

RECOMMENDATIONS FOR IMPROVING THE HEALTH CARE SYSTEM—PHARMACOLOGY

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INTRODUCTION

The cost of pharmaceuticals in America is beyond the reach of many citizens regardless of insurance. Of the 3 trillion dollars spent annually on U.S. health expenditures, roughly 9.8% is spent on prescription drugs. This equates to over 900 dollars per person in the U.S.¹ In order to make the system more affordable one must analyze the reasons drugs are costly and develop improved mechanisms that will reduce costs. This is a complex dilemma to discuss, but breaking it down into separate items should make it less daunting. The intent of this article is to stimulate further discussion that can ultimately result in legislation and health policy that is more constructive, preserves the safety and effectiveness of products, and reduces burdens to access that incorporate costs and availability.

I. HISTORY OF THE FDA

At one time a pharmaceutical agent did not need to pass any qualifying tests to be sold to consumers in America. But, the growth of a nation just emerging from the Civil War forced the development of efficient methodologies in agriculture and manufacturing. The expansion in technology that fostered the industrial revolution had its byproducts in science and health, creating forerunners to products we use and enjoy today. This included chemicals, and created numerous products that had applications in medicine. Electricity revolutionized innovation and manufacturing further and as the lives of people improved, so did their desire for more and more innovation. In 1897 Felix Hoffman, a chemist at Bayer in Munich, discovered that acetylation of salicylic acid would create a medication that could be tolerated orally, would relieve pain, and lower temperature. This product became Aspirin. He also added an acetyl group to morphine, creating diacetyl morphine. When this product was given to

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¹ See *Health Expenditures*, CDC (Oct. 7, 2016), <https://www.cdc.gov/nchs/fastats/health-expenditures.htm>.

subjects, they felt euphoric and strong—like heroes.² Thus, he named the product “heroin.” At the time heroin was felt safer than morphine, and was sold by Bayer as a remedy for cough and for pain. It was finally banned for legitimate sale in the 1930s. At the time it was developed, there were no regulations in place to assure its safety. Those regulations evolved slowly.

Sulfanilamide (prontosil) was an antibiotic that grew out of the German dye industry, and was patented by Bayer in 1909, but not recognized as an antibiotic until the 1930s, when it was inexpensive and widely used. To improve its appeal to children, S.E. Massengill Company combined it with ethylene glycol (antifreeze). It was sold and distributed with no safety testing, and resulted in several mass deaths. This led to the passage of the Food Drug & Cosmetic Act of 1938 (21 U.S.C.), and there have been twelve amendments since then.³

The sleeping pill, thalidomide was developed in Germany and in use in Europe as a remedy for morning sickness when cases of neuritis were beginning to appear in the literature. Some users were giving birth to children with congenital absence of arms and limbs (amelia), although no connection as of yet was made. It had never been tested in pregnant women. The drug was scheduled for approval in the U.S. when executives at William S. Merrell, a drug company located in Cincinnati, were pressuring the FDA that the drug was safe and had a lower suicide rate than barbiturates. It had already been approved in Canada, Europe and Africa. However, the watchful examiner, Frances Oldham Kelsey, who had joined the FDA in 1960, recalled a publication in the medical literature that thalidomide was associated with neuritis. She stalled its approval claiming harmless sleeping pills should not cause severe neurological disorders. Meanwhile, data was emerging in Europe that confirmed the association between thalidomide and birth defects. In 1962, as a response to this tragedy, the Kefauver-Estes Amendment was enacted to assure that drugs approved by the FDA are safe and effective.⁴

The Balanced Budget Act of 1997 (Public Law 105-33) enabled Medicare beneficiaries to receive coverage through private insurance plans. These plans

² Felix Hoffman, CHEMICAL HERITAGE FOUND. (Sept. 11, 2015), <https://www.chemheritage.org/historical-profile/felix-hoffmann>.

³ Carol Ballentine, *Taste of Raspberries, Taste of Death: The 1937 Elixir Sulfanilamide Incident*, U.S. FOOD & DRUG ADMIN. (Oct. 7, 2010), <http://www.fda.gov/aboutfda/whatwedo/history/productregulation/sulfanilamidedisaster/default.htm>.

