PHARMACEUTICAL MARKETING IN THE UNITED STATES: HOW PRESCRIPTION DRUGS HAVE BECOME *THE* HEALTH CARE SOLUTION

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Plan II Honors Program
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May 7, 2020

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ABSTRACT

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Title: Pharmaceutical Marketing in the United States: How Prescription Drugs Have Become **THE** Health Care Solution

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The pharmaceutical industry is one of the most powerful and profitable industries in the world, valued at over a trillion dollars. People need and will always need medicine, but the enormous success of the pharmaceutical industry cannot simply be attributed to the inherent, enduring demand for their products. It is well documented that pharmaceutical companies often spend as much, or more money on marketing their existing products than on developing new ones. Developing new pharmaceuticals is extremely costly in terms of both time and money, so pharmaceutical companies often rely on marketing to create demand and drive profits. Pharmaceutical marketing spending has increased substantially over the years, and prescription drug consumption by Americans has followed the same trend. A large volume of literature has been written on the subject of pharmaceutical marketing, and there is an ongoing debate about the ethicality of the practice. This is because the marketing of pharmaceuticals differs greatly in many respects from the marketing of other consumer products. Unlike other markets, there are multiple agents involved on both the demand side and the supply side. Although patients are the end-users, physicians are the ultimate gatekeepers of prescription medications. Thus, pharmaceutical companies direct their marketing efforts towards both patients and physicians in the form of Direct to Consumer Advertising (DTCA) and Direct to Physician Promotion (DTPP). This thesis aims to provide an in-depth description of both DTCA and DTPP and the impact of these practices on physicians, patients, and prescription volume. In doing so, this thesis will examine the evidence on both sides of the debate surrounding pharmaceutical marketing practices in order to shed light on the true nature of the current situation.

ACKNOWLEDGMENTS

I would like to thank my supervisor, Dr. Kenneth Lawson, for your guidance throughout the research and writing process of my thesis. As my knowledge of the pharmaceutical industry prior to the completion of this thesis was limited, I was extremely grateful when you agreed to be my supervisor. Your thorough knowledge of the industry greatly shaped and expanded my ideas throughout this project. Your frequent feedback on both my research and writing pushed me to work harder and continuously improve my work. Additionally, I would like to thank my second reader, Lee Walker. I have deeply appreciated each one of our meetings, not only those throughout this thesis process but also during your Pathways to Civic Engagement course my freshman year. You have always pushed me to recognize my full potential and I will forever be grateful for the wisdom you have shared. Lastly, I would like to thank my family and friends for their continuous support and their willingness to listen to my ideas. I am eternally grateful for my time at the University of Texas and the opportunity to participate in the Plan II Honors program.

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Introduction

Whether we realize it or not, the minds of Americans are being manipulated and influenced by money-seeking institutions at each moment of every day. As humans, we possess a psychological tendency to continuously want and strive for more. Over the years, businesses have discovered how to increase their profits by catering to this psychological tendency, and as a result, we have come to live in a society where we are constantly being told we *need* something that we don't have. This strategy is called advertising. The power of advertising is enormous and its presence is ubiquitous. Brands have made their way into every aspect of our lives to the point where we almost don't notice them anymore. But when advertisements start to impact the prescription medication that we take and in turn, our physical health and well-being, it is imperative that we *do* notice them and understand the incentives behind these advertising efforts. While advertising can present numerous potential benefits in terms of providing consumers with information and product alternatives, there are a number of ethical considerations that must be taken into account with regard to the marketing of prescription medication by the pharmaceutical industry. From 1997 to 2016, medical marketing spending increased from $17.7 billion to $29.9 billion and during that same time period, prescription drug use by Americans increased by 85% while the population rose only 21%.[1,2] These advertisements are having their intended financial effect on the pharmaceutical industry's bottom line, but what impact are they having on the health of the American population? While it is nearly impossible to measure the patient health implications of pharmaceutical marketing and that is not the focus of this paper, it is possible measure the impact in terms of the number of prescriptions filled and related expenditures.

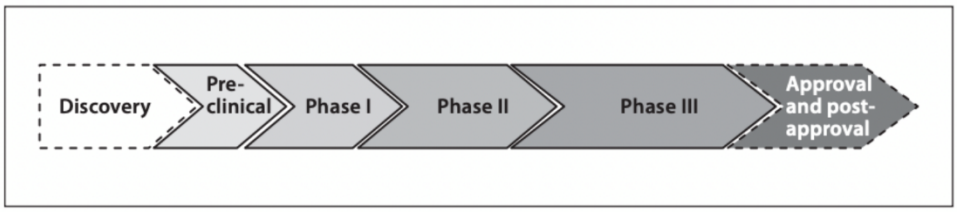
As a society, we hope that the pharmaceutical industry's primary duty is to American healthcare consumers and that it is committed to the research, discovery, and development of new medicines to improve the lives of patients. Moreover, it is true that the pharmaceutical industry has introduced extraordinary health-care advances. The lives that the industry has saved and significantly improved through prescription medications are innumerable. But one must consider the other reality. Pharmaceutical companies are profit-making enterprises and like every other for-profit business, their duty to their shareholders to maximize profits also looms large. It is imperative that the pharmaceutical industry produces large profits in order to foster innovation and support the continuous development of life-saving drugs, but it is also crucial for society to consider the ethical concerns and potential conflicts of interest that arise from the use of advertising to maximize these profits. Before delving into pharmaceutical marketing practices, it is important to explain the prescription drug development process as a whole in order to more clearly understand the role of marketing in pharmaceutical success. Part I of this report will describe the process of bringing a new pharmaceutical product to market, examine the role of marketing in that process, and analyze pharmaceutical marketing expenditures over the years. Part II of this report will look specifically at the pharmaceutical practice of marketing to physicians to examine trends in spending, describe the different marketing methods used and analyze the impacts of the different practices. Part III of this report will focus the pharmaceutical practice of marketing to directly to consumers to examine trends in spending, describe the types of advertisements and the nature of the promotional content, and discuss the pros and cons of the practice. Lastly, Part IV of this report will examine the impact of using DTPP and DTCA in combination to market a pharmaceutical product.

Part I: The Bigger Picture

Background: Bringing a New Drug to Market

The process of developing a pharmaceutical medication is extraordinarily expensive and time consuming. According to a study published by the Tufts Center for the Study of Drug Development in 2016, the cost of bringing one single new drug to market is $2.6 billion.[3] Moreover, the likelihood of a drug candidate making it to the market is extremely low. According to *The Truth About Drug Companies*, the number is close to one in five thousand.[4] In recent years, many individuals have accused the pharmaceutical industry of investing more resources into their marketing efforts than into the research and development (R&D) process. Many feel that the pharmaceutical industry should allocate the majority of their budget to researching and developing *new* life-saving medicines, rather than marketing the ones they already have. The pharmaceutical industry argues that marketing is necessary for profit, and profit is necessary to foster innovation within the R&D sector. While this report primarily focuses on pharmaceutical marketing, it is important to understand the drug development process as a whole in order to fully understand the role of marketing in the larger success of a pharmaceutical product. With that being said, this report will briefly describe each of the costly phases involved in the creation of a new drug which are illustrated in Figure 1 below.

Figure 1. Phases of Pharmaceutical Drug Development[5]



The process begins with the Discovery phase, which is comprised of research and development (R&D) activities. The research aspect of this phase is usually the most time-consuming, and most difficult portion of the entire process, as those involved must develop an intense understanding of the disease in question in order to have any hope of developing a drug that will safely and effectively interfere with the chain of events that is causing the condition. The majority of the time, this research is carried out at universities or government research laboratories. In the United States, most research efforts are supported by the National Institute of Health (NIH).[4] Once research is completed, and the individuals involved have a thorough understanding of the disease and potential ways to address it, the development process begins.

In the development phase, scientists begin searching for or constructing a molecule that could effectively and safely treat the disease. Pharmaceutical companies usually become more heavily involved at this point if the research was conducted by outside sources like a university or the government. Choosing the therapeutic area for investment of time and resources depends on number of factors such as: medical need, technical feasibility, research and development costs and commercial considerations such as market place competition and potential market share.[5] The pharmaceutical companies research and development budget is limited, so only those projects with the highest potential can be selected. Once a project has been selected, the development process consists of two main stages—the pre-clinical phase and the clinical phase.

During the pre-clinical phase, a number of potential drug candidates, which are small molecules that have strong therapeutic potential, are identified. Drug candidates are either

selected from extensive "libraries" kept by pharmaceutical companies, synthesized, or extracted from animal, plant, or mineral sources.[4] The chosen candidates then undergo laboratory and animal testing in order to answer basic questions about the drug safety. According to *The Truth About Drug Companies*, only one in one thousand candidates survive the preclinical testing phase.[4] It is also during this phase that decisions about whether to patent the compound or chemical series are made. This is because it becomes very difficult to keep information about the potential product a secret after this point. The life of a patent is typically around 25 years, and unfortunately it typically takes 10-15 years to develop the drug.[5] Thus, once the drug is on the market, there could only be about 10 years remaining to sell the drug and make up for the high development costs. Thus, pharmaceutical companies are very eager to complete the trials and obtain FDA approval so that they can begin marketing the new drug.

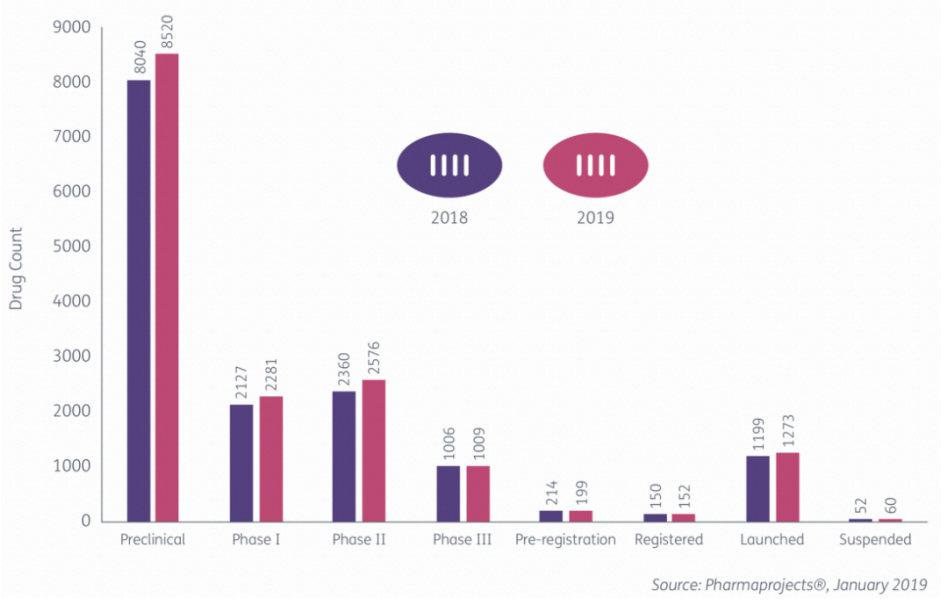
The clinical stage of developing a pharmaceutical product is divided into three phases, as illustrated in the diagram above. All three of these phases are regulated by the FDA. Before the clinical trials can begin, pharmaceutical companies must file an investigational new drug application (INDA) with the agency.[4] The evidence presented in the three phases is used in the FDA's decision-making process when determining a drug's safety and efficacy. Beginning in Phase I and continuing through Phase III, the product is administered to human volunteers. During Phase I, the drug is given to a small number of usually normal volunteers (humans that do not have the disease). The purpose of Phase I is to "evaluate the safety, tolerability, pharmacodynamic (effect of the drug on the body [e.g., effect on heart rate, blood pressure, electrocardiogram (ECG), etc.]) and pharmacokinetic (effect of the body on the drug [i.e.,

absorption, distribution, metabolism and excretion]) effects of the tested drug."[5] In simple terms, they evaluate the drug's metabolism and side effects and establish safe dosage levels.

During Phase II, the drug is tested for efficacy and safety on the target population (the people with the condition that the drug is meant to treat). This phase involves as many as a few hundred volunteers who are given the drug at various doses. As with any other scientific study, the effects on the patients given the drug are usually compared with a placebo group (group of volunteers who do not receive the drug). Phase II is a key stage of development during which a detailed analysis of the drug and the market are conducted. This analysis includes: "drug efficacy relative to the competitors, safety profile, probability of technical and regulatory success, remaining patent life of the drug, cost of goods to produce the drug, potential market share and pricing and reimbursement."[5] Subsequently, the drug is compared to all of the other candidates in the portfolio before it is selected to move onto Phase III. The results of this phase are discussed with the FDA and regulatory agencies as well.

During Phase III, the drug is tested on several thousand patients in order to build an adequate database to assess the efficacy and safety profile and enable accurate drug labeling. This phase will "confirm the clinical doses, frequency and timing of administration for approval."[5] Furthermore, "phase III trials are primarily designed and powered to test the hypothesis of efficacy but at the same time, adverse events are collected to assess benefit-risk potential of the drug."[5] A drug successfully making it through all three phases of clinical testing is rare. According to *The Truth about Drug Companies,* only one in five drugs survive clinical testing and make it to market.[4] Figure 2 illustrates the number of drugs and their location in the development pipeline during 2018 and 2019.

Figure 2. Pipeline by Development Phase, 2019 versus 2018[6]



If a drug is successful in clearing the phases of clinical testing, the drug moves on to the regulatory submission and approval stage, during which the pharmaceutical company compiles all of the results from the clinical trials, along with other supporting evidence, and submits it to the regulatory agency (the FDA). The FDA reviews new drug applications with the help of eighteen advisory committees consisting of outside experts.[4] In the United States, a routine New Drug Application (NDA) can take up to 15 months for review.[5] Once a drug has been approved to go to market, pharmaceutical "companies are permitted to promote the product only for the uses and at the doses for which they were approved, although once they are on the market, doctors may prescribe them for any use and at any dose they deem appropriate."[4] Many pharmaceutical industry representatives have long been critical of the lengthy process of getting a new drug approved by the FDA, claiming that they put "bureaucratic obstacles in the way of getting 'lifesaving drugs' to the market."[4] While 15 months may seem long when considering patients' lives (as well as the dwindling patent life), the time for FDA approval only

accounts for a small fraction of the total development time. Additionally, the review by the FDA is a vital step in the development process that should not be rushed. It is imperative that an impartial agency carefully reviews the scientific data about a potential new drug in order to protect the welfare of Americans.

