaceutical industry, some corporate honesty and commitment to acknowledging the high failure frequency, which would make the industry’s accomplishments even more remarkable, may be a better approach.

Since sustaining innovation is the dominant excuse for its prices, the industry also needs to make a more convincing case that it promotes innovation. An unhelpful consequence of the Turing and Valeant stories is that they resonate with a pharmaphobic caricature based on an absolutist fallacy that private industry places profits above all other ends (and that physicians and academic institutions never do):

Drug companies—like other investor-owned businesses—are charged with increasing the value of their shareholders’ stock. That is their fiduciary responsibility, and they would be remiss if they didn’t uphold it. All their other activities are means to that end.<sup>47</sup>

Leaving aside that most medication companies are not publicly traded, rebutting such charges can be difficult because they involve complex philosophical trade-offs and very grey territory differentiating “greed” from “no margin, no mission” considerations. Nevertheless, singling out pharmaceutical companies as somehow

different from other stakeholders because of their profitability mandate is intellectually dishonest. For example, lower drug prices markedly benefit pharmacy bottom lines.<sup>48</sup>

One encouraging sign is that the trade associations of medication companies have begun to shed some of their reluctance to address activists' criticism by taking a stand to differentiate the companies that engage in drug innovation from those that arguably are less committed to it. BIO, the major biotechnology organization, evicted Turing from its ranks. The pharmaceutical industry's trade organization PhRMA has criticized Valeant for drastically reducing its internal research activities and instead acquiring other companies with sales of already regulator-approved products. Such financial engineering is perfectly legal, but it is harder to defend than the need for profits to finance innovation. The fact that Valeant's share price rose markedly in response to its business strategy confirms that investors are sensitive to the risks of drug development.

A major opportunity for the industry to improve its image is to ramp up its efforts to provide drug payment assistance to financially challenged patients. Little quantitative data exist documenting how many patients really have problems affording drugs. If companies can demonstrate that the number is low, that information would be a strong antidote to the pricing criticism.

*All stakeholders should work on solutions.* Physicians can certainly do a better job of helping their patients faced with high drug costs by steering them to assistance programs, especially those operated by drug companies. Making this happen requires rejecting elements of the phrophobia narrative that sabotage patient assistance programs. In addition to segregating health care providers from company representatives knowledgeable about their assistance programs, phrophobia has been the basis of legislation precluding companies from directly subsidizing drug costs of patients covered by Medicare Part D. The theory underlying that legislation is that such assistance amounts to a kickback that will result in expensive brand drugs being dispensed rather than cheap generics. Companies are permitted to assist Medicare

patients indirectly through nonprofit organizations dedicated to helping patients with particular diseases pay for their drugs. But some companies have been reluctant to pursue that strategy out of fear that the government will abuse the false-claims debarment strategy to prosecute them. The prosecutors' exploitation of phrophobic ideation claiming that the disease foundations are simply industry fronts to encourage "disease-mongering" and unnecessary drug promotion is the basis of this concern.

Insurers might propose payment vehicles that address the nuances of the outcomes produced by new drugs. In the hepatitis C drug case, for example, the appearance of expensive drugs to treat many eligible patients has imposed an acute financial stress. However, rather than expect immediate payment, spreading payment over time could make the actual expenditures fall more into line with usual anticipated amounts paid for chronic illnesses. In this case, since the treatment is curative, the insurers ultimately no longer have to pay, and everybody potentially benefits.<sup>49</sup>

Arguably, the insurance industry did not anticipate that specialty drugs would increasingly replace the older model of cholesterol-lowering or blood pressure-lowering drugs that could be priced more cheaply because large numbers of patients use them. Since specialty drugs are likely the norm for future development, perhaps better actuarial efforts directing patients likely to need them to plans that cover them could ease the financial stress going forward.

Avoiding the temptation to impose price controls requires understanding that current drug prices address future events over which we have little control. Unfortunately, we are not hardwired to think that way. Our penchant for short-term deliberation is why we need hepatitis C drugs: they address tomorrow's consequence of a disease caused by today's pleasurable habit of intravenous substance abuse that spreads the condition. In calling for drug price controls, the critics epitomize this kind of tunnel vision. In the interests of our health and that of my grandchildren, I hope that we can hold the line.

## About the Author

**Thomas Peter Stossel** is a visiting scholar at AEI where he studies the interface between medicine and the medical products' industry. He is also a practicing hematologist and researcher at Boston's Brigham and Women's Hospital, American Cancer Society Professor of Medicine at Harvard Medical School, and founding scientist of BioAegis Therapeutics, which is developing a therapy based on his research.

## Acknowledgments

The author is indebted to Joseph Antos, Alex Brill, Lance Stell, and Stan Veuger for their helpful comments and criticisms.

