

In her upcoming book, The Truth About the Drug Companies, Marcia Angell reports information about the pharmaceutical research industry that is inaccurate and misleading. Likewise, she ignores significant achievements of the industry that enable patients to live longer, healthier, and more productive lives. This document identifies major claims made in the book and provides accurate information that dispels Angell's errors and omissions.

### **Drug Costs**

Angell states that "Drugs are the fastest-growing part of the health care bill...One of the biggest drains on state budgets is Medicaid, and the fastest-growing component of that is prescription drug spending." (xii; p. 222)

This doesn't tell the whole story. While Rx spending is, for good reason, increasing, it remains a small portion of the health care dollar. Of every health care dollar spent in the U.S., about 10.5 cents is spent on prescription drugs, including brand medicines, generic drugs, and pharmacy.<sup>1</sup> Brand manufacturers accounted for 7 cents, which includes funding for research that results in better medicines. Generics and distribution costs for brand and generic drugs account for the remaining 3.5 cents of pharmaceutical spending. Moreover, between 1997 and 2002, increases in spending on prescription medicines accounted for 18.8% of the increase in the nation's health spending, while spending on other services not discussed by Angell, such as hospitals, doctors, and nursing homes accounted for the remaining 81.2% of spending increases.<sup>2</sup>

Likewise, prescription medications are not responsible for Medicaid's cost problem. In 2002, Medicaid spending for prescription drugs accounted for 11.4 percent of total expenditures, and from 1997 to 2002 Medicaid prescription drug increases accounted for less than one-fifth of the total increase in Medicaid spending, before accounting for savings such as the avoided costs of emergency and hospital care when medicines are used to control conditions such as asthma, diabetes, depression, and high blood pressure.<sup>3</sup>

Even more important than these omissions of basic facts, Angell's view seems to be that faster growth on drug spending than on other aspects of health care is itself a problem. She never explains why it would be better for health care spending to be allocated the same way to different types of services year after year. After all, for example, when a patient begins taking medicines that control cholesterol, thereby avoiding a heart attack and bypass surgery, drug spending goes up and hospital spending is lower than it would have been, meaning that drug spending grows as a share of the health care dollar. In fact, disease management, one of the leading health care quality improvement and cost containment strategies used today, often leads to higher spending on prescription drugs but lower overall health care spending, as patients stay healthier and avoid the complications of conditions like diabetes and congestive heart failure. This, too, means that drug costs increase as a share of health care spending. Does Angell really believe this is a problem and that patients would be better off reverting to the old patterns of care?

Angell also fails to mention that private health insurance plans pay a much lower percentage of members' Rx drug costs than hospital and physician costs, which leads consumers to believe that prescription drugs cost more than other health services. In fact, persons under 65 with private health insurance during all of 2000 paid 37.2% of prescription drugs costs out-of-pocket, compared to just 2.5% out-of-pocket for hospital inpatient care.<sup>4</sup>

Angell also fails to mention that insurance copays for medicines have been increasing much faster than prescription drug prices, further fueling the perception that drug costs are larger

than they actually are. Depending on the timeframe, dataset, and formulary tier examined, average cost-sharing charged by managed care plans increased at 1.6 to 4.6 times the consumer price index (CPI) for prescription drugs.

These increases in co-payments can have negative consequences for patients and overall health costs. According to a RAND Health study published in the *Journal of the American Medical Association*, doubling copayments in a two-tier plan results in approximately a 45% reduction in the use of anti-inflammatory drugs and antihistamines; approximately a 35% reduction in cholesterol-lowering drugs, ulcer and asthma medications; and a 25% reduction in high blood pressure, depression, and asthma medications. And as Rx drug use declined, visits to emergency rooms increased 17% and hospital stays rose by 10% among patients with diabetes, asthma, and gastric acid diseases.<sup>5</sup> Results such as these mean that prescription drug spending grows slower than it otherwise would—but surely Angell can not believe that this is a good result for patients.

Prescription medicine spending should be put in the context of overall health care spending, including the avoided costs of surgery, visits to emergency rooms, or lengthy stays in hospitals or nursing homes.

“From 1960 to 1980, prescription drug sales were fairly static as a percent of U.S. gross domestic product, but from 1980 to 2000, they tripled.” (p. 3)

Although prescription drug spending as a share of GDP increased from 1980-2000, Angell fails to mention that overall medical spending as a share of GDP also increased quite significantly. According to CMS, from 1980-2000, prescription drug spending as a share of GDP increased from .43% to 1.24% or by a total of .81 percentage points, while the rest of health care spending as a share of GDP increased from 8.8% to 13.3%, or by 4.5 percentage points, about five a half times as large an increase as for prescription drugs.<sup>6</sup>

Equally important, Angell’s claim implies that prescription drug spending should still be at the 1980 level. In 1980, there were no statins for treatment of high cholesterol, no anti-AIDS drugs, no Alzheimer’s drugs, fewer types of anti-diabetics, no treatments for hepatitis C, just to name a few of many examples. Furthermore, cancer care and cardiovascular care were primitive compared to today, with much worse survival rates for patients.

Two articles recently published in *The New York Times* and *The Washington Post* illustrate the tremendous value of recent pharmaceutical advances for patient care. According to one article (“From Killer to Chronic Disease: Drugs Redefine Cancer for Many” by Rob Stein, *The Washington Post*, January 29, 2003), cancer has evolved into a “chronic disease, much like asthma, diabetes, and, more recently, AIDS,” thanks to new diagnostic procedures and new medicines developed by pharmaceutical research companies. Doctors can now prescribe pharmaceutical therapies that allow patients to maintain their normal lives, instead of being debilitated by the disease. “I feel great,” said leukemia patient Virginia Garner. “I don’t even remember I’m sick.” According to the article, “Today, an estimated 9 million Americans are cancer survivors, up from an estimated 6 million in 1990s.” The chance of surviving for five years has risen 10 percentage points over the past two decades to 62 percent today. The future of cancer treatment is also bright, with a new generation of drugs in the pipeline that target the “defects that make cells malignant.”

Similarly, an article in *The New York Times* (“Gains on Heart Disease Leave More Survivors, and Questions” by Gina Kolata, January 19, 2003) notes that better diagnostics, surgical

methods, and new pharmaceutical treatments for heart disease have caused the death rate from heart attacks to drop tremendously over the past half century. According to Dr. Teri Amolio, director of the epidemiology and biometry programs at the national Heart, Lung, and Blood Institute, “The death rate [for heart attacks] is so low now that we’re no longer able to track it.”

Because of advances since 1980, we are spending more on prescription drugs, but for good reason -- possibly saving the health care economy money on more expensive hospitalizations, nursing homes care, and other healthcare services. Incredibly, Angell seems to suggest that none of this should have made a difference in how we allocate resources, or that it has no value, and that it is much better to invest more in larger houses or bigger cars than future cures.

### Coverage

According to Angell, seniors have to “trade off drugs against home heating or food.” (xiii)
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In fact, medicines make up a much smaller share of seniors’ health costs than other types of medical care. For example, average spending on prescription medicines for Medicare’s top drug spenders was \$3,195, and average total health spending for this group was \$12,353, during 2000.<sup>7</sup> Yet Angell does not portray seniors as trading off hospital and physician care against home heating or food. The difference is that prescription drugs, which are playing a growing role in medical care, have not been covered by Medicare, while more costly physician and hospital services were covered. So the issue is coverage, not cost.

In late 2003, these gaps in prescription drug coverage for seniors were addressed by passage of the Medicare Prescription Drug, Improvement, and Modernization Act (the MMA). The MMA establishes a prescription drug discount card program for all Medicare beneficiaries including cash assistance for certain low-income beneficiaries that began in June 2004, and across-the-board insurance coverage for prescription drugs beginning in January 2006. This prescription drug benefit will offer seniors and disabled persons access to the newest breakthroughs in medicine, while controlling costs through market competition and maintaining incentives for future innovation. Low-income beneficiaries, who make up about one-third of the entire Medicare population, will receive nearly 100% coverage of their prescription drug costs, and all Medicare beneficiaries will be eligible for a benefit that includes 95% coverage of catastrophic costs.

Additionally, America’s pharmaceutical research companies continue to voluntarily address the access issue with patient assistance programs that provide prescription drugs free of charge to low-income, uninsured patients who might otherwise not have access to necessary medicines. In 2003, an estimated 6.2 million patients received free medications through these voluntary patient assistance programs at [www.helpingpatients.org](http://www.helpingpatients.org).<sup>8</sup>

PhRMA’s member companies have also voluntarily provided Medicare beneficiaries lacking prescription drug coverage with free enrollment in company-sponsored discount card programs. By presenting these cards at the counters of their pharmacies, cash-paying patients receive significant discounts off their prescriptions. In addition, several PhRMA companies have publicly stated that they will offer their medicines free of charge or at reduced rates to Medicare beneficiaries who have exhausted their \$600 transitional assistance that lower income seniors receive with the new Medicare-endorsed prescription drug discount cards. Several companies have announced that they will adapt their patient assistance or discount programs to work well in coordination with the new Medicare-endorsed discount cards.