As one can see, the process of bringing a new drug to market is extremely complex and costly in a number of ways. This cost is even higher when considering the cost of failed prospective drugs. The failure rate of pharmaceutical products is referred to as the "attrition rate," and it is remarkably high.[5] As mentioned previously, it is estimated that only one in five thousand initial drug candidates survive all phases of development and enter the market.[4] Furthermore, Tamimi explains that "increasing costs combined with the high attrition rate are forcing pharmaceutical companies to reduce investment in research and development, focusing on a more limited product portfolio."[5] Because developing a drug is so incredibly risky and costly, it is imperative that the products they are able to successfully develop perform well and produce large profits to drive innovation. Thus, pharmaceutical companies invest an enormous amount in marketing those products that do successfully make it to market. According to Ezekiel Emanuel, "of the 10 largest pharmaceutical companies, only one spends more on research than on marketing its products." Table 1 illustrates this statement, comparing R&D spending and sales and marketing spending by the top 10 pharmaceutical companies in 2014.

Table 1. Comparison of Research and Development Spending versus Sales and Marketing Spending for the Top 10 Pharmaceutical Companies (2014)[7]

World's largest pharmaceutical firms

Company	Total revenue ($bn)	R&D spend ($bn)	Sales and marketing spend($bn)	Profit ($bn)	Profit margin (%)
Johnson & Johnson (US)	71.3	8.2	17.5	13.8	19
Novartis (Swiss)	58.8	9.9	14.6	9.2	16
Pfizer (US)	51.6	6.6	11.4	22.0	43
Hoffmann-La Roche (Swiss)	50.3	9.3	9.0	12.0	24
Sanofi (France)	44.4	6.3	9.1	8.5	11
Merck (US)	44.0	7.5	9.5	4.4	10
GSK (UK)	41.4	5.3	9.9	8.5	21
AstraZeneca (UK)	25.7	4.3	7.3	2.6	10
Eli Lilly (US)	23.1	5.5	5.7	4.7	20
AbbVie (US)	18.8	2.9	4.3	4.1	22

Source: GlobalData

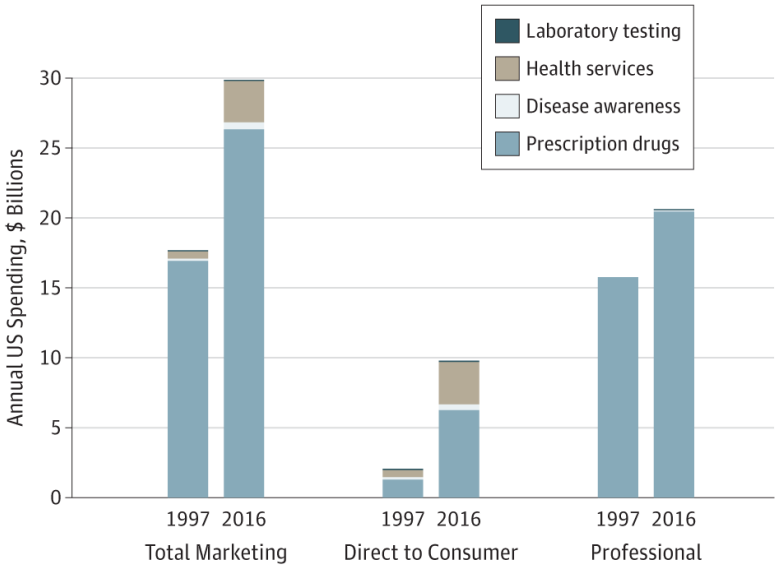
While this chart indicates that 9 out of the top 10 pharmaceutical companies spent more on sales and marketing than on R&D during 2014, it must be noted that there are no definitive reports that establish the industry's cost structure. The ambiguity surrounding the allocation of pharmaceutical expenditures is at the heart of the current debate about whether the industry is truly focused on research and developing new drugs or on driving profits through marketing efforts.[8] While this report will not delve into this argument about whether pharmaceutical companies should be allocating more of their budgets to research and development, it is important to understand the complexity of the drug development process in order to clearly see why marketing plays such an enormous role in pharmaceutical success. The remainder of this report will focus on pharmaceutical marketing—examining spending, forms of marketing,

and the impact of these practices on physicians, patients, and ultimately pharmaceutical industry profit.

Pharmaceutical Marketing

Marketing plays a massive role in the success of prescription medication sales as shown by the sheer amount of resources the pharmaceutical industry has invested and continues to invest in their marketing efforts. Figure 3 illustrates the increase in medical marketing spending by pharmaceutical companies from 1997 to 2016 and shows that marketing of prescription drugs accounts for a large majority of those expenditures.

Figure 3. Medical Marketing Spending in the United States from 1997-2016[1]



As shown, medical marketing spending expanded substantially during this time period, from $17.7 in 1997 to $29.9 billion in 2016.[1] This figure has continued to increase into 2019 and pharmaceutical marketing expenditures have reached an all-time high. According to a QuintilesIMS Institute Study[2], these promotional efforts have had their intended effect of

increasing prescription medication use, as the United States is the most highly medicated country in the world.[9]

Figure 4. The Rise in Prescription Drug Use in the U.S. from 1997-2016[2]

As the total number of prescriptions filled by all Americans increased from 2.42 billion in 1997 to 4.47 billion in 2016 (Figure 4) and America's expenditures on prescription drug increased by 50% from 2010 to 2018 (reaching $535 billion), it is clear that pharmaceutical marketing is effective.[2] But what makes it so effective? This report will thoroughly examine the pharmaceutical industry's marketing methodology to answer this question, as well as the question of whether ethical lines are being crossed to achieve this effectiveness.

The marketing of pharmaceuticals differs greatly in many respects from the marketing of other consumer products. Unlike other markets, there are multiple agents involved on both the demand side and the supply side. Although patients are the end-users, physicians are the ultimate decision makers and gatekeepers of pharmaceuticals. Thus, pharmaceutical companies direct their marketing efforts towards both patients and physicians in the form of Direct to

Consumer Advertising (DTCA) and Direct to Physician Promotion (DTPP). Pharmaceutical companies have employed DTPP since the beginning of pharmaceutical manufacturing. Because physicians are the agents that ultimately enable prescription medication sales, gaining their favor and approval is imperative to meeting pharmaceutical sales goals. Thus, the majority of pharmaceutical marketing budgets have long been allocated to DTPP. Direct to Consumer Advertising has also been employed for decades, but it appears that pharmaceutical companies have significantly increased their DTCA efforts in recent years. The pairing of DTCA with DTPP is a powerful one-two marketing punch. Pharmaceutical companies encourage consumers to see physicians about prescription drugs, and furthermore, they encourage physicians to prescribe these drugs. This report examines these two practices individually in-depth, as well as the effects of combining the two.

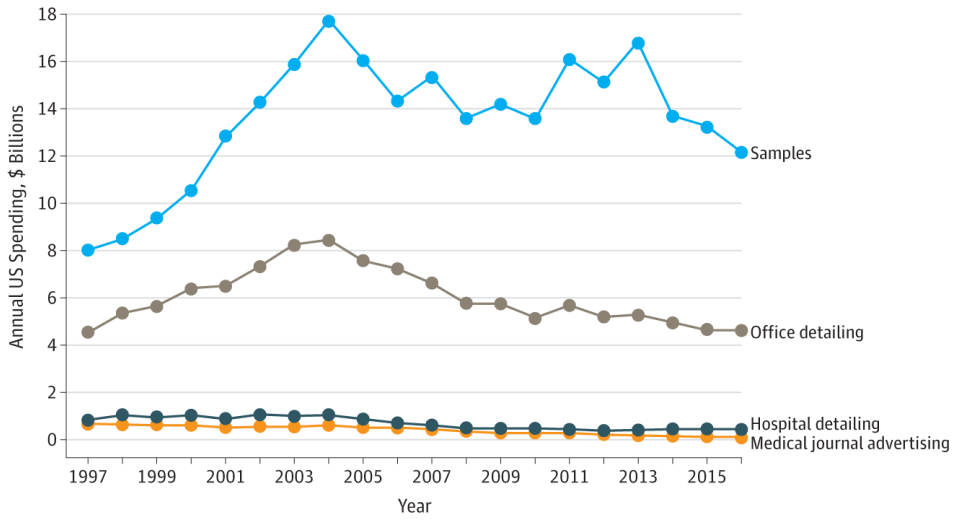
Part II: Direct to Physician Promotion

One of the most widely held concerns about pharmaceutical marketing is the practice of targeting physicians, also known as Direct to Physician Promotion (DTPP). Physicians are expected to be objective, unbiased parties who make decisions about the treatment of their patients using evidence-based medicine and other factors such as social drivers of health (e.g., the patients' health literacy level, social support system, beliefs about health and treatments, insurance status, and others factors). Their patients place an extremely high level of trust in them, and rely on them to provide the best possible treatment to their knowledge. Over the years, there has been an enormous volume of literature published on this subject. While people hold a variety of opinions about the practice of DTPP, there is an overwhelming consensus that an inherent conflict of interest arises when physicians are put in situations where they may be

tempted to deviate from their professional obligations for financial or other personal gains. The pharmaceutical industry, physicians, and society as a whole seem to be acutely aware of the existence of this issue, yet this practice continues to be an integral aspect of pharmaceutical promotion. After conducting a comprehensive literature search, it appears that the majority of studies on DTPP were conducted prior to 2015. The nature of DTPP practices may have evolved in more recent years, but it is still heavily utilized, and the information presented in many of the studies continues to be relevant. Throughout this report, I will cite relevant literature to examine a number of DTPP practices and the impact they may have on physicians and on their subsequent prescribing behaviors.

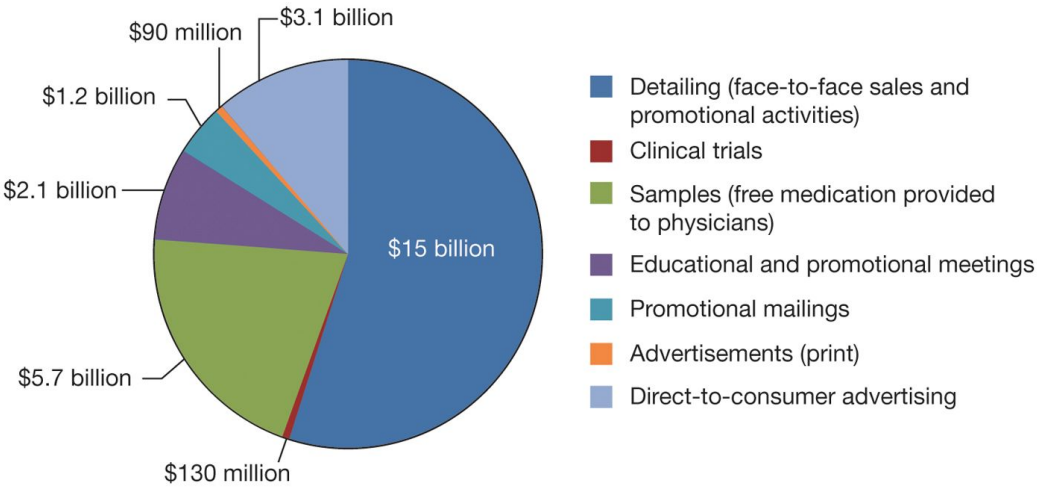
The main reason that DTPP has continued to persist in spite of its many critics is that it is highly effective, and in turn, profitable. Pharmaceutical companies rely heavily on physician acceptance and support of their drugs. While patients are the ultimate consumers of medications, physicians are the gatekeepers. Thus, the pharmaceutical industry invests a massive amount of resources into DTPP, more than any other area of promotion. The pharmaceutical industry has practiced DTPP since the origin of the industry, but their efforts have substantially increased in recent years. From 1997 to 2016, marketing to medical professionals increased from $15.6 billion to $20.3 billion.[1] Figure 5, taken from *Medical Marketing in the United States,* depicts spending patterns for specific types of DTPP during this time period.

Figure 5. Direct to Physician Promotion Expenditures from 1997-2016[1]



Given the nature of DTPP, and the variety of activities it entails (both direct and indirect) the estimates of the amount spent on the promotional practice vary. According to an article published in *The PEW Charitable Trusts*, the pharmaceutical industry spent over $27 billion on promoting pharmaceuticals in 2012 and $24 billion of that was dedicated to marketing to physicians.[10] DTPP promotion involves a number of different practices which will be covered in more detail later in this report. Figure 6 depicts the resources allocated to each of these different DTPP areas as well as DTCA in 2012.

Figure 6. Allocation of Pharmaceutical Promotional Spending (2012)[10]



The bulk of the DTPP budget is dedicated to detailing (personal selling through sales representatives) and sampling (provision of drugs to physicians at no cost to them). According to Connors, pharmaceutical companies spent around $25,000 annually per physician on marketing efforts in 2009.[9] This number increased substantially from 2000, when about $8,000 to $13,000 was spent per physician.[11] It is clear from the size of the investment just how valuable DTPP is to pharmaceutical sales success. According to Schwartz and Woloshin, for every dollar the industry invests in DTPP for new branded drugs, it returns ten.[1] But why is DTPP so effective? The remainder of this report will provide a detailed examination of specific DTPP practices and their impact, and additionally it will consider whether these practices cross an ethical line to produce such success.

The marketing efforts directed at physicians are comprised of a number of activities, some of which are directly labeled and identified as marketing efforts, while others use more indirect and discrete tactics used to gain the favor of physicians. Some of the most notable DTPP practices include: detailing, sampling, educational and promotional meetings, continuing medical education (CME), medical journal and web advertisements, promotional mailings, and grants to health advocacy organizations. While some doctors may be skeptical of interacting with pharmaceutical industry representatives, the overwhelming majority of them do. According to an article from *The New England Journal of Medicine*, 94% of physicians had a relationship with the industry in 2007.[12] So, despite the fact that many physicians deny the potential influence of pharmaceutical promotion on their behavior, it is important to analyze the interactions between the industry and physicians and the reality of the impact.

Regulation

The Food and Drug Administration (FDA) is the regulatory agency that is responsible for overseeing and regulating DTPP (as well as the pharmaceutical industry as a whole). In the United States, the Federal Food, Drug, and Cosmetic Act (FDCA) and Title 21 of the Code of Federal Regulations Part 202 are the two primary pieces of legislation that govern prescription drug advertising and promotion both to physicians and consumers.[13] The FDCA was passed in 1938, and requires that pharmaceutical companies demonstrate drug safety prior to market sale.[9] The Code of Federal Regulations contains FDA rules that prohibit pharmaceutical companies from publishing false and misleading advertisements.[9] Over the years, there has been growing concern about the extent to which the pharmaceutical industry interacts with physicians and the conflicts of interests that arise from these interactions. As a result, the Physician Payments Sunshine Act was passed in 2010, and it "requires medical product manufacturers to disclose to the Centers for Medicare and Medicaid Services (CMS) any payments or other transfers of value made to physicians or teaching hospitals."[14] Additionally, the "National Institutes of Health requires all grantees to disclose significant financial relationships with manufacturers."[14] In addition to regulation at the federal level, at least five states and the District of Colombia have passed laws "requiring that manufacturers of drugs, devices, biologicals, and medical supplies report various details of their financial relationships with clinicians."[14] In addition to regulation by the government, various groups have published a variety of voluntary guidelines in an attempt to mitigate the potential issues that arise from DTPP. These groups include "the Office of the Inspector General, AMA, the American Board of Internal Medicine Foundation, PhRMA, and the Advanced Medical Technology Association

(Advamed)."[9] All of these guidelines address specific aspects of DTPP and set standards for how the pharmaceutical industry should interact with physicians in order to protect the interest of patients. It is important to note that the guidelines published by these groups are voluntary and aspirational, meaning that pharmaceutical companies cannot be punished for straying from the voluntary rules set forth. Thus, the arguably relaxed regulation of pharmaceutical marketing has allowed the pharmaceutical industry to promote their products to physicians in a number of effective but potentially questionable ways.