## Notes

1. Anne B. Martin et al., "National Health Spending in 2014: Faster Growth Driven by Prescription Drug Spending," *Health Affairs*, December 2, 2015, <http://content.healthaffairs.org/content/early/2015/11/25/hlthaff.2015.1194.full.html>.
2. Experts in Chronic Myelogenous Leukemia, "The Price of Drugs for Chronic Myeloid Leukemia (CML) Is a Reflection of the Unsustainable Prices of Cancer Drugs: From the Perspective of a Large Group of CML Experts," *Blood* 121, no. 22 (May 30, 2013): 4439–4442; Brian P. O'Sullivan, David M. Orenstein, and Carlos E. Milla, "Pricing for Orphan Drugs: Will the Market Bear What Society Cannot?" *JAMA* 310, no. 13 (October 2, 2013): 1343–1344; and Robert Steinbrook and Rita F. Redberg, "The High Price of the New Hepatitis C Virus Drugs," *JAMA Internal Medicine* 174, no. 7 (July 2014): 1172.
3. The Editors, "A Campaign for President—and to Cut Drug Prices," *Scientific American*, January 1, 2016, <http://www.scientificamerican.com/article/a-campaign-for-president-and-to-cut-drug-prices/>.
4. Carolyn Y. Johnson, "Doctors, Hospitals Condemn Out-of-Control Drug Prices as Senate Investigation Begins," *The Washington Post*, December 9, 2015, <https://www.washingtonpost.com/news/wonk/wp/2015/12/09/doctors-hospitals-condemn-out-of-control-drug-prices-as-senate-investigation-begins/>.
5. Hagop M. Kantarjian et al., "Cancer drugs in the United States," *Justum pretium—The Just Price*, *Journal of Clinical Oncology* 31, no. 28 (October 1, 2013): 3600–3602, <http://www.jco.ascopubs.org/content/31/28/3600.full>.
6. Robert Siegel, "Doctors Speak Out Against 'Unsustainable' Cancer Drug Prices," National Public Radio, July 24, 2015, <http://www.npr.org/2015/07/23/425654456/doctors-speak-out-against-unsustainable-rise-in-cancer-drug-prices>.
7. Robert Reich, "Of Rotten Apples and Rotten Systems," *Huffington Post*, December 21, 2015, [http://www.huffingtonpost.com/robert-reich/of-rotten-apples-and-rott\\_b\\_8861526.html](http://www.huffingtonpost.com/robert-reich/of-rotten-apples-and-rott_b_8861526.html).
8. Thomas P. Stossel, *Pharmaphobia: How the Conflict of Interest Myth Undermines American Medical Innovation* (Lanham, MD: Rowman & Littlefield, 2015).
9. US Senate, Committee on Finance, *The Price of Sovaldi and Its Impact on the U.S. Health Care System*, S. Prt. 114-20, 114th Cong., 1st Sess., December 19, 2015.
10. Ayalew Tefferi et al., "In Support of a Patient-Driven Initiative and Petition to Lower the High Price of Cancer Drugs," *Mayo Clinic Proceedings* 90, no. 8 (August 2015): 996–1000, [http://www.mayoclinicproceedings.org/article/S0025-6196\(15\)00430-9/fulltext](http://www.mayoclinicproceedings.org/article/S0025-6196(15)00430-9/fulltext).
11. Joseph A. DiMasi, Henry G. Grabowski, and Ronald W. Hansen, "The Cost of Drug Development," *New England Journal of Medicine* 372, no. 20 (May 14, 2015): 1972.
12. Biotechnology Industry Organization et al., "The 340B Drug Discount Program: A Review and Analysis of the 340B Program," <https://www.bio.org/sites/default/files/340B%20White%20Paper%20FINAL.pdf>.
13. Dean Baker and Adriane Fugh-Berman, "Do New Drugs Increase Life Expectancy? A Critique of a Manhattan Institute Paper," *Journal of General Internal Medicine* 24, no. 5 (May 2009): 678–682.
14. Jerry Avorn, *Powerful Medicines: The Benefits, Risks, and Costs of Prescription Drugs* (New York: Alfred A Knopf, 2004); and Marcia Angell, *The Truth About the Drug Companies: How They Deceive Us and What to Do About It* (New York: Random House, 2004).
15. Aaron S. Kesselheim, "Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation," *New England Journal of Medicine* 363, no. 19 (November 4, 2010): 1855–1862.
16. Donald W. Light and Rebecca N. Warburton, "Extraordinary Claims Require Extraordinary Evidence," *Journal of Health Economics* 24 (2005): 1030–1033.
17. An Act to Promote Transparency and Cost Control of Pharmaceutical Drug Prices, S. 1048, Massachusetts Senate, 189th Sess., 2015, <https://malegislature.gov/Bills/189/Senate/S1048>.