## **Prescription Drug Prices**

Angell suggests that prescription drugs prices are “high and rapidly climbing.” (p. 218)

Angell fails to provide the facts about prescription drug prices, which have been increasing at nearly the same rate as other health care services, while producing some of the most important progress in maintaining health and treating disease.

In 2003, prescription drug prices increased at a lower rate than other health services. A study recently published in *Health Affairs* by analysts at the Center for Studying Health System Change includes information on hospital price trends and prescription drug price trends in 2003. According to this study, hospital prices grew by 8.0 percent in 2003. In contrast, the same study notes that prescription drug inflation “declined to 3.1 percent in 2003.”

From January 1998 to March 2004, overall medical care inflation (CPI-M) increased at an annual rate of 4.2%. Inflation for prescription medicines and medical supplies (CPI-P) increased at an annual rate of 4.6% while other major categories of health services increased at a rate of 3.4 to 6.4 percent during this period. Moreover, prescription drug price increases were actually slightly below overall health care price increases from 2000 to 2004. Angell fails to disclose these facts.

Furthermore, recent analysis by the Centers for Medicare and Medicaid Services (CMS) published in a *Health Affairs* article found that three-quarters of the increase in spending on prescription medicines from 1994 to 2002 was due to the increased use of medicines and use of new medicines. Only one-quarter was due to price increases.<sup>9</sup>

## **Research and Development, Marketing & Profitability**

“The great majority of drug candidates are thus weeded out very early on, before there has been a great deal of money invested in them.” (p. 23)

While it is true that pharmaceutical companies screen thousands of molecules and eliminate the majority before they ever enter clinical trials, Angell neglects to mention that the majority of molecules entering trials also fail. According to the Food and Drug Administration’s (FDA) recent report, *Critical Path: Innovation or Stagnation? Challenge and Opportunity on the Critical Path to New Medical Products*, “...the vast majority of investigational products that enter clinical trials fail. Often, product development programs must be abandoned after extensive investment of time and resources. This high failure rate drives up costs, and developers are forced to use the profits from a decreasing number of successful products to subsidize a growing number of expensive failures.”

The report also found that “The inability to better assess and predict product safety leads to failures during clinical development and, occasionally, after marketing.”<sup>10</sup>

“Yet the faster the approval process, the more likely it is that dangerous drugs will reach the market...But in its [FDA] rush, it is demanding less evidence of safety and effectiveness.” (p. 209)

Data from the FDA indicates that there has been no overall change in the number of drug withdrawals for safety reasons both pre- and post-PDUFA<sup>11</sup>:

- *Pre-PDUFA period.* Between Jan. 1, 1971, and Dec. 31, 1993, FDA approved 477 New Molecular Entities (NME), and 13 (2.7 percent) were eventually withdrawn. Nearly all the drugs approved in this period were received before FDA implemented PDUFA review goals.
- *PDUFA period.* Between Jan. 1, 1994, and Dec. 31, 2002, FDA approved 275 NMEs, and 7 (2.5 percent) have been withdrawn. Nearly all drugs approved in this period were reviewed under PDUFA goals.

The current standards for reviewing new drugs were put into place with the 1962 amendments to the Food Drug and Cosmetic Act, requiring all sponsors to study the efficacy of new drugs in addition to safety. There has been no legislative or regulatory initiative to change this “gold standard.”

Just over a decade ago, the average FDA review of a new drug application took about two and one-half years. Patients in the United States watched as drugs that could alleviate their diseases or conditions – or even save their lives -- were approved in other countries many months or years before they were available in the United States. With the passage of the Prescription Drug User Fee Act (PDUFA), which was first enacted in 1992 and subsequently reauthorized in 1997 and 2002, that unacceptable situation has changed.

As FDA stated in its Spring 2001 Center for Drug Evaluation and Research (CDER) Update, “PDUFA has been very effective in speeding the movement of prescription drug and biological products to the marketplace.” Furthermore, PDUFA has provided FDA with needed revenue to hire additional reviewers and upgrade information technology, thus enabling the agency to conduct more timely reviews for human drug and biological products without compromising review quality and consumer safety.

In addition, FDA has stated that their increased knowledge and understanding of certain rare safety issues, and the improved scientific tools to assess those safety issues are leading them to request more information on these issues on drugs in development. While Angell claims that the FDA is demanding less evidence on safety and effectiveness before approving a new medicine, in fact, over a 15-year period from the mid 1980’s to the turn of the century, the number of patients studied during clinical development for a new drug grew on average over 70%.

The following are a few examples of life-saving drugs that were made available to patients sooner because of PDUFA:

**Gleevec™**— A drug approved in 2001 for the treatment of chronic myeloid leukemia, a rare and deadly disease that affects some **25,000 Americans**. A priority-review drug, it was approved in just over two months.

**Xigris™** — A drug approved in 2001 for the treatment of adults hospitalized with severe sepsis that are at a high risk of dying. Prior to the approval of Xigris™, **about 1,000 people died of this condition every single day**. A priority drug, it was approved in under 10 months.

**Trisenox™** — A drug approved in 2000 for the treatment of a specific type of leukemia (acute promyelocytic leukemia) in patients who have not responded to, or have relapsed following all trans-retinoic acid and anthracycline-based chemotherapy. A priority drug, it was approved in six months.

**Mylotarg®** – A drug approved in 2000 for the treatment of a certain type of leukemia (CD33 positive acute myeloid leukemia) for patients 60 years or older who have relapsed for the first time and are not suitable candidates for the standard but poorly tolerated cytotoxic therapy. A priority and orphan drug, it was approved in about seven months.

PDUFA has made the drug review process more efficient without compromising safety or approval standards. Contrary to Angell's assertions, PDUFA does not change any safety standards, nor does it compel FDA to *approve* drugs quickly; only to *review* them more efficiently. Indeed, the scientific rigor of drug application reviews has only increased over the last decade.

“But as a general rule, a drug that can be called innovative in any usual meaning of the word is both a new molecular entity and a priority review drug.” (p. 54)

Angell claims that innovative medicines are only those drugs that are both NMEs and receive priority review status. Angell suggests that it is only these drugs that represent true innovation or clinical value for patients. In fact, FDA's Manual of Policies and Procedures (MAPP) notes that priority designation is assigned to products with the potential for providing significant preventive or diagnostic therapeutic advance as compared to standard applications. However, Angell never tells the reader that the FDA's Manual of Policies and Procedures also states that, “The priority determination does not take into consideration any information or estimate of price and is *based on conditions and information available at the time the application is filed*. ***It is not intended to predict a drug's ultimate value or its eventual place in the market.***” (MAPP 6020.3 – Priority Review Policy, italics added).<sup>13</sup>

“Priority review” is an FDA management tool—it should not be surprising that only a limited number of applications are granted this status. If priority review status were routinely granted, the concept would lose its meaning as a management tool. Thus, just because an application is subjected to a standard review does not mean it is not an important innovation or valuable addition to physician's treatment options. It is noteworthy that Angell never discloses or discusses this qualification. Moreover, many medicines not accorded priority review offer significant clinical benefit to patients. For example, the following drugs were all standard review drugs that arguably add significant value to patients and providers.

- **Natrecor:** Treatment for acute decompensated congestive heart failure. The drug, which was developed with the use of recombinant DNA technology, is a synthetic version of a human hormone that dilates veins and arteries.
- **Geodon:** Drug for the treatment of schizophrenia, a life-long illness that strikes men and women in their late adolescence or early 20s, often with multiple relapses and impaired daily functioning.
- **Reminyl:** For the treatment of mild to moderate Alzheimer's disease.
- **Invanz:** A long-acting injectable antibiotic for treatment of adults with moderate to severe bacterial infections, including complicated intra-abdominal infections, complicated skin and skin structure infections, community-acquired pneumonia, complicated urinary tract infections and acute pelvic infections.