Detailing

By far, the largest portion of DTPP expenditures are dedicated to the practice of detailing, a marketing technique in which pharmaceutical sales representatives (PSRs) visit physicians' offices in order to educate physicians about new pharmaceutical products in the hope that they will prescribe them more frequently in the future. In 2016, the pharmaceutical industry spent $5.6 billion on the practice of prescriber detailing.[1] According to a 2007 article from *PLOS Medicine*, the number of pharmaceutical sales representatives in America increased from 38,000 in 1995 to 100,000 in 2005.[15] PharmaOpportunties reported that number of pharmaceutical sales representatives world-wide will increase by 16.4 percent between 2012 and 2022, growing to 400,000.[16] The authors of the *PLOS Medicine* article note that there is about one PSR for every six physicians. They go further to argue that the actual ratio is close to one PSR per 2.5 targeted doctors because not all physicians practice and pharmaceutical companies do not detail all physicians (the lower-prescribing physicians are not prioritized). [15] According to 2013 estimates, a PSR typically details about 5-10 physicians per day.[17]

These numbers include physicians at a variety of seniority levels, as pharmaceutical companies employ detailing to target physicians throughout various stages of their careers, beginning as early as medical school and residency. Connors cites a 2009 study that revealed that "56% of medical students had three or more conversations with pharmaceutical representatives during medical school."[9] According to a 2017 systematic review conducted by Fickweiler, Fickweiler, and Urbach, "attending physicians and physician specialists had more PSR interactions and received higher numbers of medical samples and promotional material than residents," but the authors note that most residents have at least one interaction with a pharmaceutical industry representative per month.[18] A potentially troubling finding of this article noted that residents interacted with PSRs and received samples far more frequently at the beginning of their residencies.[18] Connors explains that these findings may be a cause for concern as "medical students and residents are particularly susceptible to marketing tactics, as these individuals are in a submissive position—often being overworked, without experience, or practical knowledge of ethics rules, and with respect to residents, severely underpaid."[9] Along these lines, one must consider that medical students and residents may be more vulnerable to these marketing tactics as they may not yet be able to decipher between promotional material and scientific facts and recognize the potential influence on their behavior.[11]

Regardless, PSRs play a critical role in DTPP and are highly compensated for their efforts. The average PSR in 2018 earned a salary of about $43,098-$73,178 and depending on their level of success in convincing physicians to prescribe their products, a substantial bonus.[16] For example, the base salary at one of the top pharmaceutical companies, Pfizer, was $82,374 in 2018, but their total compensation was about $99,298.[16] The practice of detailing is utilized

most heavily in the early stages of a pharmaceutical product's life cycle (6-14 months following the drug's launch).[17] According to a 2014 paper from the *National Bureau of Economic Research,* this is because "uncertainty regarding the efficacy of the drug and its attributes including the safety profile" tend to be highest during the early stages. [17] Thus, in the beginning, the role of the PSR is for the most part educational and informative. Because the role of the PSR is to educate physicians about new pharmaceuticals, one might assume that this interaction would diminish in the later stages of a pharmaceutical's life cycle, as there should be no new information to convey. But, both this article and an article from the *Yale Journal of Health Policy, Law, and Ethics* found that interactions between physicians and PSRs do continue into the later stages of a pharmaceutical's life cycle.[17,19] The authors of both of these articles came to similar conclusions in developing an explanation for this occurrence, stating that DTPP evolves from an informative role during the early stages into a more persuasive role during the subsequent stages.[17,19] Manchanda and Honka state that detailing during the later stages provides a "reminder effect" and additionally, the "constant interaction builds a stock of goodwill between a detailer (or the firm) and the physician, translating into positive physician prescription behavior."[19] This pattern reflects the well-known, but infrequently acknowledged, reality that the purpose of detailing is not only to educate, but also to build long-lasting, reciprocal relationships with physicians.

In the 2007 article from *PLOS Medicine*, co-authored by a former PSR for Eli Lilly named Shahram Ahari, the authors state that "drug reps are selected for their presentability and outgoing natures, and are trained to be observant, personable, and helpful*."*[15] What makes detailing so effective is how personal the practice is. PSRs don't just simply distribute

information in a transactional sense. As previously mentioned, PSRs attempt to befriend physicians and build relationships. The job of a pharmaceutical sales representative goes far beyond simply distributing samples of and information about new pharmaceutical products. The same former PSR, Shahram Ahari, published an article in the *Washington Post* revealing exactly what his job entailed.

> *"I took doctors out to so many fancy Manhattan restaurants that the maitre d's greeted me by name. The company hosted them at catered "speaking programs" and gave away tickets to baseball games and Broadway musicals. We even sent doctors and their families to sponsored academic conferences at tony resorts in Florida and California. During the day, if doctors didn't have time to see me, I chatted up their receptionists, plying them with food and gifts (stress balls, umbrellas, clocks) and asking, breezily, which medications their bosses preferred prescribing, and why."* [15]

Ahari makes note that his description of the industry may differ from the current situation, as he was a PSR in 2000, prior to the regulatory crackdown of 2009, after which the Sunshine Act was passed and pharmaceutical companies adopted a voluntary code of conduct that among other restrictions, permitted only "modest, occasional meals" in "appropriate circumstances," facilitating "the exchange of medical and scientific information."[20] Yet, many feel that the new regulatory requirements did little to eliminate the issues.

Still today, the way that PSRs approach each physician is unique and carefully planned. In discussing his job as a PSR in the *PLOS Medicine* article, Shahram Ahari stated, "It's my job to figure out what a physician's price is. For some it's dinner at the finest restaurants, for others it's enough convincing data to let them prescribe confidently and for others it's my attention

and friendship...but at the most basic level, everything is for sale and everything is an exchange."[15] PSRs expend a substantial amount of time and energy understanding physicians and their preferences in order to build relationships and in turn, meet their sales quotas. These long-lasting relationships, among other factors, are what create consistent and frequent prescribing, and in turn steady profits.

While the pharmaceutical industry may claim that PSRs visit physicians in order to distribute information and educate physicians, they also visit to gather information. The *PLOS Medicine* article reveals that PSRs "are also trained to assess physicians' personalities, practice styles, and preferences, and to relay this information back to the company."[15] Pharmaceutical companies rely heavily on the information collected by PSRs. The information collected by PSRs is stored in a database and utilized in developing future marketing strategies. In addition to collecting personal information about physicians to enhance PSR strategies, pharmaceutical companies also gather information on their prescribing behaviors through a practice known as data mining.[21] Pharmaceutical companies get access to this information by purchasing prescribing data from prescription drug intermediary (PDI) companies, information distribution companies, or health information organization such as IMS Health, Dendrite, Verispan, and Wolters Kluwer.[15,21] These companies purchase prescription records from pharmacies, many of which do sell these records. Patient and physician names are not included, but the data does sometimes contain physicians' state license numbers, Drug Enforcement Administration numbers, or a pharmacy-specific identifiers.[15] According to an article from *The New England Journal of Medicine*, these companies are able to link these records to physician information that they purchase from the American Medical Association (AMA).[21] The AMA maintains the

Physician Masterfile, which is "a database containing demographic information on all US physicians (living or dead, member or non-member, licensed or non-licensed)." [15]

Pharmaceutical companies are the primary customers for prescribing data.[21] Companies use this information to identify physicians known as high decile prescribers and additionally to track the impacts of their promotion efforts. Specifically, the PSRs use this prescribing data "to see how many of a physician's patients receive specific drugs, how many prescriptions the physician writes for targeted and competing drugs, and how a physician's prescribing habits change over time."[15] There has been increasing concern about pharmaceutical companies' ability to utilize physician-identifiable prescribing data. This concern prompted at least 25 states to consider legislation that would restrict pharmaceutical access to such data.[21] Vermont, New Hampshire, and Maine attempted to pass such laws but immediately faced resistance from prescription drug intermediary companies and a trade association of pharmaceutical manufacturers.[21] According to *The New England Journal of Medicine* article, "One of these challenges reached the nation's highest court this year (2011), and on June 23, the Supreme Court struck down Vermont's statute by a vote of 6 to 3, holding that in practical effect, the law unconstitutionally restricted the speech of pharmaceutical companies and PDIs on the basis of the viewpoint it expressed."[21] Given the court's decision, pharmaceutical companies still utilize this data today. With this information, pharmaceutical companies can identify those physicians who are the most receptive to their marketing tactics and personalize their strategies in an attempt to influence their prescribing behavior. By identifying these high decile prescribers, pharmaceutical companies are able to allocate their promotional resources more efficiently and in turn, produce a higher Return on Investment (ROI). One must consider the idea that if

detailing was truly a practice that served to educate physicians, then pharmaceutical companies would target all physicians, not just those who frequently prescribe their pharmaceuticals.

Detailing: Impacts

Pharmaceutical companies have continued to dedicate extensive resources to the practice of detailing because it is an extremely effective way to drive prescriptions sales. Multiple studies have documented that physicians' interactions with PSRs have a substantial effect on their prescription behavior. The pharmaceutical industry specifically acknowledges that detailing likely has an impact on physician prescribing behavior, but the industry believes it serves several beneficial purposes. They contend that "such marketing is welfare-enhancing and remains an important source of physician learning."[17] According to a *JAMA* article, these purposes include "introduction of physicians to new medications, encouragement to use the most effective medications, improvement of the likelihood that they will follow good practice guidelines, and access to medications for low-income patients."[22] Additionally, an article from the *National Bureau of Economic Resources* notes that the industry feels that "detailers provide valuable information concerning the drug's indications and counterindications, which in turn allows physicians to make better-informed choices."[17] Whether the impact of detailing on physician behavior is beneficial or detrimental is a subject of debate, but this report will describe both the positive and negative impacts found in multiple studies.

Manchanda and Honka conducted an integrative review of literature in 2005 to reveal the effects of DTPP and published their findings in the *Yale Journal of Health Policy, Law, and Ethics*. The authors found that physicians rely on detailing as an important source of information, as it is inexpensive and convenient.[19] According to a study that surveyed Iowa

physicians about the frequency with which they use certain sources of drug information, PSRs were second after pharmaceutical text books. [19] While physicians admit to frequently using the pharmaceutical industry as a source of information, the authors describe a 1994 study that revealed that only 20% of physicians "believed in the accuracy and objectivity of presented information, while 44% did not." [19] While it appears physicians do not place a high level of trust in the quality of the presented information, the study still indicated that the practice affects physician behavior in a "positive and significant manner."[19] Approximately 56% of doctors in the previously mentioned study admitted that PSRs could "influence formulary decisions if efficacy, toxicity, and cost were the same, while 28% disagreed with this statement." [19] Moreover, according to a 1990 study that surveyed doctors at teaching hospitals, "25% of faculty and 32% of residents reported having changed their practices at least once in the preceding year based on contact with a detailer."[19] Another 1994 study surveyed 262 practitioners and found that 70% admitted that detailing affected their prescribing habits. [19] This same study also found a strong positive association between the number of PSR visits and the number of prescriptions per week.[19] While the studies described in this integrative review are significantly dated, they are worth noting because many of the findings have remained constant in more recent literature.

A 2010 systematic review published in *PLOS Medicine* revealed additional relevant findings.[23] These authors examined multiple studies to reveal how the exposure to information from pharmaceutical companies affects the quality, quantity, and cost of physicians' prescribing. Overall, the study found that "with rare exceptions, studies of exposure to information provided directly by pharmaceutical companies have found associations with

higher prescribing frequency, higher costs, or lower prescribing quality or have not found significant associations."[23] Specifically, this review examined 29 studies about the effects of sales representative visits and found that 17 of the studies found an association with increased prescribing of the promoted drug. [23] Of the 11 remaining studies, six of them had mixed results—"finding a significant association with more frequent prescribing for some measures but no significant association for others." [23] The other five did not detect any significant relationship between sales representative visits and prescription volume. [23] These studies also looked at specific characteristics of the PSR visits and their corresponding impacts. They found that longer PSR visits were more likely to be associated with increased prescribing. [23] Additionally, they found that "an association with more frequent prescribing was more likely when pharmaceutical sales representatives visited groups of physicians, when physicians had lower baseline prescribing of the promoted drug, and when physicians had larger prescribing volumes overall." [23] In terms of prescribing quality, the authors discuss a study that revealed that primary care doctors who saw more PSRs and used the pharmaceutical industry as a source of information prescribed a wider range of drugs. They note that the authors of this study suggest that "this was a sign of lower prescribing quality in the context of recommendations that primary care providers use a limited list of drugs they know well."[23] Most doctors still deny that interacting with PSRs and the pharmaceutical industry in general affects their behavior, but from these reviews and the numerous studies cited, the existence of the impact of detailing is undeniable.