18. Avorn, *Powerful Medicines*; Angell, *The Truth About the Drug Companies*; and Kesselheim, "Using Market-Exclusivity Incentives to Promote Pharmaceutical Innovation."
19. Medical Innovation Act of 2015, S. 320, 114th Cong. (2015).
20. Peter J. Neumann and Joshua T. Cohen, "Measuring the Value of Prescription Drugs," *New England Journal of Medicine* 373, no. 27 (December 31, 2015): 2595–2597, <http://www.nejm.org/doi/full/10.1056/NEJMp1512009>.
21. Peter B. Bach, "New Math on Drug Cost-Effectiveness," *New England Journal of Medicine* 373, no. 19 (November 5, 2015): 1797–1799, <http://www.nejm.org/doi/full/10.1056/NEJMp1512750>.
22. Nicholas Bagley, Amitabh Chandra, and Austin Frakt, "Correcting Signals for Innovation in Health Care," Brookings Institution, October 2015, [http://www.hamiltonproject.org/assets/files/correcting\\_signals\\_for\\_innovation\\_in\\_health\\_care\\_bagley\\_v2.pdf](http://www.hamiltonproject.org/assets/files/correcting_signals_for_innovation_in_health_care_bagley_v2.pdf).
23. Kevin M. Murphy and Robert H. Topel, "The Value of Health and Longevity," *Journal of Political Economy* 114, no. 5 (October 2006): 871–904; Frank R. Lichtenberg, "Alive and Working: How Access to New Drugs Has Slowed the Growth in America's Disability Rates," Manhattan Institute for Policy Research, October 27, 2008, <http://www.manhattan-institute.org/html/alive-and-working-how-access-new-drugs-has-slowed-growth-americas-disability-rates-5934.html>; Frank R. Lichtenberg, "Despite Steep Costs, Payments for New Cancer Drugs Make Economic Sense," *Nature Medicine* 17, No 3 (March 2011): 244; and Elizabeth G. Nabel and Eugene Braunwald, "A Tale of Coronary Artery Disease and Myocardial Infarction," *New England Journal of Medicine* 366, no. 1 (January 5, 2012): 54–63, <http://www.nejm.org/doi/full/10.1056/NEJMra1112570>.
24. Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "Setting the Record Straight: Response to the Light and Warburton Rejoinder," *Journal of Health Economics* 24, no. 5 (September 2005): 1049–1053; Joseph A. DiMasi, Ronald W. Hansen, and Henry G. Grabowski, "Extraordinary Claims Require Extraordinary Evidence," *Journal of Health Economics* 24, no. 5 (September 2005): 1034–1044; Frank R. Lichtenberg, "Do New Drugs Save Lives?" *Journal of General Internal Medicine* 24, no. 12 (December 2009): 1356, <http://link.springer.com/article/10.1007/s11606-009-1102-x>; Jack Scannell, "Four Reasons Drugs Are Expensive, of Which Two Are False: An Opinion," Innogen Working Paper No. 114, October 2015, <http://www.innogen.ac.uk/working-papers/1115>; and Jack Scannell, "Four Reasons Drugs Are Expensive, of Which Two Are False," *Forbes*, November 13, 2015, <http://www.forbes.com/sites/matthewherper/2015/10/13/four-reasons-drugs-are-expensive-of-which-two-are-false/>.
25. Bhaven N. Sampat and Frank R. Lichtenberg, "What Are the Respective Roles of the Public and Private Sectors in Pharmaceutical Innovation?" *Health Affairs* 30 no. 2 (February 2011): 332–339, <http://content.healthaffairs.org/content/30/2/332.full>; and Ashley J. Stevens et al., "The Role of Public-Sector Research in the Discovery of Drugs and Vaccines," *New England Journal of Medicine* 364, no. 6 (February 10, 2011): 535–541, <http://www.nejm.org/doi/full/10.1056/NEJMSa1008268>.
26. Congressional Budget Office, "Research and Development in the Pharmaceutical Industry," October 1, 2006, <http://www.cbo.gov/sites/default/files/10-02-drug-d.pdf>.
27. Stossel, *Pharmaphobia*.
28. Kenneth W. Clarkson, "The Effects of Research and Promotion on Rates of Return," in *Competitive Strategies in the Pharmaceutical Industry*, edited by Robert B. Helms (Washington, DC: AEI Press, 1996), 238–268.
29. Stossel, *Pharmaphobia*; and Harvey A. Silverglate, *Three Felonies a Day. How the Feds Target the Innocent* (New York: Encounter Books, 2009).
30. Lowell E. Schnipper et al., "American Society of Clinical Oncology Statement: A Conceptual Framework to Assess the Value of Cancer Treatment Options," *Journal of Clinical Oncology* 33, no. 23 (August 10, 2015): 2563–2577, <http://jco.ascopubs.org/content/33/23/2563>.
31. Jack W. Scannell et al., "Diagnosing the Decline in Pharmaceutical R&D Efficiency," *Nature Reviews Drug Discovery* 11, no. 3 (March 2012): 191–200.
32. John Arrowsmith, "Phase III and Submission Failures: 2007–2010," *Nature Reviews Drug Discovery* 10, no. 2 (February 2011): 1; and Michael Hay et al., "Clinical Development Success Rates for Investigational Drugs," *Nature Biotechnology* 32, No 1 (January 2014): 40–51.
33. J. A. DiMasi et al., "Clinical Approval Success Rates for Investigational Cancer Drugs," *Clinical Pharmacology & Therapeutics* 94, no. 3 (September 2013): 329–335.
34. Ernst R. Berndt et al., "Decline in Economic Returns from New Drugs Raises Questions About Sustaining Innovations," *Health Affairs* 34, no. 2 (February 2015): 245–252; and Jonathan J. Fleming, "The Decline of Venture Capital Investment in Early-Stage Life Sciences Poses a Challenge to Continued Innovation," *Health Affairs*, 34, no. 2 (February 2015): 271–276.
35. US Senate, *The Price of Sovaldi and Its Impact on the U.S. Health Care System*.