⁴ Linda Bren, *Frances Oldham Kelsey: FDA Medical Reviewer Leaves Her Mark on History*, NAT'L CTR. FOR BIOTECHNOLOGY INFO., U.S. NAT'L LIBR. OF MED. (Mar. 2001), <https://www.ncbi.nlm.nih.gov/pubmed/11444245>.

were known as Medicare+Choice or Part C plans. The Medicare Modernization Act of 2003 (MMA) (Public Law 108-173) overhauled the public health program by changing the contracting method from fiscal intermediaries to Medicare Administrative Contractors (MAC). It provided more advantages such as basic prescription coverage through Part D, but also was more restrictive with respect to provider networks. The increased costs of this program through 2015 were projected to be over a half a trillion dollars, despite limiting patient choice of physician and only partially covering medications for chronically ill patients.

The Patient Protection and Affordable Care Act (PPACA), (42 U.S.C. § 18001 (2010)) was passed to enhance health care quality, reduce costs, increase health care access and reduce disparities of care. It mandates insurance coverage for uninsured American citizens. In the past six years, users and administrators have identified opportunities within the plan to reduce its costs and burdens. To its benefit, it has reduced the number of uninsured to 10.9% from 16.4% at the time of its passage.⁵ It has been criticized in that it does not provide health care to illegal immigrants that comprise nearly one third of the existing uninsured. It is argued that denying them benefits with the exception of emergency services, forces them to abuse costlier alternatives, and ultimately shifting costs and expenses to insured beneficiaries.

Drug development has blossomed since 1938. Many discoveries like the antibiotic, penicillin, and the antihypertensive, captopril resulted from observations, but many others were the result of a systematic search for a drug that would either block or stimulate a receptor. For example, selective Beta-adrenergic blockers led to the development of propranolol, histamine 2 receptor blockade to Tagamet and Selective serotonin reuptake inhibitors (SSRIs) to Prozac. Arguably, the most important advancement was the discovery of DNA. Once the secrets of the gene were unraveled, we were able to genetically engineer products that have an unlimited amount of potential to treat and cure diseases. These products are not made in the chemical laboratory, but by genetically engineered living organisms that have had their DNA altered to specifically produce proteins for our benefit. Now, we have taken therapy to a new level by altering a gene, inserting it into a virus that targets a specific cell—a cancer cell, or a monoclonal antibody that directly modulates the immune system. The next generation of therapy will involve using the effects of exosomes, vesicles that are secreted by cells allowing them to communicate and

⁵ *U.S. Uninsured Rate at New Low of 10.9% in Third Quarter*, GALLUP HEALTHWAYS (Oct. 7, 2016), <http://www.well-beingindex.com/u.s.-uninsured-rate-at-new-low-in-third-quarter>.

stimulate each other.⁶ Stem cell therapy has the exciting potential to either rejuvenate or replace existing cells that have failed. In the future entire organs will be replaced, and prototypes that function like an ink jet printer spew cells out in an orderly fashion on a specially designed framework.

Once the FDA approves a drug it is granted exclusivity that differs from the patent. The exclusivity differs depending upon whether it is an orphan drug, new chemical, new investigation, pediatric or ANDA.⁷

II. DRUG LIFE OPTIMIZATION

It has been demonstrated that the cost of developing a drug extends over the early phases of development and testing. The expense of research and development is then recovered during the life cycle of the drug. After the drug goes off-patent, generic competition and loss of market exclusivity result in a decline in profits. This curve ideally is represented by a small initial dip followed by a parabolic increase. The areas within the curve represent revenue. Manufacturers expect that the investment of several hundred million dollars will result in a blockbuster (defined as over \$1 billion) or even more. Some have argued that life cycle management may be applicable to many manufactured products, but does not truly apply to drugs. Instead, the manufacturers should optimize strategies to market and sell their products even before the drug has been launched and well after the drug has lost market exclusivity. An ideal application of this principle would be to continue investigative work on generic drugs, assure drug sales are distributed over as large a market as possible, and not abandon their product once competitive generics become available, but instead seek opportunities in areas where low socioeconomic conditions prevail.⁸

⁶ Isabel Huang-Doran, *Extracellular Vesicles: Novel Mediators of Cell Communication In Metabolic Disease*, TRENDS IN ENDOCRINOLOGY & METABOLISM (Oct. 31, 2016), [http://www.cell.com/trends/endocrinology-metabolism/abstract/S1043-2760\(16\)30128-X](http://www.cell.com/trends/endocrinology-metabolism/abstract/S1043-2760(16)30128-X).