Samples

The second largest portion of DTPP expenditure is allocated to the practice of providing samples, which is essentially medicine given to physicians at no cost to them. This practice is closely related to detailing, as pharmaceutical companies rely on pharmaceutical sales representatives (PSRs) to deliver these samples directly to physicians. According to *Medical Marketing in the United States*, spending on the distribution of free samples increased from $8.9 billion in 1997 to $13.5 billion in 2016.[1] At the surface, the purpose of sampling is to allow physicians and patients to "try" the new product in order to evaluate tolerance and preference before they decide to spend money on the costly product. According to a *PLOS Medicine* article, the underlying pharmaceutical objective of supplying samples "is to gain entry into doctors' offices, and to habituate physicians to prescribing targeted drugs." [15] The pharmaceutical industry claims that sampling has a number of positive impacts. Chimonas and Kassier note that, "in two separate news releases within the past year by the Pharmaceutical Research and Manufacturers of America (PhRMA) […] a senior vice president claimed that free samples improve patient care, foster appropriate medication use, and help millions of financially struggling patients."[24]

It is clearly documented that physicians appreciate samples, which allow them to "start therapy immediately, test tolerance to a new drug, or reduce the total cost of a prescription." [15] Even those doctors who are skeptical about detailing and limit their interactions with PSRs usually want and accept free samples that are provided.[15] Patients also appreciate the free samples, which eliminate the need to stop at a pharmacy on the way home when they may not be feeling well or have other considerations, such as children in the car. Additionally, Big

Pharma and many physicians assert that the practice of sampling benefits poor patients by reducing their prescription costs. However, many studies have found that this assertation is not accurate, as "poor patients are less likely than wealthy patients to receive drug samples, and free drug samples often transition to paid prescriptions that can drive significant extra costs per patient per month."[25] A nationally representative survey of the United States conducted in 2008 revealed that fewer than one-third of patients who received samples were considered low-income (less than 200% of the poverty line).[24] Kessel additionally analyzed the truth of this claim in a 2014 *Nature Biotechnology* article. He revealed that research has indicated that the majority of free samples are dispensed to insured patients whose prescriptions are covered, and that those patients who do receive samples ultimately end up paying higher prescription costs because "they are then prescribed the sampled drug rather than a less-expensive generic alternative."[26] Additionally, pharmaceutical companies don't provide samples of all of their products. Studies have revealed that the pharmaceutical products selected for sampling tend to be the more expensive, name-brand drugs rather than the less expensive, generic alternatives. It is important to note that the distribution of samples to physicians is largely unregulated nationally, as a physician's receipt of samples are exempt from Sunshine Act Reporting.[25] Thus, it is left to physicians to decide whether the receipt of such gifts has an unethical impact on their behavior. It is clear that the promotional tactic of sampling provides a high ROI by gaining the loyalty of physicians to both the pharmaceutical manufacturer and their products, and this report will subsequently examine studies that reveal evidence about this conclusion.

Samples: Impacts

The provision of free samples may have a number of positive impacts in terms of creating convenience for patients and allowing physicians to test their satisfaction with new pharmaceutical products. That being said, multiple studies have revealed that sampling also has a number of negative impacts. While pharmaceutical companies would never recognize samples as a form of "gift," in reality, they are. According to the 2017 study conducted by Fickweiler, Fickweiler, and Urbach, the most common "gift" that physicians receive are samples.[18] In his 2014 *Clinical and Translational Gastroenterology* article, Lahey discusses the idea that while sampling may not technically be considered a gift from the pharmaceutical companies' perspective, it may subconsciously feel like one to physicians and create a sense of obligation.[25] The author cites a 2003 study that reveals evidence indicating that gifts of *any value* strongly influence the recipient's behavior.[25] Upon the receipt of samples, physicians are more likely to show loyalty to both the PSRs and the drugs that they represent.[25] Multiple studies have shown that the distribution of samples results in substantial increases in new prescriptions for the promoted drug which translates to higher sales volumes and profits for the pharmaceutical industry.[11,24,25]

Wazana conducted an analysis of 29 studies about physician interaction with the pharmaceutical industry and found that the acceptance of free samples by physicians was associated with "awareness, preference and rapid prescription of a new drug, and a positive attitude toward the pharmaceutical representative."[11] Although it may increase awareness, sampling may tempt physicians to cross an ethical line and stray from their unbiased, expert medical opinion. The 2014 article written by Lahey in *Clinical and Translational*

Gastroenterology reveals that physicians are more likely to prescribe medications given to them as free samples "even if that choice is irrational or not otherwise their first choice."[25] In a 2009 article from *PLOS Medicine*, Chimonas and Kassier note a study that revealed that "residents with access to samples were more likely than their counterparts without samples to prescribe heavily advertised products and less likely to suggest an over-the-counter alternative."[24]

Chimonas and Kassier discuss another issue with sampling pertaining to the bypassing of drug interaction checks and counseling by pharmacists. "In drugstores, pharmacists often identify potentially harmful drug interactions, intercept inadvertent medication errors, and offer a patient-friendly printout of instructions." [24] The authors note that this detailed process rarely occurs when doctors dispense free samples. Relating to this, Chimonas and Kassier note the possibility of inadequate documentation in patients' records about the distribution of samples, and argue that this could cause issues with notifying patients in the event that the product is recalled or new drug complications are revealed. [24] They feel that this is especially troublesome given that many of the drugs that are offered as samples are newer products that are not time-worn and well-tested. They provide a specific example of a related situation that put patients at risk revealing that, "in 2004, four of the 15 medications most frequently given as samples to children in the US received new or revised 'black box' warnings from the US Food and Drug Administration within two years of approval." [24] The last potentially negative impact discussed by multiple articles was that samples may drive health care costs. A *JAMA* article notes that the "availability of free samples is a powerful inducement for physicians and patients to rely on medications that are expensive but not more effective."[22] As mentioned previously, this is because the majority of samples that are provided are expensive brand-name drugs

rather than less expensive generic alternatives. Thus, when patients stop receiving samples, they ultimately pay higher prescription costs, and those indigent patients that the samples were intended to help find themselves in a predicament where they can't afford their medication and must discontinue their treatment. All of these previously stated impacts seriously call into question whether the provision of samples is actually creating more positive effects than negative.

Educational and Promotional Meetings

The next largest portion of DTPP spending is dedicated to educational and promotional meetings. Pharmaceutical industry representatives invite physicians to meetings during which industry-paid physicians discuss the uses of particular drugs.[10] In discussing this category of DTPP, this report will include activities where physicians attend any kind of industry-sponsored meeting, such as educational symposia, speaking events by pharmaceutical sales representatives, or industry-sponsored medical conferences. These meetings can be local, regional, state, national, or international, and sometimes, they are combined with vacation or recreational events such as trips to resorts or desirable cities. The author of *The Truth About Drug Companies* argues that many of the pharmaceutical industry's DTPP efforts are masked as "education."[4] Angell argues that this allows pharmaceutical companies to categorize these expenditures as educational activities rather than promotional efforts, and feels that the amount of money spent on sponsoring these type of meetings is much higher than reported.[4] Pharmaceutical companies believe that physician-led meetings provide great education value. A Pfizer spokeswoman, Kristen Neese, noted, "We really do believe that these expert-led forums are a very valuable educational opportunity for them to learn about the experience of their

peers."[27] According to an analysis conducted by ProPublica, eight pharmaceutical companies spent more than $220 million on promotional speakers for their products in 2010.[28] Table 2 provides detailed figures for the amount spent by the top pharmaceutical companies on speaker payments in during 2010.

Table 2. Spending on Speaker Payments by the Top Pharmaceutical Companies (2008)[28]

Company	2010 Speaker Payments	2010 U.S. Sales
Lilly	$61,477,547	$14.3 billion
GlaxoSmithKline	$52,755,793	$13.6 billion
Pfizer	$34,382,574	$26.2 billion
AstraZeneca	$31,647,101	$18.3 billion
Merck	$20,365,446	$18.8 billion
Johnson & Johnson	$11,712,900	$12.9 billion
Cephalon	$4,241,080	$2.1 billion
ViiV Healthcare	$3,975,102	Unavailable

Attending these kinds of meetings is often very appealing to physicians, as the speakers are often leaders in their fields and many times they are held in attractive locations where there is nice food to go along with the information. According to the voluntary code of conduct adopted by the Pharmaceutical Researchers and Manufacturers of America, the meals served along with the educational meetings should be “modest” by local standards, but it appears that sometimes they exceed “modest.” For example, according to ProPublica, at least 20 doctors received meals

worth $2,000 or more from Pfizer between July 2009 and March 2010.[28] Reporting the amount of money spent on "dining" physicians was made a requirement by the Sunshine Act and is available in the federally mandated database called the CMS Open Payments database, which was created by the Centers for Medicare & Medicaid Services.[14]

Educational and Promotional Meetings: Impacts

Multiple studies have been conducted to reveal whether attending these industry-sponsored lectures and meetings has an effect on physician behavior and attitudes. In the 2017 review conducted by Fickweiler, Fickweiler, and Urbach, the authors found that these kinds of meetings did influence the behavior of the attendees, leading them to prescribe "more drugs from the sponsoring companies without sufficient evidence supporting superiority of those drugs."[18] In a troubling finding, the authors revealed that the majority of physicians who attended the sponsored meetings were not able to recognize inaccurate information about the company's drug. Lastly, this study found that those "physicians who received money to attend pharmaceutical symposia or to perform research requested formulary addition of the company's drug more often than other physicians."[18] In 2000, Wazana conducted an extensive study about physician interaction with the pharmaceutical industry, and her findings are similar to those of Fickweiler, Fickweiler, and Urbach. Wazana points out that often times, the pharmaceutical industry funds travel and lodging expenses for physicians to attend educational symposia.[11] The study reveals acceptance of this kind of funding by physicians "was independently associated with increased formulary addition requests for the sponsor's drug."[11] The study additionally found that "resident exposure to pharmaceutical representative speakers at lunch rounds was associated with dissemination and learning of inaccurate

information about the sponsor's and competitor's drug."[11] A systematic review published in 2010, discussed similar findings about the impact of pharmaceutical company-sponsored meetings.[23] The authors examined eight studies on this promotional practice and found that five of the studies revealed positive associations with prescribing frequency while the other three did not detect a significant association. [23] One of the studies that examined resident attendance at these meetings found that residents in attendance were more likely than their counterparts at the same hospital "to prescribe the sponsoring company's medication, both when it was appropriate according to the authors and when it was not." [23] While pharmaceutical company-sponsored meetings serve an important informational purpose, further action must be taken to ensure that the content remains factual and unbiased, as it is clear these events impact the attitudes and behaviors of those physicians in attendance.

Continuing Medical Education

An indirect form of DTPP related to educational and promotional meetings is the funding of CME, or continuing medical education. Most states require doctors to receive CME throughout their professional lives in order to maintain their licenses. They earn these credits by attending meetings and lectures or participating in other CME activities each year in order to learn about the latest research and developments in their specialties. These meetings, lectures, and other activities must be provided through an accredited institution, and the Accreditation Council of Continuing Medical Education (ACCME) is responsible for accrediting the organizations that provide the programs. [4] Notably, it's not usually the doctors who pay for their CME. In 2001, pharmaceutical companies paid for over 60% of the costs of continuing medical education.[4] According *to The Truth About the Drug Companies*, in the past,

pharmaceutical companies directly supported the accredited professional organizations, “but now they often contract with private medical education and communication companies (MECCs) to plan the meetings, prepare teaching materials, and procure speakers.” [4] Many speculate that the reason that MECCs are accredited by the ACCME, despite controversy, is because the pharmaceutical industry and MECCs themselves make up half of the Task Force on Industry Professional Collaboration in Continuing Medical Education.[4] This group of people are the ones responsible for helping the ACCME formulate policies on conflicts of interest.[4]

There has been much debate over the past decades about the existence of a conflict of interest when pharmaceutical companies fund the organizations who are supposed to be providing evidence-based, impartial information about new medicines and treatments. According to Jerome Schofferman, a doctor from Daly City, California, CME meetings and lectures that are funded by the pharmaceutical industry have “the potential to unconsciously bias educators and the leadership of professional medical associations—biases that might unduly influence an attendee's choice of drugs and devices, and thereby ultimately affect patient care.”[29] The existence of bias in the information presented by CME programs funded by Big Pharma is well documented, and their motives are less than subtle. One of the MECCs advertised its services with the statement, “Medical education is a powerful tool that can deliver your message to key audiences, and get those audiences to take action that benefits your product.”[4] Basically, these organizations are advertising the fact that they have the ability to influence physicians to prescribe certain pharmaceutical products. Examples of potential biases that may exist in the information presented by pharmaceutical company-sponsored CME events include: “mentioning the sponsor's drug or device by trade name and competitor's

products generically; discussing off-label uses; minimizing disadvantages, side effects or complications; emphasizing positive papers while minimizing negative ones; omitting noncommercial forms of treatment; and over-reliance on personal experience."[29] Furthermore, pharmaceutical companies admit that they are selective in choosing what kinds of CME programs to fund. According to a *JAMA* article, "companies acknowledge that they carefully evaluate the market impact of expenditures and support only those demonstrating an increased use of their products."[22]

There are measures in place that attempt to prevent this bias. Speakers at these events are required to disclose their conflicts of interest or financial ties. But despite this requirement, it appears that simply disclosing that information does not eliminate the bias or make it acceptable. The Institute of Medicine (IOM) stated that "industry influence of choice of topics and content is not rare." [29] Marcia Angell states that the pharmaceutical companies or the MECCs "often suggest the topic and the speaker and put together the graphics and other educational materials."[4] In an article from the *Journal of Pediatrics and Child Health*, the author discusses a related topic, noting that there is substantial evidence indicating that "industry-sponsored CME activities are more focused on drug therapies and are more favorable to company products than programs not funded by industry."[30]

As the debate on this controversy has intensified, it seems as though pharmaceutical companies have pulled back on the amount of funds that they dedicate to continuing medical education courses. In the summer of 2008, Pfizer was the first pharmaceutical company to make a drastic move away from funding CME programs.[31] The company made substantial cutbacks on their financial support of CME and announced that it would "support programs run

by academic institutions, teaching hospitals, and medical societies, but eliminate direct financial support for courses offered by for-profit medical education companies."[31] According to a Pew Research article, "in 2011, the pharmaceutical and medical device industries provided 32% of all funding for continuing medical education courses in the United States—$752 million out of $2.35 billion."[10] This substantially decreased from the 60% of funding they provided in 2001, but there is still a significant effort to completely eliminate pharmaceutical industry funding of these programs. In 2007, the Senate Finance Committee released a report on drug industry CME grants. The creation of this report was sparked by the Committee's "belief that the pharmaceutical industry uses educational grant funding to promote the use of their drugs, including unapproved uses of some medicines."[32] According to this article, the release of this report was likely to further the government's efforts to restrict the pharmaceutical industry's involvement in CME and their use of these programs to transmit off-label information (the use of their products for reasons not approved by the FDA).[32] In an article from the *Journal of Pediatrics and Child Health*, Ian Kerridge notes that "recent reports by the Josiah Macy Jr Foundation, the Institute of Medicine, the American Medical Association (AMA) Council on Ethical and Judicial Affairs and the Association of American Medical Colleges have all called for the establishment of independent CME that either operates completely at arm's length to industry or receives no commercial support at all."[30] According to an article from *Policy Med*, it appears that only two Academic Medical Centers (AMCs), the University of Michigan and Memorial Sloan-Kettering Cancer Center, have stopped accepting funding from pharmaceutical and medical device companies.[33] Moreover, the ACCME has announced that it would "not be

taking any action to end the commercial support" of accredited CME, but rather it planned to enhance it monitoring system to ensure compliance.[33]

CME: Impacts

The reason that pharmaceutical companies continue to pour resources into CME despite the intense controversy is because it is effective, and the industry argues that it produces a number of positive effects. Many individuals claim that industry funding of these programs results in greater CME participation by keeping the cost of attendance down and also by making the meetings more enjoyable by providing things such as free meals. They argue that, in turn, industry funding of CME benefits patients by improving physician knowledge and competence.[31] That being said, there is little evidence to indicate whether industry funding of CME benefits physicians and patients in these ways, but many studies have produced evidence indicating its potential to influence physician knowledge, attitudes, prescribing behavior.