- **Trelstar Depot:** A drug for the palliative treatment of advanced prostate cancer. According to the FDA, “It represents a new alternative for patients with prostate cancer in whom orchiectomy or estrogen administration is not indicated or is unacceptable.”
- **Acova:** An anticoagulant for the prevention or treatment of thrombosis (abnormal blood clotting) associated with heparin-induced thrombocytopenia, a serious immune disorder caused by heparin, a common anticoagulant used to prevent blood clots.
- **Colazal:** A drug for the treatment of mild to moderately active ulcerative colitis, a chronic and debilitating inflammatory disease of the gastrointestinal tract.
- **Tequin:** A new type of quinolone antibiotic for treating community-acquired respiratory tract infections such as pneumonia, acute exacerbation of chronic bronchitis and acute sinusitis.
- **Aciphex:** A once-a-day proton pump inhibitor to heal duodenal ulcers and erosive gastroesophageal reflux disease.
- **Cozaar** – First in a class of new antihypertensive agents that block angiotensin-II receptors.
- **Accolate** – First leukotriene receptor antagonist for asthma treatment.
- **Alphagan** – First alpha-2 adrenergic agonist for treatment of intraocular pressure in patients with open-angle glaucoma.
- **Copaxone** – First oral drug for treatment of multiple sclerosis.
- **Elmiron** – First oral medication approved for use in interstitial cystitis.
- **Remeron** – First in a new class of antidepressants.
- **Vistide** – First in a new class of antivirals called nucleotide analogues for treatment of cytomegalovirus retinitis in AIDS patients.
- **Detrol** – First medication approved for bladder control in more than 20 years.
- **Provigil** – First non-amphetamine therapy for narcolepsy approved in 40 years.
- **Tasmar** – First in a new class of drugs called COMT (catechol-O-methyltransferase) inhibitors for the treatment of Parkinson’s disease.
- **Zemplar** – First vitamin D analog to be approved for suppression of parathyroid hormone in chronic renal failure.

Angell states, “research and development (R&D) is a relatively small part of the budgets of the big drug companies—dwarfed by their vast expenditures on marketing and administration, and smaller even than profits.” (xv)

In addition to erroneously including “administration” in her calculation of marketing expenses, Angell simply uses incorrect numbers (see below). In 2003, PhRMA member companies alone spent much more on R&D initiatives, an estimated \$33 billion, than the entire industry (PhRMA members and non-members) spent on all combined drug promotional activities, \$25.3 billion. Direct-to-Consumer (DTC) advertising represented \$3.3 billion of total promotion, a figure consistent with other major industry spending levels. This is supported by a 2002 report by the General Accounting Office (GAO)<sup>14</sup> that confirmed that in 2001 companies spent more on R&D and than on all promotional activities. Furthermore, over half of total marketing expenses went to providing free samples to doctors for distribution to patients.

In terms of R&D investment, the U.S. pharmaceutical industry spends much more on R&D than other American industries, the National Institutes of Health (NIH) and the non-U.S. pharmaceutical industry.

Last, Angell *incorrectly* attempts to categorize all selling, general, and administrative expenses reported in filings to the Security and Exchange Commission (SEC) as marketing costs. But this accounting line-item includes marketing and non-marketing (i.e., administration) costs.

- According to Princeton professor Uwe Reinhardt, “...the [selling, general, and administrative] category represents many expenses other than selling expenses and should not be seen as an estimate purely of outlays on marketing, as the industry’s critics occasionally do.”<sup>15</sup>
- Expenditures on marketing, advertising, and administration reported in SEC reports and cited by industry critics, such as Angell, encompass spending on much more than just marketing. In addition to marketing expenses, “selling, general and administrative” expenses can include, for example, free medicines provided to medically indigent patients under companies’ patient assistance programs, systems and IT support, distribution and shipping expenses, and corporate functions, including legal, communications, dues, procurement, plus utilities and property taxes.

According to Angell, the pharmaceutical industry is “ <i>really</i> profitable.” (p. 11)
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While the pharmaceutical industry is a profitable industry, its profits are not out of line with other industries and not as high as Angell suggests. For example, in July 2002, the *Wall Street Journal* reported, “So far the pharmaceutical industry has avoided outright crisis, but it’s not nearly as profitable as some statistics suggest.”<sup>16</sup>

A 1993 Congressional Office of Technology Assessment (OTA) report on the costs, risks, and rewards of pharmaceutical R&D studied accurate measures of profitability, especially compared with other industries. OTA stated, “Unlike other kinds of investments, such as a new manufacturing plant, the success of a pharmaceutical R&D investment is highly uncertain and may take many years to be realized.”<sup>17</sup> Using a technique to adjust accounting profits to obtain a closer approximation of return on investment, OTA found that returns to the pharmaceutical industry between 1976 to 1987 were higher by just 2 to 3 percentage points annually than average returns to non-pharmaceutical firms after adjusting for differences in risk.<sup>18</sup> A.D. Little, a management consulting firm, updated the OTA report and found similar results for the period from 1991-2000.<sup>19</sup>



According to a 1994 report by the Congressional Budget Office (CBO), “properly measured, pharmaceutical company profits are only slightly above the average for companies in all industries.”<sup>20</sup> Another study by F.M. Scherer of Harvard University’s Kennedy School of Government concludes that eliminating profits would mean removing the incentive to develop new drugs. Profits attract investment, investment leads to pharmaceutical research, and research yields new cures and medicines.<sup>21</sup>

Princeton Economist Uwe Reinhardt has stated that if the pharmaceutical industry had no profits, little effect would be had on health expenditures. He estimates that in 1996 pharmaceutical profits accounted for about 1.16 percent of total national health spending. Thus, even if all of the profits on that year’s drug spending had been confiscated and rebated to American health care users, it would not have made much of a dent in total national health spending—only about \$50 per person.

Finally, according to a 2004 *Health Affairs* article authored by leading health economists and Harvard professor Joseph Newhouse, “... usual profit figures greatly overstate the [pharmaceutical] industry’s economic profit rate. The U.S. Congress Office of Technology Assessment (OTA) estimated that the industry’s economic rate of return from 1976 to 1987 was only two to three percentage points above the return in other industries, not the four to six percentage points estimated using standard accounting conventions. That the pharmaceutical industry would have a somewhat above-average profit rate is not surprising because of its extensive use of patent protection and the riskiness of its R&D investments.”<sup>22</sup>

Angell cites the work of Public Citizen to suggest that the cost of developing a new drug is only \$100 million, instead of Tufts University’s most recent estimate of \$802 million<sup>23</sup>. (p. 38; p. 46)

In an unusual choice for an individual whose reputation is based on her editorship of a peer-reviewed journal, Angell relies upon on a non-peer reviewed “study” by Public Citizen to suggest that the cost of developing a new medicine is \$100 million, not \$802 million as has been reported in the peer-reviewed *Journal of Health Economics*. However, according to analysis by Ernst & Young, “In several key aspects, the Public Citizen approach deviates from standard methodologies adopted by previous research and the financial and accounting communities. On many issues, the report presents selective evidence and ignores strong evidence to the contrary. These methodological shortcomings cause Public Citizen to underestimate the cost of pharmaceutical R&D.”<sup>24</sup>

While Public Citizens’ highly flawed “study” suggests that the often-quoted Tufts study, which appeared most recently in the *Journal of Health Economics*, and which has been updated several times, is inaccurate, several other studies corroborate the Tufts’ figures. For example:

- After review of the data used in Tufts study, the OTA cited a “substantial consistency” between aggregate R&D spending estimates and cash outlays per new chemical entities (NCE) estimated by Tufts. OTA concluded from the corroborative evidence available that the estimates made by Tufts are reasonably accurate.
- \$608 million for drugs beginning development in 1995 per Lehman Healthcare.
- Between \$590 and \$880 million per Boston Consulting for drugs entering development in 2001.

- According to a report by Accenture, “the estimated average R&D cost has escalated from less than \$150 million in the 1970s to over \$800 million today...the average cost to develop a drug today is even greater than that shown by the latest economic studies.”<sup>25</sup>
- According to a data from Bain & Co., “Declining R&D productivity, rising costs of commercialization, increasing payor influence and shorter exclusivity periods have driven up the average cost per successful launch to \$1.7 billion and reduced average expected returns on new investment to the unsustainable level of 5%.”<sup>26</sup>

### **Taxes**

“In any case, when all the tax benefits are taken together, big pharma pays relatively little in taxes.” (p. 46)

Angell’s claim that the pharmaceutical industry pays relatively little in taxes is fundamentally flawed. Angell relies on a report by Common Cause to argue that between 1993 and 1996 the tax rate paid by pharmaceutical companies was considerably lower than other industries. However, according to a PriceWaterhouseCoopers (PWC) analysis, the pharmaceutical industry continues to pay more corporate taxes relative to assets or revenues than either the manufacturing sector as a whole or all corporations. Moreover, PWC also found that “the pharmaceutical industry paid more taxes than 97 percent of all industries (ranking 6 out of 180).”