⁷ Carolyne Hathaway et al., *Exclusivity Strategies in the United States and European Union*, FOOD AND DRUG LAW INSTITUTE (May 2009), https://www.lw.com/upload/pubcontent/_pdf/pub2655_1.pdf.

⁸ Stan Bernard, *Why Product Lifecycle Management Fails Pharma: Time for a Rethink?*, PHARMACEUTICAL EXECUTIVE (Feb. 2013), http://www.bernardassociatesllc.com/wp-content/uploads/2013/08/PE_Drug-Life-Optimization_StanBernard2.pdf.

III. SPECIFIC ISSUES

A. *The Pharmacological Research Process*

Pharmacological research and subsequent development is the combined effort of basic science investigators who often have received funds from the National Institute of Health (NIH). Once the clinical research phases are reached, the investigation is outsourced to clinical research organizations (CRO). Both academic centers as well as physicians and providers in the private sector carry out these investigations, funded and sponsored by the industry. The NIH funding is a discretionary budgetary item and funded by taxpayers. Pharmaceutical investment in research is recouped through sales that begin once the drug receives FDA approval and continues until the exclusivity period has ended and less costly generics replace it. “Me too” medications with equal benefits and “biosimilars” compromise the ability to recover development costs. Often, a similar agent with fewer side effects, more effectiveness or better tolerance emerges and the drug is pulled from the market at considerable loss to the pharmaceutical company. While the costs of research vary, it is estimated that well managed companies may spend a minimum of 150 million to 300 million dollars in expenses. The enormous costs of absorbing drugs that were replaced by better options may push this burden to 2 billion dollars. In some instances the therapy is only going to be used for a limited target of patients. This raises the costs considerably to payors insuring patients with rare disorders such as Fabry Disease, a rare inherited disease affecting the cell storage mechanisms in organs such as the heart and kidney, and caused by a deficiency in an enzyme known as alpha-galactosidase A. It can be treated by a synthetic known as Fabrizyme, made by Sanofi-Genzyme. In Fabry Disease, cost effectiveness of enzyme replacement therapy has been critically discussed and challenged.⁹ The atypical hemolytic uremic syndrome is a rare genetic disorder that is caused by abnormalities in the complement system that activates an accelerated immune response that can damage blood vessels, the kidney and the brain. It can now be treated successfully by eculizumab, a very expensive complement inhibitor.¹⁰

⁹ Saskia M. Rombach et al., *Cost-effectiveness of enzyme replacement therapy for Fabry disease*, ORPHANET J. OF RARE DISEASES (Feb. 19, 2013), <https://ojrd.biomedcentral.com/articles/10.1186/1750-1172-8-29>.

¹⁰ Arif Asif et al., *Atypical hemolytic uremic syndrome in the setting of complement-amplifying conditions: case reports and a review of the evidence for treatment with eculizumab*, J. OF NEPHROLOGY 1–16 (Nov. 15, 2016), <http://link.springer.com/article/10.1007/s40620-016-0357-7>.