According to a study outlined in a 2017 *BMJ* article, those physicians who attended company-sponsored CME events had more positive attitudes toward the pharmaceutical company or product and had an inclination to prescribe the branded-product. [18] Additionally, the article noted that those physicians who refused CME sponsorships, "were seen to prescribe higher proportion of generics and lower expenditure medicines when compared with physicians who attended CMEs."[18] The study conducted by Wazana in 2000 also focused on the impact of CME sponsorship by pharmaceutical companies.[11] Wazana's results emphasized the previously stated notion that pharmaceutical company-sponsored CME events preferentially highlight the sponsor's drug(s) compared to other CME programs not sponsored by the industry. [11] Additionally, physicians self-reported the fact that there were changes in their prescribing

practices in favor of the sponsor's drug after attending CME events.[11] Lastly, the article notes that physician attendance of sponsored CME events was associated with increased prescription rates of the sponsor's medication.[11] Industry funding of CME has an undeniable influence on the content of the education that physicians are receiving, and in turn an undeniable influence on their prescribing behaviors. It appears from the actions already taken by Pfizer and a few Academic Medical Centers that this influence may be ethically questionable, and it will be interesting to observe how the medical industry proceeds in coming years.

Gifts

The next aspect of DTPP that this report will address is not technically its own category of promotion, but rather a component of all the promotional efforts I previously mentioned. It is widely documented that physicians receive "gifts" from the pharmaceutical industry, and these gifts come in many forms. Pharmaceutical sales representatives distribute small, inexpensive "reminder" items such as pens, notepads, and coffee mugs labeled with the pharmaceutical company's name or product. Pharmaceutical companies additionally distribute more "moderately priced gifts (valued at $20 to $100), such as reference tools, books and meals."[34] A systematic review conducted by Fickweiler, Fickweiler, and Urbach in 2017 revealed that the most common gifts received by physicians were "medical samples, promotional material, invitations for dinners, invitations for CMEs, scientific journals and free lunches."[18] In the past, pharmaceutical companies provided much more expensive gifts such as "tickets, trips, and large 'honoraria' for participation in pharmaceutical-sponsored activities."[34] These types of gifts became much less common after the Sunshine Act was passed in 2010 as part of the Affordable Care Act. As mentioned earlier in this report, this act "requires medical product

manufacturers to disclose to the Centers for Medicare and Medicaid Services (CMS) any payments or other transfers of value made to physicians or teaching hospitals."[14] Pharmaceutical companies report this data annually and it is published in a publicly searchable database called CMS Open Payments.[14]

While the government has increased regulation of high-value gifts, the pharmaceutical industry still regularly dispenses gifts within the required price limits. A 2006 analysis from *Science Direct* explains that pharmaceutical advertising items are frequently found in the coats of resident physicians. [34] The cited study revealed that "97% of 164 house officers studied carried at least 1 item with pharmaceutical insignia."[34] Physicians begin receiving gifts from the pharmaceutical industry very early in their careers, and the frequency and forms of gifts received vary as they evolve into different positions within the medical hierarchy. One study found that residents typically receive about 6 gifts a year. [11] While there was no comparable data in this study for physicians, it is generally understood that as physicians enter practice, the gifts they receive are more related to research funding, honoraria, and conference travel. [11] Another study conducted in 2013 directly analyzed the interactions between physician trainees and the industry and found that "among 1,610 student (49.3 % response rate) and 739 resident (43.1 %) respondents, industry-sponsored gifts were common, rising from 33.0 % (first-year students) to 56.8 % (fourth-year students) and 54 % (residents). These gifts included meals outside the hospital (reported by 5 % first-year students, 13.4 % fourth-year students, 27.5 % residents) and free drug samples (reported by 7.4 % first-year students, 14.1 % fourth-year students, 14.3 % residents)."[35] As gifts from the pharmaceutical industry take on a number of different forms, it is hard to measure the exact amount of resources dedicated to this practice.

Nevertheless, it is clear that the number is significant and that the practice plays a vital role in gaining the favor of physicians. Michael Oldani, an anthropologist and former pharmaceutical sales representative, notes, "the importance of developing loyalty through gifting cannot be overstated."[15]

Gifts: Impacts

A number of studies have documented that gifts from the pharmaceutical industry (of any value) have a significant impact on physician's attitudes and prescribing behavior. Moreover, physicians have different attitudes towards the practice of gifting by the industry. Some readily accept gifts while others adopt strict avoidance policies. Wazana revealed that "85% of medical students believe it is improper for politicians to accept a gift, whereas only 46% found it improper for themselves to accept a gift of similar value from a pharmaceutical company." [11] It seems that most doctors are positioned in the middle of the two extreme attitudes, finding that some forms of gifts are appropriate while others are not. Fickweiler, Fickweiler, and Urbach found that physicians usually consider "conference registration fees, informational luncheons, sponsorship of departmental journal clubs, anatomical models and free drug samples" as appropriate gifts.[18] The authors also reveal that the majority those doctors who do accept gifts consider themselves immune to the influence of gifts.[18] Although they may feel this way, studies have documented that this assumption is not accurate. To this point, Wazana found that "receiving a gift and the number of gifts received correlated with the belief that pharmaceutical representatives have no impact on prescribing behavior." [11] It appears that as physicians receive more gifts, they either become more oblivious or more willing to overlook the potential influence on their behavior.

The pharmaceutical industry and physicians defend the practice of gift exchange by citing the Sunshine Act, claiming that small gifts do not influence physician behavior and that disclosure of financial conflicts of interest protect patients' interests. But many individuals call into question the validity of these assumptions, and argue that requirements of the Sunshine Act are not enough to eliminate potential conflicts of interest. These authors cite studies that reveal that gifts of any value (no matter how small) impact physicians by inducing reciprocal feelings. Authors of a 2006 *JAMA* article explain that, "social science research demonstrates that the impulse to reciprocate for even small gifts is a powerful influence on people's behavior."[22] The authors go on to explain that "individuals receiving gifts are often unable to remain objective; they reweigh information and choices in light of the gift."[22] In this discussion, the authors emphasize that the primary reason for gift giving is often the expectation of reciprocity.[22] Thus, these authors argue that the requirements of the Sunshine Act are not enough to resolve the issues created by physician's acceptance of gifts from the pharmaceutical industry. The gifts of small value that continue to be distributed are influencing physicians' attitudes and behaviors. The article cites study results concluding that "receiving gifts is associated with positive physician attitudes toward pharmaceutical representatives."[22] Moreover, the authors reveal that "physicians who request additions to hospital drug formularies are far more likely to have accepted free meals or travel funds from drug manufacturers." [22] A 2016 study examined the association between physicians' receipt of industry-sponsored meals and rates of prescribing the promoted drug to Medicare beneficiaries.[59] The authors found that "physicians who received a single meal promoting the drug of interest, with a mean value of less than $20, had significantly higher rates of prescribing

rosuvastatin as compared with other statins; nebivolol as compared with other β-blockers; olmesartan as compared with other angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers; and desvenlafaxine as compared with other selective serotonin and serotonin-norepinephrine reuptake inhibitors."[59] This finding strongly indicated that those physicians who receive industry-sponsored meals or payments are much more likely to prescribe the promoted brand-name medication to Medicare patients at an increased rate. This study also supports the claims made in the 2006 *JAMA* article[22], that even gifts of small value have a substantial impact. From the evidence presented throughout these studies, the impact of gifting is clear, and it may be time for the government to consider heightening the restrictions set forth in the Sunshine Act.

Journal and Web Advertisements

One of the last prominent categories of DTPP that this report will discuss is the publication of advertisements in medical journals (many of which are increasingly online). These advertisements provide an important source of revenue for medical journals and in early years, journal advertising was the pharmaceutical industry's most effective source of promotion. According to one study, "journal advertising generated the highest return on investment of all promotional strategies employed by pharmaceutical companies, with returns ranging from $2.22 to $6.86 per advertising dollar spent between 1995 and 1999."[10] In recent years, these advertisements have received less funding than other promotional activities such as detailing and sampling. According to Schwartz and Woloshin, pharmaceutical spending on medical journal advertising declined from $744 million in 1997 to $119 million in 2016.[1] While spending in this area has declined, it remains an attractive marketing technique because a large

majority of physicians continue to utilize medical journals as an important source of information. According to a 2018 article, print versions of these journals reach 90% of physicians, and when combined with digital versions, they reach 96% of physicians.[36] Milton Liebman, president of the Association of Medical Publishers, emphasizes this point in his statement, "Print promotion usually provides higher message penetration than detailing because print (most notably journals) obtains higher reach into the target audience with great consistency of message delivery."[37] Moreover, journal advertising acts as a very effective complementary promotional effort when combined with the practice of detailing. Marshal Paul, chairman of PERQ/HCI Research which conducts media research for the pharmaceutical industry, stated, "Advertising magnifies the detailing effort at a fraction of detailing expense. In effect, detailing provides the power in the marketing effort and advertising provides the efficiencies." [37] In the integrative review conducted by Manchanda and Honka in 2005, they discuss evidence that emphasizes the notion that physicians still heavily utilize medical journals.[19] The authors note a 1980 study that involved a survey of "general practitioners on their most recent, regular, and most useful sources of information about therapeutics and prescribing."[19] All of the respondents ranked journals first on all three criteria (recency, regularity, usefulness).[19] This review goes on to cite multiple studies that indicate the extent to which physicians rely on medical journals, but many of the referenced sources are significantly dated. Physician reliance on printed medical journals as a source of information may have decreased in recent years, but it is still imperative that these sources are distributing factual, unbiased information.

In recent years, there has been growing concern about the quality of the information published in medical journals by the pharmaceutical industry. The U.S. Food and Drug Administration (FDA) is the party responsible for regulating the accuracy of the advertisements published in medical journals, and over the years, they have grown increasingly critical of pharmaceutical advertisements. Their most common complaint is that the industry often publishes advertisements that highlight the effectiveness of their products without pointing to the risks. Specifically, in April 2009, the "FDA warned 14 major drug makers for running search ads for many of their products that highlighted the products' effectiveness without noting any of their risks."[10] Schwartz and Woloshin discuss a 2008 study of advertising in nine "high-impact journals."[1] The results of the study revealed that 58% of the advertisements "did not quantify serious risks, 48% lacked verifiable references, and 29% did not quantify efficacy."[1] Moreover, a *PubMed* review analyzed 109 full-page pharmaceutical advertisements and "concluded that 44% would lead to improper prescribing if a physician relied only on the information presented in the advertisement."[38] In a 2006 *PLOS Medicine* article, the authors argue against the industry claims of the educational value of their advertisements.[37] The authors note that while there are more than 10,000 drugs in the US market, over half of pharmaceutical journal advertisement expenditures are spent on the 50 best-selling drugs, and they additionally emphasize the promotion of new drugs.[37] They argue that "new" and "best-selling" drugs are not always superior to old or competing drugs, invalidating the "educational-value" claim.[37] None of the medical journals require companies to demonstrate product superiority in their ads, making it questionable as to whether these ads are really enhancing the prescribing decisions of physicians. Additionally, these authors remain skeptical about the quality of the data and

studies cited within these advertisements. In this discussion, they note a 2005 study of ads in 10 US medical journals conducted by Cooper and Schriger.[37] They reveal that, "Of 312 advertisements with references, 55% cited journal articles and 19% cited 'data on file' (proprietary information that companies are not obligated to provide to clinicians)."[37] Moreover, "only 20% of references to data on file were available." The authors also explain that many of the studies cited in the advertisements are sponsored by the pharmaceutical industry, creating the potential for biased results.[37] In the 2005 study by Cooper and Schriger, "58% of original research cited was sponsored by or had an author affiliated with the product manufacturer, compared with 8% of references to original research within research articles."[37] There have been a number of allegations of pharmaceutical companies withholding or failing to report negative data when marketing their products, and subsequently a number of individuals have become skeptical of the of the information presented in journal ads. This growing concern has caused important medical journals to reconsider their advertising relationship with the pharmaceutical industry. According to a *Nature Biotechnology* article, "Journals like the *British Medical Journal* have considered banning all submissions from industry authors; the *Lancet* and the *New England Journal of Medicine* decline to publish any review articles by industry authors; and several clinical conferences no longer allow big pharma speakers to present their results."[26] As clearly presented in subsequent evidence, it is not hard to find a pharmaceutical advertisement in a medical journal that presents biased or nonfactual information, and it is for this reason that clinical journals and learned societies are considering such extreme measures to limit their interaction with the industry.

Promotional Mailings:

The last major area of DTPP that this report will address is promotional mailings. This promotional practice involves sending promotional materials and brochures to physicians' offices. While investment in this form of marketing pales in comparison to investment in other promotional areas, in 2012, $1.2 billion of the pharmaceutical marketing budget was spent on producing and distributing these materials.[10] There has been a substantial amount of literature written about the pharmaceutical practice of promotional mailings, and many authors question the quality of the information presented in the brochures. Authors of a 2006 *BMC* article conducted a study in which they asked physicians from five clinics to send all of the promotional mailings they received to one centralized location.[39] These materials were subsequently examined by two "blinded-reviewers" who compared the information presented in the brochures to the data found in the original study. After reviewing a total of 20 distinct promotional brochures, the reviewers found that "75% of the studies were found to be valid, 80% were funded by the pharmaceutical company, 60% of the studies and the corresponding brochures presented patient-oriented outcomes, and 40% were compared to another treatment regimen."[39] Furthermore, "Of the 19 brochures that presented the data as graphs, 4 brochures presented a relative risk reduction while only 1 brochure presented an absolute risk reduction."[39] Lastly, "15% of the promotional marketing brochures presented data that was different from what was in the original published study."[39] As this study revealed, the majority of the cited studies in these brochures are funded by the pharmaceutical company themselves. This finding is troubling when considering the article's additional finding that those "studies that were sponsored by pharmaceutical companies were four times more likely to have

outcomes favoring the sponsor's product than were studies that had other types of sponsors."[39] It appears that many individuals become more skeptical about the validity of studies highlighted in promotional mailings when they are funded by the industry. Another commonly noted complaint about promotional mailings is that pharmaceutical companies "selectively report trials in which the sponsored drug out performed that of competitors."[10] This criticism was similarly brought forth in the previous discussion about pharmaceutical advertisements in medical journals. It appears from the overwhelming complaints existent in today's literature that there is a growing need for more stringent evidence-based review of pharmaceutical promotional material distributed in all settings, whether it be promotional mailings, journal advertisements, or pharmaceutical sales representative speeches.