According to the PWC analysis (which was based on 1997 IRS data), before reduction for the foreign tax credit and the possessions tax credit, the pharmaceutical industry’s total tax liability (as percent of income subject to U.S. tax) is 33.8 percent, which is slightly higher than all manufacturing (33.7 percent) and for all industries (33.5 percent).

While Angell also criticizes the orphan tax credit as a boon to industry, the fact is in the decade after this credit took affect, 99 medicines were made available to patients with rare diseases, compared to 10 in the previous decade. This information—which demonstrates that the credit has accomplished exactly what it set out to do and is a boon to patients—is nowhere to be found in Angell’s book.

Another point Angell fails to mention is the fact that incentives have real-world consequences on what research gets done. According to a report by the Congressional Research Service (CRS), “Federal taxation of drug industry income affects the incentive to invest in the development of new therapeutic drugs through its impact on the cost of capital for drugmakers. Increases in the industry’s marginal effective rate of taxation raise this cost of capital, and when the cost of capital rises, drug firms in general can afford to undertake fewer new drug development projects than they otherwise would.”<sup>27</sup> In other words, taking away these incentives could hurt patients.

“[Clinical] trials can be rigged in a dozen ways, and it happens all the time.” (p. 95)

According to the FDA, the vast majority of investigational products entering clinical trials fail. If trials were so easy to rig, as Angell suggests, this would not be the case. With the average cost of developing a new drug now exceeding \$800 million, pharmaceutical companies have a critical interest in assuring that the data they collect to support product licensure is of the highest quality. Concerns about the questionable authenticity of a clinical study or even a single patient’s record can lead to data being disqualified, placing approval of the drug in jeopardy.

The human clinical trials that evaluate safety and efficacy are the most critical step in the drug development process. Extensive discussions are held with the FDA leading to agreements on clinical trial design and the type of data that will be required to support licensure. Clinical trials on a specific drug are conducted at multiple research sites, including many of the major American medical schools. Companies have quality assurance units that are separate and independent from the clinical research group to audit trial sites. Sites are visited every 6-8 weeks to assure good clinical practice (GCP) compliance, check on data quality and insure relevant procedures regarding the conduct of the trial are being followed. Contrast this practice with that of the NIH that suggests auditing be done every 2-3 years. It's not uncommon for academic investigators to question the need for such frequent audits, but when so much is at stake, data quality is paramount. PhRMA has sponsored workshops on fraud detection, inviting FDA to participate in sessions on how we collectively can better uncover fraudulent investigators.

Throughout the development process drug safety is continually studied. Important adverse drug events are reported to the FDA and if the Agency has concerns the trial may be stopped and placed on a clinical hold. FDA receives safety data on serious adverse events in a timely manner regardless of whether the drug or new indication is ever approved. FDA can use this safety data to require new safety studies for other drugs in the class or suggest that the warnings section of the drug label be updated.

After this development phase, which usually lasts five to six years, the analyzed data is submitted in a New Drug Application (or NDA) to the FDA. The full application consists of tens of thousands of pages and includes all the raw data from the clinical studies. This data is reviewed by the FDA under time frames established by PDUFA. Not every application is approved during the first review cycle. FDA may have significant questions that the company must answer before the new drug is approved for marketing.

Critical to the impartiality of new drug reviews is the fact that FDA is charged by Congress with protecting and promoting the public health. The Agency's over 2000 talented and highly dedicated drug employees involved in drug product reviews cannot have any financial interests in companies that the FDA regulates. As one might imagine, the drug review process is not something that is accomplished without significant work. According to the most recent FDA cost estimates, a little over 13 people years are spent reviewing a new license application. During this review period FDA conducts its own independent analysis of the clinical studies against the agreed upon end points.

Another two people years are spent during the various interactions and reviews with the company during the drug development process. At the successful end of this process is a new drug with full FDA-approved prescribing information, otherwise known as the drug label, that tells physicians and other health care providers how to maximize the benefits of the drug as they treat patients.

"There are two legitimate reasons for Phase IV studies...to see whether a drug is effective for an additional use... [and] to look for side effects or other properties that were missed in the earlier trials. However, the majority of Phase IV studies fall into neither of these two categories. Their purpose is not to get FDA approval for a new use. Nor is it to fulfill a commitment. Instead, they are mainly gimmicks to increase sales..." (p. 162-163)

Companies are interested in selling the medicines for which they receive FDA approval. The marketing of these drugs is done under the exacting standards promulgated by the FDA.

Materials that the company prepares for either DTC advertising or for the health care professional must be truthful and balanced and directly linked to the FDA approved indications that are on the drug label. Phase IV studies are done for two principal reasons. First, the study or studies may be part of an agreement with the FDA to study a particular safety issue or to confirm a surrogate end point that was used by the Agency for the approval of the drug. The second reason is to study new indications or patient populations that were not part of the original clinical study program. In each of these cases, the results of the trials are submitted to the FDA and the prescribing information (e.g., drug label) may or may not be changed depending on the results of the trial. It's hard to see how this can be considered a "gimmick."

### **DTC Advertising**

"There is no doubt in my mind that DTC ads mislead consumers far more than they inform them, and they pressure doctors to prescribe new, expensive, and often marginally helpful drugs." (p. 125)

Contrary to what Angell believes, numerous studies show that DTC advertising provides a valuable educational tool for consumers. Recent surveys have demonstrated that DTC advertising makes consumers aware of new drugs, as well as informs consumers of the benefits and risks or side effects of the drugs advertised.

Angell ignores this large body of research, including research published in peer-reviewed journals, emphasizing the benefits of advertising. She also ignores the well-established fact that large percentages of patients with serious medical conditions such as high blood pressure, depression, high cholesterol, asthma and diabetes, including insured patients, go wholly untreated with medicines. For instance, even in the heavily advertised category of cholesterol lowering medicines, only about 1/3 of patients who should be using medicines according to current guidelines are doing so. At the same time that Angell criticizes advertising that gets patients into needed treatment, she offers no alternative solution to getting patients into needed treatment.

Angell also ignores the fact that U.S. patients use a higher share of generic drugs than patients in other developed countries—with about 50% of all prescriptions being filled with a generic substitute. If DTC had the effects Angell claims, why are so many patients not using any medicines at all and why do Americans use more generics than their counterparts in other countries?

DTC advertising has a positive impact on patients and the doctor-patient relationship. For example:

- According to results from the 2002 FDA survey of physicians, many physicians believe that DTC advertising can play a positive role in their interactions with their patients. For example, 73 percent agreed that, because their patients saw a DTC ad, he or she asked more thoughtful questions during the visit; 72 percent thought that the ad made their patients a 'great deal or somewhat' aware of possible treatments; and 58 percent of physicians also thought that DTC ads made their patients 'great deal or somewhat' more involved in their healthcare.<sup>28</sup>
- As stated above, DTC advertising raises awareness of diseases and conditions that are often undiagnosed and untreated or undertreated, such as elevated cholesterol, depression, obesity, diabetes, and hypertension. Results from the 2002 FDA survey of

patients on DTC advertising found that 18 percent of respondents asked their physicians about a condition they had not discussed before.<sup>29</sup>

- DTC encourages patients to talk to their doctors. A 2002/2003 survey by Prevention Magazine about DTC advertising found that, as a result of DTC advertising, since 1997, an estimated 29.4 million Americans talked to their physicians about a medical condition they had never previously discussed with a doctor.<sup>30</sup>
- A 2002 FDA survey of consumers demonstrated that consumers learn about risk and benefit information from DTC ads. According to the survey “close to 90% of patients recall seeing risk and benefit information in DTC advertisements.”<sup>31</sup>

While DTC advertising prompts patients to seek professional help, it does not dictate the outcome of the doctor visit or the type of help patients eventually receive. Survey data, again ignored by Angell, consistently show that when patients ask a physician to prescribe a DTC-advertised medicine, many receive a different medicine or a non-pharmaceutical alternative.

- According to results from the FDA survey of physicians, 91% of the respondents said the patient did not try to influence the course of treatment in a way that would be harmful to him/her.<sup>32</sup>
- According to a GAO report, of the 61.1 million people (33% of adults) who had discussions with their physician as a result of a DTC advertisement in 2001, less than one out of seven (5% of adults) actually received a prescription for the product, a small percentage of the total volume of prescriptions dispensed.<sup>33</sup>
- Similar results were found in the FDA survey of consumers that found among the respondents who said advertisements had caused them to talk with a physician and ask for a drug, less than half said their doctor gave them the prescription drug they asked about.<sup>34</sup>
- FDA research also found that of those asking about a specific brand drug, 88 percent has the condition the drug treats.<sup>35</sup>

Furthermore, patients, physicians and health policy experts support the educational impact of DTC advertising.