B. *The Cost of Drug Development*

In some instances, the burdens for drug development are so high that they are distributed over several pharmaceutical companies, each eager in recouping its share of the development cost. In the end, each of these respective companies may market the product under a separate brand. The costs are kept high, and the enormous expense of competing for market share are passed along to the consumer. In the case of epoetin alfa, Amgen and Johnson & Johnson shared in development costs, marketing the product to different segments of the population. Amgen's Epogen was primarily intended for the end stage renal disease (ESRD)—the dialysis population, while Johnson & Johnson's Procrit was intended for the non-dialysis population of kidney patients as well as those with malignancy. Epogen and Procrit both became blockbuster drugs. A major conflict between the two corporations ensued when Amgen developed a glycosylated hemoglobin form of epoetin known as darbepoetin (Aranesp) that had a longer half-life. It was marketed in direct competition with Procrit for patients with chronic kidney disease as well as cancer.¹¹

C. *Clinical Study Reports*

Yet, these CSRs are not publically available. Manufacturers claim CSRs are unsuitable for publication, but proponents of greater transparency argue that this information is invaluable.¹² CSRs provided nearly twice the percentage of outcomes as publically available sources, particularly more information of adverse events.¹³ In publishing every trial regarding a drug and making sure its CSR is also publically available, information about safety and effectiveness would be readily available to physicians, pharmacologists and members of formulary and pharmacy and therapeutics (P&T) Committees. Among other benefits, this information would be invaluable in helping to evaluate associated side effects. Hiding and suppressing this information, and publishing only positive results, deprives the industry of potential new opportunities, and as well defers aspects of the drug's margins of safety. Often, articles are not published because they have negative results; the data confirms the drug being investigated

¹¹ Deena Beasley et al., *Amgen to pay J&J \$200 million to settle antitrust suit*, REUTERS (July 11, 2008, 7:22 PM), <http://www.reuters.com/article/us-amgen-jj-lawsuit-idUSN1136149420080711>.

¹² Daniel Cressey, *Secrets of trial data revealed*, NATURE (Oct. 8, 2013), <http://www.nature.com/news/secrets-of-trial-data-revealed-1.13913>.

¹³ Beate Wieseler et al., *Completeness of Reporting of Patient-Relevant Clinical Trial Outcomes: Comparison of Unpublished Clinical Study Reports with Publicly Available Data*, PLOS MED. (Oct. 8, 2013), <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001526>.

is no better than placebo. Often when published, the paper does not completely mention negative drug effects or serious adverse events. Sometimes, the paper is not published in a timely manner. An analysis in 2013 reported that of 600 trials in clinicaltrials.gov, only one half were published.¹⁴

D. Marketing Tactics

Manufacturers also sponsor satellite symposium offered as dinner presentations and led by key thought leaders. Marketing often takes place at the physician's office where representatives of the pharmaceutical industry leave glossy brochures, samples, and spend a few moments meeting and greeting providers. Often they provide a lunch for the office staff. Speakers are limited to speaking on label with respect to their product, and any complex questions regarding off label use are referred to drug liaisons that are highly informative about products in the pipeline. Often manufacturers will provide non-promotional lectures where an unrestricted grant is provided to the sponsoring organization. Lectures can then be on any topic and are in no way controlled by the manufacturer. Generally, they explain the basic physiology and clinical studies that demonstrate why the company's product is necessary. An example is a lecture on anemia by Amgen, the manufacturer of Epogen. Consumer directed marketing is permitted so long as it is fair balanced and conveys major risks, indications and limitation. It has grown to be a 4.5 billion-dollar business. By some estimates, it has led to a significant increase in drug prices and the AMA has called for its ban.¹⁵ Omeprazole (Prilosec) was discovered in 1979 as a proton pump inhibitor. By inhibiting the enzymatic release of acid into the stomach, a variety of disorders ranging from acid-reflux to Zollinger-Ellison syndrome (acid secreting tumors in the stomach) could be treated. It was marketed in the USA starting in 1989 and its US patent expired in 2001. During that time period it generated around \$26 million in sales for AstraZeneca. In 1995 the company developed a strategy to avoid the decrease in revenue that usually is associated with patent expirations. It successfully kept generics at bay through patent litigation while spending a half billion dollars a year on advertising to convert patients to the successor, esomeprazole—Nexium. While Prilosec was a racemic mixture of both the left and the right-handed versions of

¹⁴ Carolina Riveros et al., *Timing and Completeness of Trial Results Posted at ClinicalTrials.gov and Published in Journals*, PLOS MED. (Dec. 3, 2013), <http://journals.plos.org/plosmedicine/article?id=10.1371/journal.pmed.1001566>.