After thoroughly examining each of the promotional tactics used by the pharmaceutical industry to target physicians, it appears that while there are some benefits of DTPP, there are also a number of issues that need to be resolved. The practice of detailing, sampling, and providing gifts of any form to physicians, puts doctors in a situation where their medical and moral obligations may be compromised. It is clear these promotional tactics influence the prescribing behavior of physicians whether they realize it or not, and the government, the pharmaceutical industry, and the medical community as a whole must consider DTPP's potential impact on patient care. While there are regulations and guidelines in place, it appears that there are still existing conflicts of interest, and these parties must work harder to resolve these issues and protect the interest of patients. The other apparent issue with the practice of DTPP is the quality of the educational content being distributed. Doctors rely on the pharmaceutical industry in a number of ways to enhance their knowledge and practice, but it

appears that the information they are receiving is not always unbiased and factual. It is important for doctors to continue to learn about the latest advances in medicine from the pharmaceutical industry, but regulatory agencies must work harder to ensure that the educational content distributed by the industry is grounded in science and not biased to promote a particular product or company.

Part III: Direct to Consumer Advertising

While Direct to Physician Promotion has been employed for decades, in more recent years, pharmaceutical companies have rapidly increased their use of Direct to Consumer Advertising. Direct to Consumer Advertising (DTCA) is the practice of marketing and advertising pharmaceutical products directly to consumers as patients via mass media platforms. The United States and New Zealand are the only two countries that currently allow DTCA that includes product claims. Canada allows pharmaceutical companies to employ DTCA that mentions either the product or the indication but not both.[40] Besides these three countries, the rest of the world has completely outlawed the pharmaceutical practice of DTCA. This fact alone should indicate that there is considerable controversy surrounding the practice of marketing prescription medication directly to consumers. An enormous volume of literature has been written on the subject of DTCA. Authors hold a variety of opinions on the practice and a number of studies have been conducted that reveal evidence supporting both sides of the argument. This report will go into more detail later on about the pros and cons of pharmaceutical marketing and the corresponding evidence, but before one can develop an opinion on the subject, it is important to have a thorough understanding of the practice as a whole. Regardless of the arguments presented by DTCA advocates or DTCA critics, it cannot be

denied that the inherent goal of advertising it to drive profits. Thus, at its foundation, the aim of DTCA is to encourage consumers to request the advertised medication from their physicians and subsequently increase prescription medication sales. Whether these advertisements are actually creating a more informed, empowered, and responsible healthcare consumer will be subsequently discussed, but their effect on the pharmaceutical industry's profits are clear. Direct to Consumer Advertising is the fastest growing segment of pharmaceutical marketing spending as indicated by the high prevalence of television ads for prescription medications. But why *now*? No federal law has ever banned Direct to Consumer Advertising, so when and why did these advertisements become so pervasive?

Background and Regulation

In 1981, the first Direct to Consumer Advertisement was printed in *Reader's Digest* by Merck to advertise its new antipneumococcal vaccine, Pneumovax.[40] During this time period, the U.S. political climate became more favorable to deregulation and in turn, to pharmaceutical companies. Additionally, a cultural shift occurred that caused patients to take a more active role in their health care decision making. Thus, pharmaceutical companies began to increase their DTCA efforts. From 1980 to 1990, total spending on DTCA increased from $12 million to $47 million, and by 1995, it had increased to $340 million. [40] But this 3,000% increase over 15 years pales in comparison to the boom in DTCA after 1997. [40] It was in this year that the Food and Drug Administration relaxed the guidelines for prescription drug advertisements, and subsequently, the budgets for DTCA more than tripled to $1.2 Billion in 1998.[40] Prior to 1997, the FDA's regulations mandated that prescription drug advertisements "(1) not be false or misleading, (2) present a 'fair balance' of information describing both the risks and benefits of a

drug, (3) include facts that are 'material' to the product's advertised uses, and (4) include a 'brief summary' that mentions every risk described in the product's labeling."[40] Describing every risk and including the complete information to satisfy the "fair balance" and "brief summary" regulatory requirement was very time consuming, making broadcasts ads very costly.[40] The FDA recognized that the cost of purchasing enough time to include all of the necessary information was prohibitive, and subsequently issued draft guidance on this topic in 1997.[40] With the new rules, broadcast DTC product claim ads only had to include the "major risks" and an "adequate provision" that would direct the viewers to a place where they could access a complete "brief summary."[40] This new relaxed set of rules triggered a boom in the pharmaceutical DTCA efforts that have persisted through today.

Categories of DTCA and Current Regulation

Direct to Consumer Advertisements are generally characterized into three categories: "Product-Claim," "Reminder," and "Help-seeking." The FDA recognizes these categories and has created specific requirements based on each category. Product-Claim advertisements are the most common. They name a drug and make a therapeutic claim about the product. Product-claim advertisements must include: "the name of the drug, at least one FDA-approved use for the drug, and the most significant risks of the drug."[41] Additionally, they must present the risks and benefits of the drug in a balanced fashion to satisfy the "fair balance" requirement.[41] While print product-claim advertisements must also include a "brief summary" about the drug that includes all of the risks, the FDA makes an exception for broadcast ads because of the prohibitive nature of the time expense. Broadcast product-claim advertisements must only include a "major statement" of the most important risks and provide consumers with access to

more complete information.[41] This is usually satisfied by providing a toll-free telephone number, a health care provider's contact information, a Web site address, or a link to a concurrently running print advertisement with the complete information.[41]

Reminder advertisements name a specific drug, but they do not reference the health condition the drug is used to treat. These ads assume that the audience already knows the drug's use, so they are typically directed at health care professionals. A reminder ad does not have to include information about risks (nor can it include anything about benefits), because the advertisement does not state what the drug does or how well it works. However, the FDA does not allow these types of advertisements for prescription drugs with serious risks. These drugs have a special warning, often called a "boxed warning," in the drug's FDA-approved prescribing information.[41]

Help-Seeking advertisements describe a particular disease or health condition and advise the consumer to see his/her doctor, but they do not recommend or suggest a specific drug treatment. Properly done help-seeking advertisements are not technically considered drug advertisements, as they do not mention a specific product.[42]

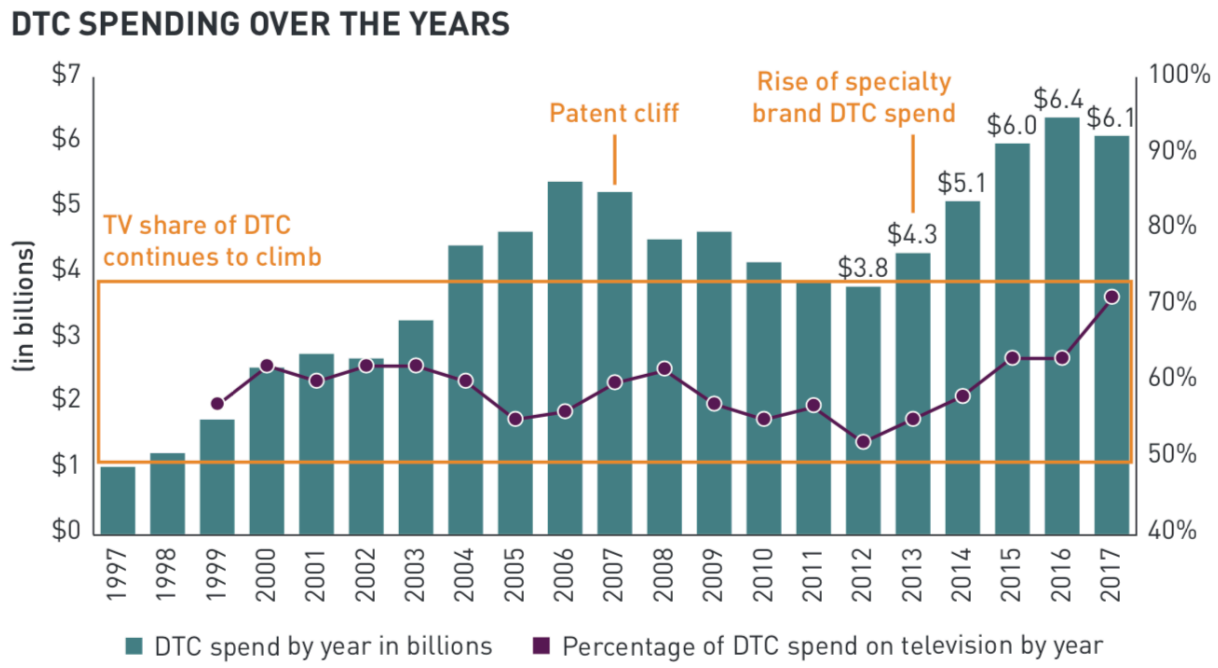
Pharmaceutical companies are required to submit copies of their advertisements to the FDA before they are published or aired, but no preclearance approval is required. That being said, if after airing, the FDA finds that an advertisement violates an FDA provision, it can issue letters of violation. While they can issue letters, the current system does not allow the FDA to issue fines to violating pharmaceutical companies unless they call for an administrative hearing.[9] This regulatory process is supposed to protect consumers and hold drug companies accountable for the information they distribute. In addition to government regulation, PhRMA

(Pharmaceutical Research and Manufacturers of America) has created a set of guidelines for the practice of DTCA. These guidelines state that pharmaceutical companies should "spend an appropriate amount of time on physician education prior to running DTC ads."[9] Additionally, the guidelines recommend that "companies should submit all new DTC advertisements to the FDA before releasing these advertisements for broadcast."[9] Lastly, the guidelines explain that DTC advertisements should "contain information about the availability of other options such as diet and lifestyle changes where appropriate and that DTC ads should be presented in clear, understandable language, without distraction from the content."[9] It must be emphasized that these guidelines are simply a recommendation and by no means an enforceable requirement. The relaxed regulations and arbitrary guidelines that pharmaceutical companies adhere to when using DTCA today have allowed pharmaceutical companies to directly market their products to consumers in a variety of ways to exponentially drive profits in recent years.

Spending

An in-depth study of medical marketing in the United States found that the most rapid change in spending from 1997 to 2016 was for DTC advertising, which increased from $1.3 billion (79,000 ads) to $6 billion (4.6 million ads [including 663,000 TV commercials]), accounting for a 361% increase.[1] While pharmaceutical companies are rapidly investing more resources in DTCA, the $6 billion spent on DTCA in 2016 represented only 20% of the total medical marketing expenditure ($29.9 billion), as the majority of the budget is still allocated to Direct to Physician Promotion (DTPP).[1] Figure 7 illustrates DTCA spending by the pharmaceutical industry during the 1997 to 2016 time period.

Figure 7. DTCA Spending from 1997-2016[58]



As illustrated in Figure 7, the DTCA declined from 2016 to 2017, and this is largely due to the fact that the industry lost some of its biggest DTC spenders due to the loss of exclusivity.[58] As the practice of DTCA is relatively new with respect to the long history of pharmaceutical promotion, the gap between investment in DTCA versus DTPP is still large. Nonetheless, DTCA has proven to be extremely effective in driving prescription sales and in turn profit. A study conducted in 2000 found that every dollar the pharmaceutical industry spent on DTCA yielded an additional $4.20 in drug sales.[43] Furthermore, the study revealed that DTCA "was responsible for 12% of the increase in prescription drugs sales, or an additional $2.6 billion, in 2000."[43] Tsai and Lancaster, authors of a 2012 analysis, note that, "brands with high DTC spending are typically among the best-selling drugs" and additionally, "a closer look at the sales data of prescription medicine reveals that, among the 50 most heavily advertised drugs, the

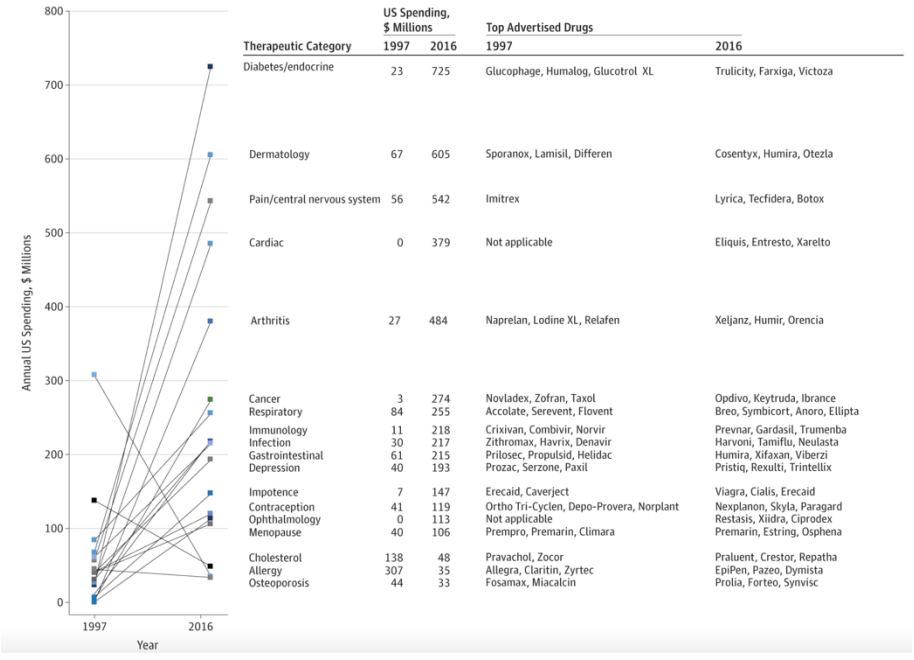
number of prescriptions dispensed rose 25% between 1999 and 2000, compared to a mere 4% increase for other drugs."[44] An article from Forbes noted that the "2008 House Commerce Committee found that for every $1,000 spent on prescription drug ads, 24 new patients were added for the pharma industry."[45] This author additionally explained that "a 2003 research report found that rates for prescription drugs with ads were almost seven times greater than for those without ads."[45] A systematic review published in the *BMJ* examined two interrupted time series studies in the US that revealed a "a significantly increased trend in the prescribing volume of drugs that had been the subject of DTCA campaigns."[46] Furthermore, the study indicated that "the effect of DTCA seemed to both increase the number of new diagnoses of a condition and tended to increase the proportion of prescriptions specifically for the advertised drug."[46] Numerous studies reveal that DTCA is having its intended effect of driving sales and profits, and it is clear why DTCA is the fastest growing segment of pharmaceutical marketing.