- On September 13, 2002, the Federal Trade Commission (FTC) submitted comments to the FDA in support of DTC advertising, stating that “Many physician groups have expressed support for DTC advertising, emphasizing that balanced DTC advertising provided important information to consumers...DTC advertising of drugs has permitted an increase in the flow of truthful information about these products to consumers, and available empirical evidence suggests that this approach may benefit consumer welfare.”<sup>36</sup>
- According to an October 2002 study by the National Consumer League (NCL), most consumers find prescription drug advertisements “useful” and “don’t want limits put on them.”<sup>37</sup> In release of the study Linda Golodner, NCL’s President stated, “With DTC ads, large numbers of consumers are made aware of medical conditions and treatments that they may otherwise not know exist.”

- In its report released in early 2002, the National Health Council concluded, “The more information patients have, the more effective they can be in working with their doctor to make decisions about their health care....The Council recognizes that DTC advertising provides important information to consumers and patients, which is beneficial to their health.”<sup>38</sup>
- According to Dr. Lucille Perez, President of The National Medical Association (NMA), “Doctors are finding that these ads are helping patients talk to us about medical conditions they’re at risk for. When you consider the majority of drugs advertised can treat the diseases that disproportionately affect the African-American community, there is incredible potential...The NMA will advocate for increasing the awareness of the disease states in such advertisements. Further, we must view them as one of the several tools that are potentially beneficial to the physician-patient dyad.”

Pharmaceutical advertising plays a valuable role in the health care system by delivering the newest, FDA-regulated information regarding drug therapy to patients.

“One could make a strong argument that Americans with minor ailments suffer more from overmedication...than from undermedication.” (p. 126)

Although Angell suggests that DTC advertising encourages the use of medicines that are not necessarily needed, she does not address data demonstrating that much of DTC advertising is for categories of medicines that have been underused, not overused. According to a landmark study by RAND Health that was sponsored by the Robert Wood Johnson Foundation and published in the *New England Journal of Medicine*, “about half of adults in the U.S. fail to receive recommended health care” for serious conditions such as heart attack, colorectal cancer, and high blood pressure. The study found underuse of prescription medications in 7 of 9 health conditions that require treatment with prescription medicines, including asthma, cerebrovascular disease, congestive heart failure, diabetes, hip fracture, hyperlipidemia and hypertension.<sup>39</sup> While the RAND study does not address underuse in the context of DTC advertising, it is interesting to note that drugs to treat the majority of the conditions with demonstrated underuse in the study have prescription drug advertising. Despite its publication in the *New England Journal of Medicine*, Angell ignores this study and its extraordinarily important implications for patient care.

Another recent study published in the *Journal of Managed Care Pharmacy*, which examined claims data from 3 of the 10 largest health plans in California to determine the appropriateness of prescription medication use based upon widely accepted treatment guidelines, found that “effective medication appears to be underused.” Of the four therapeutic areas for study – asthma, CHF, depression, and common cold or upper respiratory tract infections – asthma, CHF, and depression were undertreated. (Data on asthma and depression care from the National Committee on Quality Assurance point in the same direction.) The researchers concluded that “the results are particularly surprising and disturbing when we take into account the fact that three of the conditions studied (asthma, CHF, and depression) are known to produce high costs to the healthcare system.”<sup>40</sup> Notably, while Angell suggests that DTC advertising promotes overuse of medicines, 2 of the 3 conditions found to be undertreated are DTC advertised. Angell never attempts to explain how there can be so much well documented underuse of medicines among insured patients if advertising has the effects she claims.

Major national surveys and studies from Harvard University, Massachusetts General Hospital, and the FDA show that DTC advertising brings patients into doctors’ offices and allows

physicians to treat people who might otherwise go untreated. According to a Harvard University/Massachusetts General Hospital and Harris Interactive (Harvard/Harris) national survey about health care experiences associated with DTC advertising of prescription drugs, one-quarter of adult patients who visited their physician after seeing a DTC ad received a new diagnosis of a condition.<sup>41</sup> Some of the most common new diagnoses made—high cholesterol, hypertension, diabetes, and depression—are often underdiagnosed and undertreated in the general population. Angell ignores this study, which was published in the peer reviewed journal *Health Affairs*.

The Harvard/Harris survey also found that approximately 43 percent of new diagnoses and 51 percent of existing diagnoses were for conditions classified as “high priority” by the Agency for Healthcare Research and Quality (AHRQ) and the Institute of Medicine (IOM). These conditions include diabetes, high cholesterol, hypertension, arthritis, asthma, depression, and anxiety.

Despite Angell’s suggestion that DTC advertising leads to inappropriate use of medicines or to negative health outcomes, the Harvard/Harris survey failed to find any large negative health consequences resulting from patients viewing DTC advertising. Rather, what this study and others have shown is that DTC advertising educates patients about serious diseases and conditions, encourages patients to visit their physician, increases compliance with needed medicines, and helps to solve the serious public health problem of underdiagnosis and undertreatment of disease. Further, Nancy Ostrove, Deputy Director, Division of Drug Marketing, Advertising at the FDA has stated that there is no evidence that DTC advertising is increasing inappropriate prescribing.<sup>42</sup>

### **Relationship between industry and medical professionals**

<p>“The pharmaceutical industry contends it educates the medical profession and the public about its drugs and the conditions they treat, and many doctors and medical institutions -- all recipients of the industry’s largesse – pretend to believe it.” (p. 135)</p>
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In addition to helping address undertreatment and underuse of needed medications, interactions between pharmaceutical representatives and healthcare professionals, as well as other types of promotion, play an important role in both physician and patient education.

Professional education programs fulfill an important role in our healthcare system. Educational conferences, when sponsored by a pharmaceutical company that conducts research in the relevant field, serve an important function in the professional development of treating physicians and provide important feedback to industry researchers. These activities play a valuable role in helping to remove the stigma associated with some diseases; educate physicians about available treatments; help patients find the right medicine; help translate new technologies and therapies into practice; and raise physician awareness of the most recent clinical practice guidelines and most recent medical technology.

Pharmaceutical detailing helps remove the stigma associated with some diseases and helps patients find the right medicine. According to a study by Harvard economists David Cutler and then-Stanford researcher Mark McClellan, through promotional activities, “manufacturers of SSRIs [depression medications] encouraged doctors to watch for depression and the reduced stigma afforded by the new medications induced patients to seek help.”<sup>44</sup> As a result, diagnosis and treatment for depression doubled over the 1990s.

Pharmaceutical detailing also raises physician awareness of the most recent clinical practice guidelines and the most recent medical technology. According to an article in the *Journal of American Medicine Association* (JAMA), “physician adherence to practice guidelines is critical in translating recommendations into improved outcomes. Their [guidelines] successful implementation should improve quality of care by decreasing inappropriate variation and expediting the application of effective advances to everyday practice. However, a variety of barriers undermine this process,” such as physicians’ lack of awareness and/or lack of familiarity of a guideline.<sup>45</sup>

Pharmaceutical promotion provides a solution to these barriers. According to an October 2002 article in the *American Journal of Managed Care*, “concurrent public and private efforts aimed at physicians and consumers were related to increased diagnosis and treatment...Physician-directed initiatives have included pharmaceutical industry marketing, continuing medical education programs, and promotion of NCEP [National Cholesterol Education Panel] guidelines. Consumer-directed initiatives have included direct-to-consumer advertisements sponsored by various pharmaceutical companies and patient education programs sponsored by many managed care organizations.”<sup>46</sup>

Pharmaceutical detailing can also help patients find the right medicine. According to a *Wall Street Journal* article from 2002, “If you’re open to switching prescriptions, ask your doctor for samples...Not only will you stave off having to pay, but doctors advise trying various medicines because they differ.” Samples are “an important way of trying to find out which ones work” for patients, says Anthony Montanaro, chairman of the Asthma and Allergy Foundation’s Medical-Scientific Council.<sup>47</sup>

Although Angell suggests that nothing limits the interactions between pharmaceutical representatives and physicians or academics, this is wrong. Federal law regulates both “professional education” and “promotion” and ensures that the distinction between the two remains clear. In addition, national accrediting bodies such as the American Academy of Continuing Medical Education (ACCME) have implemented standards which ensure that accredited Continuing Medical Education (CME) programs are independent and free of any influence from the companies that provide necessary funding for such programs.