¹⁵ Justin W. Moyer, *American Medical Association urges ban on TV drug ads*, THE WASH. POST (Nov. 19, 2015), <https://www.washingtonpost.com/news/morning-mix/wp/2015/11/19/american-medical-association-urges-ban-on-tv-drug-ads/>.

the molecule (known as an enantiomer), Nexium was only the S-enantiomer. The D-enantiomer was converted to the active form in the body, and it could be argued, and even shown in clinical trials that the drugs had nearly identical actions (esomeprazole 94.1% vs. omeprazole 86.9%).¹⁶ But, AstraZeneca successfully argued that their new molecule deserved a different patent, extending exclusivity until 2014 while they continued to capitalize on their purple pill.¹⁷ In 2013, PPIs such as Prilosec and Nexium were used by 15 million Americans. It was suggested that 25 percent of users could have stopped this drug without recurrent heartburn and that around 70 percent of the time the drug was inappropriately prescribed. In an evaluation of prescription and self-reported patient data, there was an increased risk of chronic kidney disease. In the Geisinger Health System cohort twice-daily PPI users had a higher risk, an adjusted Hazard Ratio (HR 1.46; 95% CI, 1.28-1.67) than once-daily users (adjusted HR 1.15; 95% CI, 1.09-1.21). In the Atherosclerosis Risk in Communities study, albeit users had a higher incidence of obesity and hypertension, the adjusted HR was 1.76(95% CI, 1.13-2.74) when compared with matched non-users.¹⁸

E. Subsidizing Access to Care

Access to care is a major issue. Right now pharmaceutical products developed in the United States, or at least studied in the U.S., to the extent they have achieved FDA approval, are sold in different markets at lower prices. A drug such as Rituxan may cost over twice as much in the U.S. as in Norway. This in effect causes the U.S. consumer to pay more for the product, and in effect unfairly subsidizes its use in markets where negotiations were more successful. Pharmaceutical companies that sell their products at a cheaper rate in other countries do not give American consumers the same price. Foreign state-run health system negotiators are able to set price caps and drive harder bargains. Meanwhile, there are many buyers in the U.S., reducing the negotiating power. Legislative action need to be taken to specify that products approved by the FDA

¹⁶ PJ Kahrilas et al., *Esomeprazole improves healing and symptom resolution as compared with omeprazole in reflux oesophagitis patients: a randomized controlled trial*, NAT'L CTR. FOR BIOTECHNOLOGY INFO., U.S. NAT'L LIBR. OF MED. (Oct. 2000), <https://www.ncbi.nlm.nih.gov/pubmed/11012468>.

¹⁷ Gardiner Harris, *Prilosec's Maker Switches Users to Nexium, Thwarting Generics*, THE WALL STREET J. (June 6, 2002, 5:22 PM), <http://www.wsj.com/articles/SB1023326369679910840>; Tracy Staton, *Top 10 Drug Patent Losses of 2014*, FIERCE PHARMA (2014), <http://www.fiercepharma.com/special-report/top-10-drug-patent-losses-of-2014>.

¹⁸ Benjamin Lazarus et al., *Proton Pump Inhibitor Use and the Risk of Chronic Kidney Disease*, JAMA INTERNAL MED. 238-46 (Jan 11, 2016), <http://www.aahs.org/medstaff/wp-content/uploads/PPIKidneyDisease.pdf>.

cannot be sold at a lower price in other markets than to CMS, the VAH and other government purchasers.¹⁹