Trends and Timing

While DTCA may appear to be a ubiquitous practice utilized by the pharmaceutical industry as a whole, research has revealed that spending on DTCA has been concentrated amongst a relatively small number of brands. Authors of an article in *The New England Journal of Medicine* uncovered this finding in a detailed analysis they conducted of industry-wide trends in spending by pharmaceutical companies on DTCA.[47] The authors noted that "the 20 drugs with the highest (DTCA) spending made up 54.4% of total industry spending on [DTC] advertising in 2005."[47] The authors additionally examined a number of specific drugs and their associated advertising spending. They revealed that "in 2005, 8 of the 10 top drug classes in terms of dollar sales had at least one product with advertising spending."[47] They gave specific

examples of drugs with higher DTC advertising budgets and explained that "manufacturers of proton-pump inhibitors, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins), and erythropoietin medications spent 34%, 34%, and 31% of their total marketing budget, respectively, on direct-to-consumer advertising in 2005."[47] Compared to advertising spending for these medications, the authors found advertising spending for antidepressant agents, seizure-disorder medications, and antipsychotic agents to be lower.[47] Schwartz and Woloshin additionally analyzed DTCA spending across specific therapeutic categories in their analysis of medical marketing in the United States between 1997 and 2016.[1] The authors found that during this time period, DTCA spending for prescription drugs increased across all therapeutic categories, except for allergy, cholesterol, and osteoporosis drugs.[1] Figure 8 displays detailed information about the trends in DTCA spending for specific therapeutic categories.

Figure 8. Trends in DTCA Spending Across Therapeutic Categories from 1997-2016[1]



Therapeutic Category	US Spending, $ Millions 1997	2016	Top Advertised Drugs 1997	2016
Diabetes/endocrine	23	725	Glucophage, Humalog, Glucotrol XL	Trulicity, Farxiga, Victoza
Dermatology	67	605	Sporanox, Lamisil, Differen	Cosentyx, Humira, Otezla
Pain/central nervous system	56	542	Imitrex	Lyrica, Tecfidera, Botox
Cardiac	0	379	Not applicable	Eliquis, Entresto, Xarelto
Arthritis	27	484	Naprelan, Lodine XL, Relafen	Xeljanz, Humir, Orencia
Cancer	3	274	Novladex, Zofran, Taxol	Opdivo, Keytruda, Ibrance
Respiratory	84	255	Accolate, Serevent, Flovent	Breo, Symbicort, Anoro, Ellipta
Immunology	11	218	Crixivan, Combivir, Norvir	Prevnar, Gardasil, Trumenba
Infection	30	217	Zithromax, Havrix, Denavir	Harvoni, Tamiflu, Neulasta
Gastrointestinal	61	215	Prilosec, Propulsid, Helidac	Humira, Xifaxan, Viberzi
Depression	40	193	Prozac, Serzone, Paxil	Pristiq, Rexulti, Trintellix
Impotence	7	147	Erecaid, Caverject	Viagra, Cialis, Erecaid
Contraception	41	119	Ortho Tri-Cyclen, Depo-Provera, Norplant	Nexplanon, Skyla, Paragard
Ophthalmology	0	113	Not applicable	Restasis, Xiidra, Ciprodex
Menopause	40	106	Prempro, Premarin, Climara	Premarin, Estring, Osphena
Cholesterol	138	48	Pravachol, Zocor	Praluent, Crestor, Repatha
Allergy	307	35	Allegra, Claritin, Zyrtec	EpiPen, Pazeo, Dymista
Osteoporosis	44	33	Fosamax, Miacalcin	Prolia, Forteo, Synvisc

The authors found that DTCA spending for allergy, cholesterol, and osteoporosis drugs declined during this time period because the top-selling drugs lost patent protections or became available over the counter "without replacement by equally large advertising campaigns for new drugs in the category."[1] They additionally found that the greatest spending increases during this time period were associated with drugs for "diabetes/endocrine diseases, dermatology conditions, pain/central nervous system disorders, arthritis, cardiac diseases and cancer, largely reflecting competition among expensive new biologics and cancer therapies."[1] However, the author of *The Truth About Drug Companies* makes a broad statement about the type of drugs advertised in 2006, stating that "most (DTC) ads do not introduce drugs for rare or previously untreatable conditions but rather promote drugs for well-known conditions for which there are plenty of treatments already at hand."[4]

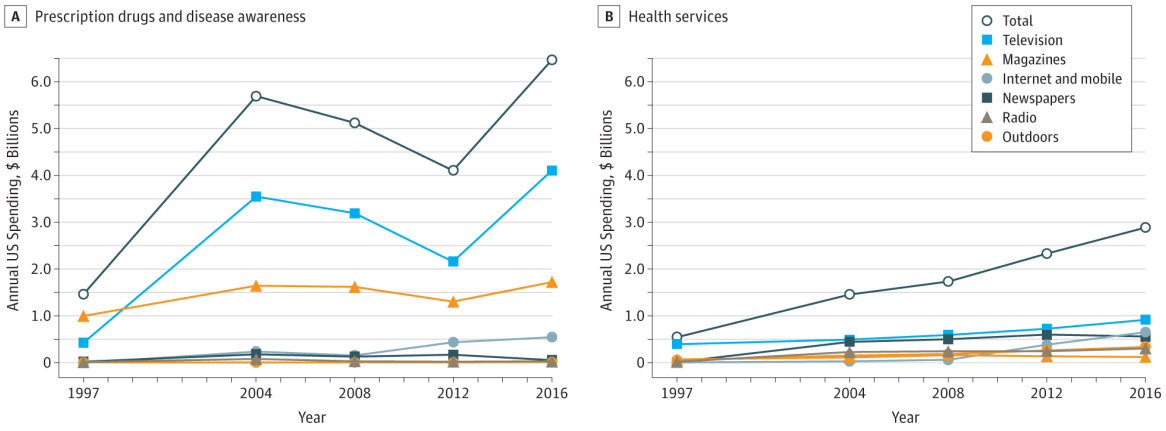
The authors of *The New England Journal of Medicine* article found that the medications most prominently and frequently advertised to consumers in 2007 were *new* drugs used to treat chronic conditions.[47] To this point, the authors examined trends in timing of DTCA. They reveal that DTCA campaigns "generally begin within a year after the approval of a product by the FDA."[47] The authors note this finding as a cause for concern, explaining that it "raises questions about the extent to which advertising increases the use of drugs with unknown safety profiles."[47] The authors mention multiple parties that have come forward and expressed apprehension about the advertising of drugs that are not time-worn and well-tested to consumers. They note that, "At least one pharmaceutical manufacturer (Bristol-Myers Squibb) recently announced a voluntary moratorium on direct-to-consumer advertising for drugs in the first year after FDA approval."[47] The authors additionally reveal that "PhRMA, the industry

trade group, has recommended that manufacturers delay such campaigns for new drugs until after health professionals have been sufficiently educated, although no details have been provided on how long a period was deemed necessary."[47] Lastly, the "Institute of Medicine called for a 2-year moratorium on DTCA for newly approved drugs in 2007, and the American Medical Association voted in favor of a ban on DTCA in 2015."[48] With that being said, no action has been taken to prohibit pharmaceutical companies from advertising new drugs with unknown safety profiles.

Media Distribution Channels

The relaxation of the FDA rules after 1997 not only affected the amount pharmaceutical companies were spending on DTC advertisements but also the media channels through which they were distributed. Figure 9 displays the spending on Direct to Consumer Advertising for prescription drugs and health services from 1997 to 2016, categorized by media distribution channels.

Figure 9. DTCA Spending by Media Distribution Channel 1997-2016[1]



Pharmaceutical companies traditionally distribute DTC ads via tv, radio, magazines, newspapers, billboards, and lastly, they are increasingly making use of the internet as an

effective dissemination channel. The two main types of advertisements this report will discuss in depth are television advertisements and internet/social media advertisements. This is because, as depicted in the previous graph, the majority of the DTCA budget is spent on television commercials, and internet/social media advertisements are proving to be one of the fastest growing components of DTCA.

Television

While the large increase in spending on TV advertisements from 1997 to 2016 coincides with a shift to more costly television commercials, it is also representative of an increase in the number of ads. During this time period, the number of television commercials increased from 72,000 to 663,0000.[1] According to Nielson, "in 2009, the pharmaceutical industry was the second largest product category by ad spending with approximately $4.5 billion in advertising expenditure, second only to the automotive industry."[44] In 2011, the average American television viewer watched as many as nine drug advertisements a day, totaling to 16 hours per year. This number far exceeds the amount of time the average American spends with a primary care physician.[40] The number of ads, and in turn, the amount of time spent by Americans viewing these ads has increased exponentially into 2019. Numerous studies have analyzed the nature of televised DTCA ads due to their increasingly pervasive nature.

Nature of Televised DTCA

Over the years, the DTCA landscape has evolved as a number of noteworthy controversies have resulted from televised DTCA. Applequist and Ball discuss some of these controversies including "the recall of Vioxx in 2004 and the revelation that ads falsely depicted the Lipitor spokesperson, Dr Jarvik, as a licensed physician."[48] This report will subsequently

discuss the details of these controversies when considering the negative ramifications of DTCA. Moreover, the authors explain that regulation has evolved as the FDA published the Amendments Act of 2007 which "required drug makers to submit television advertisements 45 days before the first airing" and additionally, the agency "drafted updated guidance to standardize the appearance of drug brand names, to clarify points regarding the fair and balanced presentation of benefit and risk information, and to specify regulatory guidelines to be applied to online advertisements."[48] Due to these significant events, the authors felt that a more updated analysis of DTC television advertisements was necessary to investigate whether these events had an effect on the content of prescription drug commercials. In turn, Applequist and Ball examined pharmaceutical advertisements that appeared on 4 major US television networks over a 13-week period in 2016.[48] After sifting through 868 DTC product claim advertisements that aired during the collection period, the authors removed duplicates and analyzed a total of 61 unique product claim advertisements for 35 prescription drug brands.[48] This report will discuss the results of this study in detail, as it appears to be the most recent and thorough analysis of current DTC television advertisements. The majority of DTC television advertisements are product-claim ads, as advertisers have recognized that the other two types (reminder and help-seeking) can be confusing and are less effective in terms of driving sales.[44] After the collection period, Applequist and Ball examined a number of different characteristics of the 2016 TV advertisements and compared their findings to commercials from a similar study conducted in 2004.

First, the authors found that while the advertisements have become 30% longer, their potential education value has declined.[48] They note that the gap between the educational and

promotional content has increased, with more emphasis on the promotional content. They revealed that the "2016 ads conveyed a greater emphasis on the reported drug benefits at the expense of information about the health condition."[48] Furthermore, they explain that fewer of the 2016 ads "provided information related to the biologic nature, risk factors or causes, or prevalence of the condition compared with the 2004 sample."[48] Additionally, the authors noted a shift in the way the advertisements describe the prevalence of the condition.[48] Rather than describe the conditional prevalence in quantitative terms (such as 1 in 4), more advertisements use qualitative descriptions such as "thousands" or "many."[48] The authors also examined the frequency with which the advertisements used rational and positive emotional appeal. They discovered that the frequency of these appeals remained consistent between the 2004 and 2016 ads, but that there was a decrease in the use of negative emotional appeals.[48] Positive appeal often involved portraying the patient's happy mood after taking the advertised medication, while negative appeal often involved portraying the patient's experience with the medical condition before taking the product.

Another characteristic the authors examined was "lifestyle portrayals." The authors revealed that, "the 2016 ads had increased portrayals of medical conditions interfering with healthy or recreational activities and of the product enabling healthy or recreational activities."[48] Additionally, they found that, "physical activity was featured in 58% of the 2016 ads, with characters shown engaging in moderate or vigorous physical activity, such as bicycling, hiking, running, or playing sports."[48] Applequist and Ball also point out that many of the advertised conditions had treatment options that involve some behavioral change, but "none of the ads offered behavioral change as an alternative to taking medication and fewer

ads in the 2016 sample presented the drug as a beneficial addition to lifestyle changes such as diet and exercise."[48]

The last characteristic of the advertisements that the authors analyze is "medication portrayals." Applequist and Ball found that almost all of the advertisements "portrayed a character regaining control as a result of obtaining a prescription drug."[48] They further explain that, "all ads that portrayed a loss of control due to the condition (59.7%) offered the drug as the solution to this negative experience."[48] Additionally, the authors note that the majority of the advertisements "associated the medication with greater social approval, often depicted by showing more friends, family, and recreational activities after a character obtained a prescription."[48] Many of the advertisements they analyzed dramatically depicted the medication as being a scientific breakthrough by using words and phrases such as "revolutionary" or "for the first time ever."[48] The last major finding in the examination of the 2016 television advertisements was that, "the portrayal of endurance increasing as a result of medication use (e.g., showing a character being able to go to work, participate in family activities, etc.) nearly doubled in the 2016 sample."[48] The authors note that this increase indicates a "further broadening of claims that the medications can help with patient's daily tasks and responsibilities."[48] This study reveals that even though regulation has evolved since 2004, the commonly cited issues pertaining to the nature of the content in pharmaceutical commercials have persisted and even grown more extreme in recent years. Proponents of DTCA emphasize the educational value, but this study unfortunately indicated that over the years the educational value of these advertisements has declined rather than increased.

A study conducted by Tsai and Lancaster additionally examined the nature of DTC television advertisements in 2012. [44] These authors applied "Taylors six-segment message strategy wheel" to analyze 96 commercials that promoted a specific branded drug in order to gain a better understanding of the message strategies typically used by pharmaceutical companies in their advertisements.[44] "Taylors six-segment message strategy wheel" is a tool that was developed in 1999 to help advertisers create effective message strategies for consumer-product advertising.[44] This model is made up of two dimensions, characterized as the "ritual view," and the "transition view."[44] Each of these views encompass three segments which are described in Exhibit 1 below.

Exhibit 1. Taylors Six Segment Strategy Wheel[44]

The ritual view encompasses three segments.

1. The ego segment: this postulates that consumer's purchase products with the aim of enhancing their self-image; products advertised emotionally appeal to the consumer's ego.
2. The social segment: this places great focus on the collective and advertises products as a means of gaining approval, affection and respect from others with emphasis placed on the need for belonging
3. The sensory segment: this draws on the consumer's five senses of taste, smell, touch, sight or hearing.[25]

The transmission view encompasses a further three segments,

1. The routine segment: this draws on the habitual nature of consumer behaviour, these types of advertisements are more for necessity products rather than luxury items.
2. The acute need segment: this is catered for those products which consumers may need abruptly and urgently and due to the limited time they may have to purchase the item, the main point of such advertisements is to ensure product quality through brand recognition or brand familiarity.
3. The ration segment: this is oriented towards advertisements for products, which are bought on special occasions, where consumers take time deliberating their choices. These advertisements work to emphasize the quality, attributes and competitive edge of products to persuade consumers to choose their products over others.