36. Lewis Krauskopf and Anand Basu, “Gilead Bets \$11 Billion on Hepatitis in Pharmasset Deal,” Reuters, November 21, 2011, <http://www.reuters.com/article/us-gilead-pharmasset-idUSTRE7AKOXU20111121>; and Russ Britt, “Four-Fifths of Investors Think Gilead Overpaid: Survey,” *MarketWatch*, November 21, 2011, <http://blogs.marketwatch.com/thetell/2011/11/21/four-fifths-of-investors-think-gilead-overpaid-survey/>.
37. Hagop Kantarjian and S. Vincent Rajkumar, “Why Are Cancer Drugs So Expensive in the United States, and What Are the Solutions?” *Mayo Clinic Proceedings* 90, no. 4 (April 2015): 500–504.
38. Robert K. Merton, *The Sociology of Science: Theoretical and Empirical Observations* (Chicago: University of Chicago Press, 1973); and Thomas S. Kuhn, *The Structure of Scientific Revolutions*, 2nd ed., (Chicago: University of Chicago Press, 1970).
39. Sara Fisher Ellison and Wallace P. Mullin, “Gradual Incorporation of Information: Pharmaceutical Stocks and the Evolution of President Clinton’s Health Care Reform,” *Journal of Law and Economics* 44, no. 1 (April 2001): 89–129.
40. Kevin A. Hassett, “Stocks and the Clinton Effect,” *National Review*, November 2, 2015, <https://www.aei.org/publication/stocks-and-the-clinton-effect/>.
41. US Senate, Committee on Finance, “Sovaldi Report Executive Summary,” December 1, 2015, p. 1, <http://www.finance.senate.gov/download/sfc-sovaldi-report-executive-summary>.
42. Carmelo Giaccotto, Rexford E. Santerre, and John A. Vernon, “Drug Prices and Research and Development Investment Behavior in the Pharmaceutical Industry,” *Journal of Law and Economics* 48, no. 1 (April 2005): 195–214.
43. Gary P. Pisano, *Science Business. The Promise, the Reality, and the Future of Biotech* (Boston: Harvard Business School Press, 2006); and Charlie Grant, “Drug Makers Face Dwindling Targets—Heard on the Street,” *Wall Street Journal*, January 2, 2016, <http://iadweek.me/2016/01/03/drug-makers-face-dwindling-targets-heard-on-the-street/>.
44. Barry Werth, *The Antidote: Inside the World of New Pharma* (New York: Simon and Schuster, 2014); and Barry Werth, *The Billion-Dollar Molecule: The Quest for the Perfect Drug* (New York: Simon & Schuster, 1995).
45. Jeffrey Loo, “Industry Surveys: Biotechnology,” S&P Capital IQ, September 2015, <https://gskkr.files.wordpress.com/2015/01/biotechnology.pdf>.
46. Joseph Walker, “Patients Struggle with High Drug Prices,” *Wall Street Journal*, December 31, 2015, <http://www.wsj.com/articles/patients-struggle-with-high-drug-prices-1451557981>.
47. Marcia Angell, “Big Pharma, Bad Medicine,” *Boston Review*, May 1, 2010, 8–22, <http://www.bostonreview.net/angell-big-pharma-bad-medicine>.
48. Adam J. Fein, “Pharmacy Profits from Authorized Generics,” *Drug Channels*, September 22, 2011, <http://www.drugchannels.net/2011/09/pharmacy-profits-from-authorized.html>.
49. Biotechnology Industry Organization et al., “The 340B Drug Discount Program: A Review and Analysis of the 340B Program,” Winter 2013, <http://www.bio.org/sites/default/files/340B%20White%20Paper%20FINAL.pdf>.