F. Labor Laws

U.S. labor laws have been well established, and generally include collective bargaining, the right to organize, the establishment of minimal wages, and most recently the right to affordable health care. So long as companies engage only in domestic trade, businesses can remain competitive as they all operate under the same labor laws. However, multinational companies are able to take advantage of the absence of regulations abroad. However, this cheap labor may not actually benefit Americans.²⁰ Aside from the ethical arguments in favor of universal fair trade policy, one can argue that improving working conditions in foreign countries where we trade will have a greater economic benefit for all participants in commerce. Businesses, in seeking cheaper labor, have closed factories across the U.S. and moved production to countries where labor is considerably cheaper. This has resulted in increased unemployment in the U.S. Goods made in foreign countries are exported back into our country, and if made by a business in another nation, our gross national product decreases while our trade deficit increases. Many workers in foreign countries where goods are manufactured have very limited access to health care, including vaccinations and medications. This limits market demands for newly developed medications to only those that can afford to pay for them, excluding both the unemployed in the U.S. and the majority of factory workers in developing countries. The solution is for countries with strong, fair labor laws to restrict trade only to those countries that also engage in fair trade, including the provision for health benefits to workers. This will create a higher standard of living. Just the opening of more health clinics and hospitals in developing areas will boost their economy and enable them to create wealth. Their increased buying power and their demand for medications and goods produced in the U.S. will reduce our trade deficit and increase our GNP. While it is taken for granted that many of the types of jobs that are performed overseas cannot be done in the U.S. at the same price, the advent of

¹⁹ Jeanne Whalen, *Why the U.S. Pays More Than Other Countries for Drugs*, THE WALL STREET J. (Dec. 1, 2015, 9:27 PM), <http://www.wsj.com/articles/why-the-u-s-pays-more-than-other-countries-for-drugs-1448939481>.

²⁰ Terry Collingsworth, *American Labor Policy and the International Economy: Clarifying Policies and Interests*, 31 B.C.L. REV. 31, 32 (1989).

robotics and automation gives the U.S. an opportunity to bring back competitive manufacturing of consumer products that can be marketed elsewhere.²¹

G. *Undocumented Aliens*

The PPACA has excluded undocumented aliens. Yet, The Emergency Medical Treatment and Active Labor Act (EMTALA) of 1986 (42 U.S.C. §1395dd) as well as our medical ethics as physicians, dictate that patients receive emergency care when they arrive acutely ill to a hospital emergency center. The price of care for an unfunded patient is shifted to the general operations costs of the institution, and either passed along to other patients, or forced as a loss to the hospital. In county hospital systems, the costs may be reflected in higher property taxes. Many undocumented workers are gainfully employed, yet employers enjoy not having to pay withholding or Medicare taxes for this segment of their workforce. While labor costs are kept low, other tax burdens, as well as a challenge to hospital solvency, rise. A patient seen only in an emergency room may do so because of a lack of opportunity to prevent a progressive disease. Undocumented persons do not have benefits subtracted from their pay, which results in higher health costs for all other beneficiaries. It has been estimated that a comprehensive immigration plan will increase tax revenue by 1.5 billion dollars a year, and increase the gross domestic product by 1.5 trillion dollars over a ten-year period.²²

H. *The Illicit Drug Trade*

The illicit drug trade is estimated at a 300 million dollar global enterprise. Its adverse impact on Americans is enormous. Illicit drug-related health costs are estimated at around 11.4 million dollars. This is in addition to 120 million dollars in productivity and incarceration costs and 61 million dollars in crime. The financial impact to society goes well beyond the pharmaceutical industry, and is a social-justice-economic problem.²³

²¹ Charles Duhigg & Keith Bradsher, *Apple's Jobs to Obama: "jobs aren't coming back" to U.S.*, HERALD TRIB. (Jan. 23, 2012, 12:01 AM), <http://www.heraldtribune.com/news/20120123/apples-jobs-to-obama-jobs-arent-coming-back-to-us>.

²² Lorraine Woellert, *Amnesty for Illegal Immigrants Has Economic Benefits*, BLOOMBERG (Mar. 14, 2013, 9:31 PM), <https://www.bloomberg.com/news/articles/2013-03-14/amnesty-for-illegal-immigrants-has-economic-benefits>.

²³ Jose M. Insulza, *The Drug Problem in the Americas: Studies*, ORG. AM. ST. 1, 31 (2013), http://www.cicad.oas.org/drogas/elinforme/informeDrogas2013/laEconomicaNarcotrafico_ENG.pdf; *The Economic Impact of Illicit Drug Use on American Society*, U.S. DEP'T OF JUST. Nat'l Drug Intelligence Ctr. (Apr. 2011), <https://www.justice.gov/archive/ndic/pubs44/44731/44731p.pdf>.