FDA regulates the content of prescription drug advertising and promotion directed to physicians. The Federal Food, Drug, and Cosmetic Act requires that promotional materials present accurate information and fairly represent both the benefits and the risks of the drugs promoted. In addition, companies and their employees are limited to discussion of approved uses of the drug. FDA’s Division of Drug Marketing, Advertising and Communications (DDMAC) monitors prescription drug promotion to physicians in every venue, including audio conferences for physicians, pamphlets distributed at professional meetings, conversations between industry representatives and physicians at professional meetings, mailings to healthcare professionals, advertisements in professional journals, and the like.

“Many promotional practices can only be described as bribes and kickbacks....By calling it education or consulting or market research or some combination of those things, but not marketing, companies needn’t worry about antikickback laws” (p. 130; p. 142)

Federal and state antikickback laws strictly regulate the relationship between pharmaceutical companies and medical professionals. The federal anti-fraud and abuse law (also known as the antikickback law) makes it unlawful to pay or receive any “remuneration” in exchange for purchasing, prescribing, or recommending any item or service, or referring any patient for



treatment, for which payment may be made under Medicare or Medicaid. As a practical matter, this prohibits pharmaceutical manufacturers from offering or paying financial incentives in return for purchasing, ordering, or prescribing prescription drugs. A number of state antikickback laws prohibit the same kinds of activities with respect to products reimbursed under state health care programs or even private insurance.

In addition, in April of 2002, PhRMA adopted a new marketing code to govern the pharmaceutical industry's relationships with physicians and other healthcare professionals. Under the voluntary code, which took effect on July 1, 2002, interaction between pharmaceutical representatives and healthcare professionals is intended to focus on educating the healthcare profession about scientific information and supporting scientific medical research and education to maximize patient benefits.

Although Angell suggests the PhRMA code has an "exemption for educational or research activities," this is simply not accurate. The PhRMA code recognizes that there are many situations in which pharmaceutical companies have a legitimate need to hire healthcare professionals as consultants, such as to provide scientific expertise regarding an investigational treatment. The PhRMA Code thus permits the hiring of physicians as consultants but only if such consultancies are "bona fide." Factors that support the existence of a bona fide consulting arrangement include: a written contract defining the services and payment terms; a legitimate need for the services clearly identified in advance; and selection of consultants based on their expertise and ability to provide the services requested. The PhRMA Code explicitly states that "[t]oken consulting or advisory arrangements should not be used to justify compensating healthcare professionals..."

### **Pharmaceutical Innovation**

"The pharmaceutical industry is not especially innovative." (xv)
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Over the past decade, pharmaceutical companies have pushed the scientific envelope, working at the cellular and molecular levels to dramatically advance the treatment of disease. At the end of 2002, 28 percent more medicines were being investigated by pharmaceutical companies for approval by the FDA than was true one decade before. More than 1,000 medicines are now in the development pipeline.<sup>48</sup>

Between 1993 and 2003, more than 300 new drugs, biologics, and vaccines that prevent and treat over 150 conditions were approved by the FDA. The FDA also gave the go-ahead for numerous new indications for previously approved medicines, allowing physicians to tailor treatment strategies to meet a patient's individual disease status, past medication history, side effect tolerance, and preferences. The new medicines that are the product of this decade of innovation have dramatically changed the "standard of care" for several major conditions. Medical treatment guidelines have been revised to recommend early intervention with these new, more effective medicines.

Just a few examples of the new innovations in just the last decade include:

- Four generations of medicines to treat HIV/AIDS that have sharply reduced the death rate in the U.S. and allowed patients to lead productive lives;
- The first treatments for Alzheimer's that allow patients to delay or avoid costly long-term care and reduce the total cost of treating the disease;<sup>49</sup>

- Cholesterol lowering medicines that prevent first and second heart attacks, yet which are now taken by less than one-third of the 36 million who should take them according to federal government guidelines;
- The first medicine to fight sepsis – a disease that kills more than a thousand people every day;
- Anti-psychotic and anti-depressant medicines that allow people once condemned to mental hospitals and agonizing lives to lead healthy, productive lives<sup>50</sup> and that are reducing the total cost of treating mental illness;<sup>51</sup> and
- Hundreds of new medicines now in clinical trials, offering opportunities for greatly improved treatment for a broad range of diseases, such as Alzheimer’s Disease, osteoporosis, diabetes, cancer, AIDS/HIV, and various infectious diseases.<sup>52</sup>

“Every now and then drug companies bring an innovative drug to market, but mainly they turn out a seemingly inexhaustible supply of leftovers – “me-too” drugs.” (p.74-75); “There is little evidence to support the notion that if a particular drug doesn’t work for a patient, a virtually identical one will.” (p. 90)

First, as discussed above, a wide array of new types of medicines have been brought to patients in recent years. Second, while Angell dismisses the majority of prescription drugs as “leftovers” (which Angell describes as drugs that are not NMEs with priority review status), these medicines can provide immense value to patients. Despite a wealth of data available to consider, Angell never discusses the value of multiple drugs within a therapeutic class, as she derides as “me-too” drugs. According to Janet Woodcock, MD, Director of the FDA Center for Drug Evaluation and Research (CDER), “The FDA would like to offer patients a choice of drugs within the same class, since not every patient responds to every drug in the same manner.”<sup>53</sup> While patients and physicians know from common experience that different medicines have different effects on patients and it sometimes takes trying several medicines of a given type before finding one that has the desired effects while avoiding side effects, for Angell, “one drug fits all.”

According to experts at Temple University School of Pharmacy, “Incremental advances, rather than ‘breakthrough’ discoveries, constitute the basic mechanism of all technological innovation. Newer drugs in a therapeutic class often have fewer side effects, improved drug safety and effectiveness, and greater ease of use which facilitates compliance with prescribed therapeutic regimens. Product alternatives permit treatments to be better tailored to individual patient needs.”<sup>54</sup>

In addition, new uses for existing agents are continually discovered and bring significant benefits to patients. These improvements and discoveries are especially important for optimal treatment of elderly patients, because their diverse response to medications requires individualized care. A broad range of medicines provides physicians with a “tool chest” to treat each patient with precision and provides options when particular agents are ineffective or poorly tolerated by a given patient.

For example, for diseases of the central nervous system, overall response rates are often 50% or less.<sup>55</sup> Patients who fail to respond to one drug will often respond to another drug in the class. Examples of widely used drug classes associated with great variation in patient response are the selective serotonin reuptake inhibitors (SSRIs) and the non-steroidal anti-inflammatory agents

(NSAIDs). In patients treated with SSRI agents for depression, 26% of non-responders to fluoxetine did respond to sertraline.<sup>56</sup> Conversely, another study reported that 63% of patients who failed to respond to sertraline did respond to fluoxetine.<sup>57</sup>

The NSAIDs also differ greatly with respect to efficacy and patient tolerance. Often, multiple drugs must be tried before success is achieved. For example, in one two-year study of patients on NSAIDs, 49% of patients were switched to another NSAID; 20% were switched two times or more; and 7% received four or more different NSAIDs.<sup>58</sup>

The currently available beta-blockers offer differences in potency, cardioselectivity, effects on the nervous system, pharmacokinetic properties (which determine appropriateness for patients with impaired kidney or liver function), additional pharmacological benefits, potential for interaction with other drugs, efficacy in specific racial groups, complexity of the dosage regimen and adverse effects profile—all of which have important implications for the treatment of high blood pressure. The array of differences among these drugs allows for customized treatment for patients. This array of differences enables doctors to customize treatment to the patient's specific needs.<sup>59</sup>

“There is almost no evidence of price competition in the me-too business. (p. 89)

According to a 2004 article in the *New England Journal of Medicine*, “When a second product comes along in the same class, its manufacturers must offer better value. That means that the product must lead to better patient outcomes, or it must be less expensive.”

The article continues by stating that, “Evidence that such market forces are at work in U.S. health care can be found in the lower prices for products introduced after the first-in-class drugs or devices. The current monthly costs of statins at doses that are expected to reduce the levels of low-density lipoprotein cholesterol by 45 to 49 percent are lower for products that received FDA approval more recently. Lower costs for me-too drugs are also seen in other commonly used classes of drugs.” The article concludes that additional entrants in a market, “reflect and create competition among drug and device manufacturers, and that competition is also a powerful driver of better quality and lower costs.”<sup>61</sup> Angell ignores this article, despite its appearance in the *New England Journal of Medicine*.

Additionally, other academic studies have highlighted the potential for price competition among potential therapeutic substitutions. One study, analyzing 130 drug launches between 1978-1987, concluded that the number of existing drug substitutes had a significant downward effect on manufacturer's launch price of a new drug.<sup>62</sup> Another study, commissioned by the Department of Health and Human Services during the Clinton Administration, analyzing retail drug prices between 1995-1999, found that most new drug entrants examined were launched at discounts (sometimes substantial) relative to both the class price leader and to the average price in the class. The study further concluded that average prices for drug subclasses did not on the whole increase substantially over general price inflation, and in many cases were shown to be either flat or to have declined slightly. Of the 20 drugs launched within existing drug sub-classes, 13 were launched with at least a 5 percent discount relative to the average price of the sub-class and several drugs saw discounts ranging as high as 30-40 percent.<sup>63</sup>

Thus, new drug introduction has been found to provide significant health benefits, and also, through competition, to reduce pharmaceutical costs.

“Truly important drugs” are “mostly based on taxpayer-funded research at academic institutions, small biotechnology companies, or the National Institutes of Health (NIH).” (xv); “These laws [Bayh-Dole] mean that drug companies no longer have to rely on their own R&D for new drugs, and few of the large ones do. Increasingly, they rely on academia and the NIH for that.” (p. 7)

The research-based pharmaceutical industry continues to spend more on biomedical R&D than the NIH and discovers and develops the vast majority of the medicines in the U.S. In 2003, pharmaceutical research companies invested approximately \$33 billion in drug R&D. The total NIH budget, which includes support for its basic research-focused agenda, is now about \$27 billion. Since 1980, pharmaceutical companies have multiplied their R&D investment 16-fold.

In a report issued to Congress in July of 2001, the NIH thoroughly disproved the contention that the government pays for most of the research for top-selling prescription drugs. The report found that contravening the provisions of the Bayh-Dole Act could have a “deleterious effect on biotechnology development” and that if direct financial recoupment of the federal investment in biotech was required, it could impede the development of promising new technologies. After finding only 4 of 47 drugs meeting the \$500 million standard, NIH concluded that the current system involving technology transfer between federally funded projects and industry was the best option in protecting taxpayers’ interests.<sup>64</sup>

A similar report by the GAO which examined the relationship between pharmaceutical manufacturers and the NIH, the Department of Defense (DoD) and the Department of Veterans Affairs (VA) as it relates to the government’s rights to inventions created by federally funded research, found that the government had licensing rights in only 6 brand name drugs associated with the top 100 pharmaceuticals that the VA procured and in 4 brand name drugs associated with the top 100 pharmaceuticals that the DoD dispensed. In other words, the government had licensing rights in only 6% of the drugs purchased by the VA and 4% of the drugs purchased by DoD.

“Bayh-Dole requires that work licensed to drug companies be made ‘available to the public on reasonable terms.’ That could certainly be interpreted as meaning that it should be priced reasonably. And until 1995, the NIH explicitly required reasonable pricing for drugs stemming from collaborations [with NIH]...” (p. 69)

According to the NIH report discussed above, government funding has contributed substantially to general advances in the health sciences, but it is virtually impossible to determine direct government contributions to any final therapeutic product. A survey quoted in the NIH report found that more than 75 percent of licensed innovations amounted only to proofs of concept, such as basic research that confirmed HIV is the cause of AIDS.<sup>65</sup> It is up to private industry to take the inventions through the longer, more expensive, more elaborate R&D process that leads, in some cases, to a commercial product. After all, it is private industry, rather than the NIH, that has the expertise and resources to engage in such later stage R&D.

Second, according to former Senators Bayh and Dole, the Bayh-Dole Act “did not intend that government set prices on resulting products. **The law makes no reference to a reasonable price that should be dictated by the government. This omission was intentional**; the primary purpose of the act was to entice the private sector to seek public-private research collaboration rather than focusing on its own proprietary research.”<sup>66</sup> (emphasis added)

Third, the NIH's prior experience with a "reasonable pricing" clause shows why the idea is a bad one. The NIH previously adopted such a policy, but rescinded it because doing so promoted needed medical research.

- In 1989, the NIH adopted a policy of a "reasonable relationship between the pricing of a licensed product, the public investment in that product, and the health and safety needs of the public." The NIH required that this "reasonable pricing" policy be followed in exclusive licenses to inventions made under Cooperative Research and Development Agreements (CRADAs) entered into by the NIH.
- The NIH came to the realization that the "policy had the effect of posing a barrier to expanded research relationships, and, therefore, was contrary to the Bayh-Dole Act."<sup>67</sup>
- The NIH convened panels (including scientists, government administrators, industry, academia and patient groups) that concluded that the policy "did not serve the best interests of technology development" and recommended that the policy be rescinded.<sup>68</sup>
- When the NIH abandoned the policy in 1995, the NIH Director declared that, "the pricing clause has driven industry away from potentially beneficial scientific collaborations with [NIH] scientists without providing an offsetting benefit to the public. Eliminating the clause will promote research that can enhance the health of the American people."<sup>69</sup>

The flat growth in the number of CRADAs shows that adopting a "reasonable pricing" policy can have negative consequences. There was a relatively flat growth rate of CRADAs entered into by NIH and industry between 1990 and 1994, but a subsequent rebound in CRADAs following the policy's revocation.<sup>70</sup> Given that the vast majority of important new medicines are not developed with technologies created with federal funds, it is important to foster scientific collaborations, rather than impose a requirement that could be a disincentive to licensing and developing new products.

"While it [Hatch-Waxman] was meant to stimulate generic competition it has often had exactly the opposite effect." (p. 180)

In July 2002, the FTC released its report, *Generic Drug Entry Prior to Patent Expiration*. The report found that, "Beyond any doubt, Hatch-Waxman has increased generic drug entry. Generic drugs now comprise more than 47 percent of the prescriptions filled for pharmaceutical products – up from 19 percent in 1984, when Hatch-Waxman was enacted." Angell ignores this report.

Generics' share of the pharmaceutical market is now larger in the United States than virtually any other developed country in the world.

"Hatch-Waxman also lengthened the patent life for brand name drugs." (p. 9)

Patent expiration dates are firmly set by law and cannot be extended through litigation. The pharmaceutical industry can not manipulate expiration dates. While Hatch-Waxman did authorize a limited restoration of the patent term for no more than one patent for a product, this restoration does not mean that the statute lengthened the actual patent life for brand name drugs.

“The companies list any patents they choose [in the Orange Book]” (p. 181)

This is factually wrong, plain and simple. The patents to be listed by companies are determined under Hatch-Waxman and FDA regulations. In 2003, FDA issued a Final Rule that provides additional clarification about which types of patents should be listed in the Orange Book. So, companies cannot list any patents they choose in the Orange Book, as Angell suggests. In addition, the Rule requires brand-name drug companies to submit more detailed patent information in a declaration to list a patent in the Orange Book, another point left out by Angell.

Angell states that Hatch-Waxman caused brand-name companies to “routinely file not just one patent on their blockbusters but a series of them spread throughout the life of the first one...The result is that generic companies are routinely charged with infringement on one of these secondary patents, which immediately triggers thirty months of additional exclusivity.” (p. 181)

Again, this is simply untrue. Companies continue to innovate, even after a compound is first marketed, and may obtain patents covering such innovation. This is so even in situations where Hatch-Waxman does not apply, including other industries. In addition, under the MMA, Congress limited the application of thirty-month stays to those patents listed in the Orange Book prior to submission of a generic application.

### **Medicare Modernization Act of 2003**

“They passed a bill that explicitly prohibits Medicare from using its enormous purchasing power to bargain for low prices...Every other large purchaser – from the Veterans Affairs system to Aetna and General Motors – negotiates for favorable prices.” (Page 194)

Angell refers to a provision in the recently enacted Medicare prescription drug legislation, often termed the noninterference provision, and claims that it prevents cost containment. However, a prohibition on government price controls does not mean there is no cost containment in the Medicare Act. The new Medicare law contains significant cost-containment mechanisms, including:

- Plans are required to utilize cost management techniques, including a drug utilization management program that uses incentives to reduce costs when those actions are medically appropriate. The Secretary can not contract with a plan unless it demonstrates that it has these cost management techniques.
- Beneficiaries receive the benefit of negotiated prices which must be disclosed to them. Thus, plans have further incentives to negotiate hard since beneficiaries may well be selecting a plan based on its discounted prices.

### ***CBO Identifies Large Cost Savings Through Negotiation in Medicare Bill***

In addition, according to the non-partisan CBO, multiple competing private-sector plans can contain costs more effectively than a government-controlled benefit. Through competition and plans' use of price discounts, rebates, utilization controls, and other tools, CBO says the private sector approach has the potential to best control spending. The CBO has since reaffirmed this position and also stated that the noninterference provision did not add costs and repealing it would not yield significant savings.<sup>71</sup>

It is exactly the same type of plans that Angell cites as achieving “steep discounts” (see p. 14) earlier in her book that will be doing the negotiating in Medicare. However, in this instance, Angell chooses not to acknowledge the steep discounts. These plans’ ability to negotiate is evident from the fact that several already negotiate on behalf of tens of millions of persons each:

- AdvancePCS manages benefits for more than 75 million people.
- Medco manages benefits for more than 62 million people.
- Express Scripts manages benefits for more than 50 million people.

### ***Noninterference Originated with and is Praised by President Clinton***

The noninterference provision was created by and praised by Democrats in the past, a fact missing from Angell’s book. In fact, a bill (S. 2451, the Medicare Expansion for Needed Drugs Act of 2000) by Sen. Tom Daschle, (D-S.D.), contained nearly identical language: “NONINTERFERENCE.—In administering the prescription drug benefit established under this part, the Secretary may not: require a particular formulary or initiate a price structure for benefits; interfere in any way with negotiations between private entities and drug manufacturers or wholesalers; or otherwise interfere with the competitive nature of providing a prescription drug benefit through private entities.”

Further, when President Clinton introduced his Medicare modernization proposal in 1999, he described such a provision, stating, “Seniors and the disabled will save even more on their prescription drugs under my plan because Medicare’s private contractors will get volume discounts that they could never get on their own. By relying on private sector managers, I believe that my plan will help Medicare beneficiaries and ensure that America continues to have the most innovative research and development-oriented pharmaceutical industry in the world.”<sup>72</sup>

### ***Noninterference Prohibits Government from Establishing a National Formulary***

Not mentioned by Angell, but also important to remember, is that the noninterference provision also prevents the government from setting a national formulary, which would restrict patients’ access to medicines. Other government agencies that don’t allow private sector competition restrict access to medicines through a variety of tools, including national formularies. Barring a national formulary, while developing other means to control costs, is good policy and better for patients.

### ***VA Prices Result of Statutory Price Control, Not Negotiation***

While Angell states that the VA “negotiates” to get better prices, the fact is Federal Supply Schedule (FSS) pharmaceutical prices charged to the VA (and certain other federal agencies including the DoD, PHS, and Coast Guard) are capped by statute.<sup>73</sup> Federal law spells out a specific formula which dictates a maximum price for each drug. A company that does not sign a contract agreeing to this formula cannot have its products reimbursed in state Medicaid programs or purchased by entities that receive certain public health grants [so-called 340(b) clinics]. Thus, VA prices are the result of statutory price controls and an onerous enforcement mechanism, not a negotiating process.

### ***Government “Negotiation” = Government Price Controls***

As former Administrator of the Health Care Financing Administration (HCFA), now CMS, stated, "Let's be clear. Government doesn't negotiate prices – it sets them. We see how the government views 'price negotiation' elsewhere in Medicare, and we see some of the consequences."<sup>74</sup> Price controls have many negative consequences, particularly for patients, including delaying patient access to new medicines and harming incentives for innovation. Unlike systems with government-set or regulated prices, competitive systems spark innovation, creating powerful incentives for new, improved, and more cost-effective medicines and treatments.

### **Importation**

"But there is absolutely no reason to think counterfeiting is more likely with drugs imported from Canada than with drugs that never crossed the border, and some reason to think it is less likely." (p. 222)

The FDA has testified on numerous occasions that counterfeit or unapproved drugs are being imported from Canada. According to a July 2004 FDA analysis of three of the most commonly prescribed drugs purchased from a Web site advertised as Canadian, all three so-called "Canadian Generics" were "fake, substandard and potentially dangerous."<sup>76</sup> The products purchased were so-called "generic" versions of Viagra, Lipitor, and Ambien. None of these products has a U.S.-approved generic version. In response to the findings, FDA Acting Commissioner Dr. Lester M. Crawford stated, "The test results of our analyses offer proof positive that buying prescription drugs online from unknown foreign sources can be a risky business. As was the case here, even where a website looks legitimate, FDA has clear evidence that the Web site is dispensing misbranded drugs that are not the same quality as those approved by the FDA for sale in the United States."<sup>77</sup>

Furthermore, on July 22, 2004, the FDA sent a letter to Wisconsin Governor Jim Doyle, whose state website allows patients to purchase prescription drugs through Canadian Internet pharmacies, denouncing the program because the state was not able to control the "quality of foreign drugs being dispensed through this program."<sup>78</sup>

Specifically, FDA found that "55 of 79 parcels originating from the Canadian pharmacies participating in the Wisconsin pharmacy program contained either generic medications for which there is no equivalent approved by the FDA for sale in the U.S.; or drugs that FDA considers high risk because they have been counterfeited in the past or pose potential safety concerns." According to the FDA, "These violations continue to present ongoing safety concerns for Wisconsin residents who are led to believe they will get foreign drugs that are identical to or the same as FDA approved products, while leaving them with very limited recourse when in fact they receive drugs that are unapproved foreign versions that violate the State agreement and are not what they ordered."

Finally, Canada has confirmed it will not guarantee the safety of illegal drug imports. According to Diane Gorman, Assistant Deputy Minister, Health Canada, "The Government of Canada has never stated that it would be responsible for the safety and quality of prescription drugs exported from Canada into the United States, or any other country for that matter."<sup>79</sup> Even if Canada did regulate exports, its regulatory system almost certainly would be quickly overwhelmed. Currently, the Canadian drug market is less than 10% of the U.S. drug market.



“Most of the drugs they were buying had been made by major drug companies, based in either the United States or Europe, and approved by the FDA.” (p. 220)

The FDA and U.S. Customs and Border Protection (CBP) recently conducted a series of spot examinations of mail shipments of foreign drugs to U.S. consumers to help FDA and CBP target, identify, and stop counterfeit and potentially unsafe drugs from entering the United States. The spot examinations revealed that these shipments often contain “dangerous unapproved or counterfeit drugs that pose potentially serious safety problems.” Of the 1,153 imported drug products examined, the overwhelming majority, 1,019 (88%), “were violative because they contained unapproved drugs”.<sup>80</sup>

In addition, it is often difficult to trace the true country of origin for these imported drugs. According to former FDA Commissioner Mark B. McClellan, M.D., Ph.D., “During the import blitz, we have examples where our examinations revealed that products were manufactured in countries other than Canada, yet were exported from Canada. For example, at the Dallas, Seattle and Buffalo mail facilities, imported drugs were encountered which were manufactured in Canada, Mexico, Costa Rica, India, Pakistan, New Zealand, Taiwan, Thailand, and a host of other countries. However, in some cases, the drugs that had obviously been manufactured in other countries were exported from Canada.”<sup>81</sup>

### **Conclusion**

The research-based pharmaceutical industry is the most innovative industry in the world, producing new drug therapies that improve quality of life through declines in hospitalizations, increases in life expectancy, and decreases in overall health care spending. In addition, the replacement of older drugs with newer drugs often results in reduction in mortality and morbidity.

For example:

- Several studies have found that use of statin therapy to treat people with high cholesterol reduces hospital admissions and invasive cardiac surgeries. For example, a study of one statin showed that it reduced hospital admissions by a third during five years of treatment. It also reduced the number of days that patients had to spend in the hospital when they were admitted, and reduced the need for bypass surgery and angioplasty.<sup>82</sup>
- A study sponsored by the Agency for Health Care Policy and Research concluded that increased use of a blood-thinning drug would prevent 40,000 strokes a year, saving \$600 million annually.<sup>83</sup>
- A January 2004 study by Duke researchers found that “beta-blocker therapy improves the clinical outcomes of heart failure patients and is cost saving to society and Medicare.” The study, which was written before enactment of the Medicare drug benefit, notes: “If medication costs were completely reimbursed by Medicare, program savings from beta-blocker therapy would remain positive.”<sup>84</sup> Looking at the overall societal perspective, the researchers found that five years of treatment for heart failure without beta-blockers cost a total of \$52,999. With beta-blockers added to treatment, total treatment costs fell by \$3,959, patient survival increased by an average of about three-and-a-half months, and patients needed fewer overnight hospital stays.

- Disease management programs are encouraging the use of Rx medicines, lowering overall health costs. A heart failure disease management program that increased appropriate use of medicine resulted in decreased use of hospital services (24.6% fewer ER admissions, 22.2% fewer days in the hospital) and a decreased overall spending per member per month by 28%.<sup>85</sup>
- New medicines also benefit the economy by increasing worker productivity and reducing absenteeism. One study, which evaluated the effect of migraine treatment on productivity, found that more than 50% of workers who received a triptan drug injection for a migraine attack returned to work within two hours, compared with 9% of workers who received a placebo.<sup>86</sup>

Pharmaceuticals are a vital component of healthcare. Promoting prices controls and limiting intellectual property protections impede efforts to discover new medicines that can produce improved health and quality of life while helping control total healthcare spending.

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