After analyzing the collection of advertisements according to this framework, the authors found that "for commercials that feature explicit product claims, the majority of the commercials adopted a combination strategy (77.2%)."[44] This combination strategy involves using the ration

and ego approaches together. The ration approach involves providing consumers with medical and drug information, while the ego approach involves "appealing to the viewer's ego-related needs and desires (i.e., pursuing personal goals without worrying about or being hindered by a medical condition) through the ad narratives and imagery."[44] The authors examined the prevalence of each of these message strategies individually, and found that "ration-based" (92.4%) was the most common approach.[44] They explained commercials utilizing the ration-based approach attempted to persuade consumers by using logic and reasoning. The concluded that overall, "the purpose of most DTC commercials appears to be about educating consumers about the medical condition and the brand being advertised."[44] The "ego-based" approach was the second most frequently used message strategy (77.2%).[44] The authors explain that "these campaigns stressed how taking the drug would make the viewer feel better about him/herself, improving their life quality, or allowing the consumers to actualize their lifestyle goals."[44] The other message strategies (social, routine, and acute-need) were less common, and sensory was the least common.[44]

eDTCA

The pharmaceutical industry's use of the internet to distribute advertisements is sometimes referred to as "eDTCA," and it is one of the fastest growing components of DTCA. In 2015, of the $4.2 billion spent on DTCA, $1.86 billion was dedicated to online DTCA.[49] This number increased to $2.02 billion in 2016.[50] Table 3 shows the changes in spending in different areas of DTCA from 2005 to 2009.

Table 3. DTCA Spending by Distribution Channel from 2005-2009[51]

DTCA category	2005 expenditure	2009 expenditure	Change (%)
Television	$3,390,587,472	$2,943,000,894	-13.20
Print media + radio + outdoor ads	$1,396,225,125	$1,403,438,560	0.52
Internet	$56,180,283	$117,403,346	108.98
Total DTCA	$4,842,992,880	$4,463,842,800	-7.83

Table1: DTCA expenditure in 2005 and in 2009 (Kornfield et al., 2015)

While estimates of the current (2020) amount that the pharmaceutical industry is spending on eDTCA were unavailable, one can only assume that the figure has increased substantially as our society has undergone a massive digital transformation. Additionally, data has revealed that searching for health-related information has become the third most common activity for internet users.[40] The 2005 study that included more than 6,000 adults found that "although the physician was still the most trusted source of information, 48.6% of the subjects went online first and then consulted their physician, whereas only 10.9% talked to their physician first."[40] Another study examined the frequency with which Americans are using the internet and social media to disclose and receive health information and found that "over 80% of young adults have disclosed health information and have sought health information at least once through a social media channel."[49] Because the majority of Americans regularly use the internet, and additionally use the internet to seek health-related information, eDTCA provides the pharmaceutical industry with a lucrative opportunity to reach millions of potential customers.

It is clear from a number of studies that pharmaceutical companies are increasingly capitalizing on this opportunity. Liang and Mackey conducted a study in 2011 to investigate the prevalence of eDTCA 2.0, which is online DTCA using interactive social media technology, for

the top 10 pharmaceutical companies. The results revealed that all 10 of the top pharmaceutical companies utilized eDTCA 2.0.[52] Additionally, they found that "80% of the pharmaceutical companies also had YouTube channels and had developed health care communication related mobile applications."[52] The study also revealed that "for the top 10 highest grossing drugs in 2009, 90% had dedicated websites and 80% have televised DTCA advertisements on YouTube and 70% have dedicated Facebook pages."[52] It is clear that pharmaceutical companies are increasingly incorporating social media channels such as Facebook, Twitter, and YouTube into their marketing strategies. In a study conducted by Tyrawski and DeAndrea in 2015, the researchers revealed that "all pharmaceutical companies, with the exception of one, had a presence on at least one social media platform."[52] This study also analyzed the type of advertisements that pharmaceutical companies were posting on social media. The researchers found that "40.7% of pharmaceutical companies posts were for help-seeking DTC advertisements, only 1.6% were drug product claims."[52] They also found that a significant proportion of consumers (23.9%) interacted with the posts by leaving comments.[52] Another study investigated how DTCA distributed through different mediums impacted the consumers intention to seek additional information. The study revealed that "eDTCA was associated with frequency to seek further information from a reliable source (i.e. a medical professional) whereas other forms, including newspaper and spam email were not associated with frequency."[52] The financial figures support these findings, indicating that eDTCA is a very effective sales technique with an ROI of 5:1.[40] With online DTCA, pharmaceutical companies are able to target consumers more effectively and reach their intended audience in ways that are not possible with print and television ads.

While eDTCA does represent a significant opportunity for the pharmaceutical industry to increase sales by connecting with consumers on platforms that are increasingly attracting a growing body of users, this new avenue of advertising may present a huge challenge for policy makers and regulatory advisors. It appears from an analysis conducted by Hyosun Kim that it already has. To shed light on the emerging issue, Kim thoroughly examined "all US Food and Drug Administration (FDA) warning letters and notices of violations issued to drug manufacturers regarding their online promotional activities to consumers over the 10-year period spanning 2005 to 2014."[49] In total, Kim examined 73 citations, and found that "nearly half were in reference to a company-controlled webpage or website. A fourth of the letters concerned paid advertisements in the form of sponsored links or banner ads. Just two of the letters referred to social media messages, both of which regarded Facebook use."[49] Additionally, she examined the nature of the complaints and found that "the common theme within the body of letters regarded information quality; lack of risk information and mischaracterized efficacy information were the most prevalent allegations, followed by incomplete product names and insufficient ingredient information."[49] Continued regulation of eDTCA is extremely important in order to ensure that the information being distributed is accurate and balanced, even more so, as it appears that consumers place more trust in the information they find online than any other form of advertisement. According to Carpentier, "Consumers who actively seek out online health information tend to believe the information to be credible, irrespective of whether a medical expert has actually authored the information."[49] The author continues to explain that, "unlike their perceptions of other methods of DTCA, consumers are less skeptical of online information." [49] Because the use of the internet and

social media to disseminate pharmaceutical ads is so new, the FDA is having to re-evaluate and update regulations. In June of 2014, the FDA released a report focusing on Twitter and issued requirements for pharmaceutical promotional posts on the platform. The report indicated that, "a company may embed a direct link within a message that directs a user to additional information about the product. However, in the initial message and in the linked information, risk information must be complete and be afforded the same prominence as benefit information. Furthermore, all information and links must be branded."[49] It seems as though the FDA will need to continue to update and add regulations as pharmaceutical companies continue to grow their presence on these platforms, and additionally as new platforms evolve.

Carpentier additionally discusses the emerging issue of "un-branded" social media advertisements.[49] Un-branded social media advertisements are user-generated posts that are sometimes paid for directly by pharmaceutical companies while other times they are organic. The author note that these types of advertisements are "particularly problematic for both consumers and regulators, as these messages often appear to be word-of-mouth information offered by a fellow layperson."[49] This article gave the example of Kim Kardashian's paid endorsement on Instagram of a morning sickness drug (Diclegis). This advertisement received a lot of criticism and backlash, and on August 7, 2015, the FDA sent Duchesnay, Inc, the manufacturer of the product, a warning letter.[49] The article forecasts that the pharmaceutical industry's use of un-branded promotional content will increase in coming years, as consumers place a higher level of trust in un-branded versus branded content, and it will serve as an effective technique to attract users to the companies' branded information.[49] The distribution of un-branded pharmaceutical promotional content will require stringent regulation, as user-

generated social media content has extreme potential to spread misinformation and encourage misuse. In relation to this issue, the FDA issued a draft guidance on third party misinformation in 2014, and stated that pharmaceutical companies will not be held responsible for user-generated content, but the closer the company is to the creation of the advertisement, the greater their responsibility.[49] As Americans are using the internet and social media hour-to-hour of every day, they are consuming more pharmaceutical advertisements than ever before, so it is particularly important to examine the nature of these ads and the messages they are conveying.

Arguments for DTCA

In order to develop an informed opinion on the topic of DTCA, it is important to understand the arguments of those individuals on both sides of the controversy. Given the fact that the United States and New Zealand are the only countries who allow product specific DTCA, one might believe that the majority of the world is opposed to DTCA, but in reality, the debate is quite balanced. This report will thoroughly discuss the arguments of both sides and present corresponding evidence that exists to validate each claim.

The most commonly cited argument of those in favor of DTCA is that the advertisements provide consumers with further education about their healthcare options and encourage them to take a more active role in their healthcare journey.[40,53,54] Proponents claim that DTCA gives consumers access to a much wider variety of sources for health-information and treatment options, rather than having to rely solely on their health care providers. There has been no evidence to reveal whether health care consumers have become more informed or empowered since the emergence of DTCA. With that being said, it does appear that more Americans are

actively seeking health-related information, as data from a 2011 article revealed that searching for health-related information was the third most common activity among internet users.[40] Additionally, the *Journal of Consumer Marketing* conducted a survey of 300 patients in 2005, and 59% of the respondents admitted that they felt the practice of DTCA is potentially a good thing because it offers them empowerment.[53]

Next, DTCA proponents argue that the advertisements encourage patients to initiate conversations with their physicians about medical concerns. In support of this claim, a "2004 FDA consumer survey found that exposure to DTCA prompted 27% of Americans to make an appointment with their doctor to talk about a condition they had not previously discussed."[40] Ventola also noted that the majority of physicians agree with this statement, as the FDA survey further revealed that "53% of physicians said DTCA led to better discussion with patients and 73% believed that consumer drug advertising helped patients ask more thoughtful questions."[40] Other physicians hold different opinions about the effect of DTCA on their conversations with patients. These opinions are cited in the arguments against DTCA and will be discussed later in this report.

In relation to this argument, many claim that DTCA reduces underdiagnosis and undertreatment, as the advertisements increase the probability of consumers recognizing that they potentially have a treatable disease.[40,53,54] They claim that consumers with immediate, direct access to health information are more likely to reach out their physicians. The evidence from the 2004 FDA study supported this argument, revealing that "88% of patients who had inquired about a medication in response to a drug ad had a condition that the drug treated."[40] A study by Harvard University/Massachusetts General Hospital and Harris Interactive also

revealed evidence validating this argument. They found that "25% of patients who visited their doctor after seeing DTCPA received a new diagnosis; of these, 43% were considered to have a high-priority health condition."[40] Opponents of DTCA cite similar evidence, but feel that these advertisements increase overdiagnosis rather than reduce underdiagnosis. This argument will be subsequently in this report.

DTCA proponents additionally argue that DTCA reduces underdiagnosis by reducing stigma associated with the advertised disease.[40,54] Many DTCA advertisements are for drugs that treat health conditions that could be embarrassing to a patient, such as depression or erectile dysfunction. Many claim that advertising these diseases reduces the surrounding stigma by raising awareness. Reducing the embarrassment associated with the disease increases the likelihood of consumers reaching out to their doctors and getting treatment.

Lastly, many individuals argue that DTCA increases patient compliance, which is the degree to which patients follow medical advice. According to Ventola, the "data consistently show that small, but statistically significant, improvements in adherence occur among patients exposed to DTCPA."[40] Many believe that this is because DTC advertisements act as reminders to patients about their medical conditions or prescriptions. Additionally, individuals claim that the advertisements reinforce physicians' recommendations as patients feel more confident about the treatment option after they have requested their own treatment.[55] A number of studies have supported this claim including the 2004 FDA study which revealed that "33% of physicians reported that DTCPA increased patient adherence."[40] Additionally, a study by Harvard University/Massachusetts General Hospital and Harris Interactive indicated that 46% of physicians felt that DTCA increased patient adherence.[40] It must be noted that these studies

only indicated doctors' opinions of patient adherence. There have been no conclusive studies on patients to reveal whether DTCA truly increases compliance.

Arguments against DTCA

Over the years, a number of individuals, including the FDA and prominent medical societies, have become increasingly critical of the pharmaceutical industry's DTC advertising tactics. The complaints particularly intensified after the DTC advertising campaigns of three pharmaceutical giants raised considerable ethical concern. These campaigns included "Pfizer's Lipitor ads featuring Mr. Robert Jarvik, Merck & Schering-Plough's 'Food and Family' ads for Vytorin, and Johnson & Johnson's "cancer fatigue" ads for Procrit."[9] Pfizer's 2008 Lipitor DTC advertising campaign featured a series of television commercials portraying Robert Jarvik as a licensed physician, when in reality he had no license to practice or prescribe medicine.[48] Additionally, in the commercials, Robert Jarvik claimed to personally take Lipitor, but subsequent investigation revealed that he did not take the drug until months after the commercials began filming.[9] Merck & Schering-Plough's "Food and Family" DTC advertising campaign for Vytorin involved the advertising of the product as an effective treatment for reducing cholesterol.[9] Investigation shed light on studies that indicated the drug had no effect on cholesterol levels.[9] Additionally, investigation revealed that the pharmaceutical manufacturer, Mecrk & Schering-Plough, was aware of these studies but suppressed the results for two years and continued their DTC marketing campaigns.[9] The last controversial DTC campaign involved Johnson & Johnson marketing Procrit for uses that were unapproved by the FDA. "Procrit was approved to treat chemotherapy and dialysis-induced anemia, but Johnson &

Johnson marketed it as a way to improve patients' quality of life."[9] Incidents like this have created a number of DTCA critics who claim that the sole purpose of DTCA is to drive sales and that the advertisements create more harm to patients than good. This report will subsequently discuss the negative ramifications of DTCA proposed by critics and cite the evidence supporting these claims.

One of the most common complaints about the practice of DTCA is its potential to confuse and misinform patients. The ability to diagnose a disease and identify the best course of action when treating that disease is a complex, difficult skill that doctors acquire through years of medical school, training, and practice. Potential issues arise when pharmaceutical companies encourage consumers to take on this role when there is a high likelihood that they lack the skills necessary to evaluate comprehensive medical information. Ventola notes that the content in DTC advertisements "often exceeds the eighth-grade reading level, which is typically recommended for information distributed to the general public."[40] While consumers may not fully understand the information presented in the advertisements, studies have revealed that they place an unwarranted amount of trust in them. One survey of patients revealed that "50% of respondents thought that the ads were approved by the government, 43% thought that a medication had to be completely safe for it to be advertised; and 22% thought that a drug known to have serious side effects could not be advertised."[40] With all of this being said, it is particularly concerning that many of the advertisements omit important information. One study revealed that, "82% of DTCPA ads made some factual claims and rational arguments for use of the advertised drug; however, only 26% of the ads described risk factors or causes of the condition, and only 25% mentioned prevalence."[40] Additional studies have revealed that

doctors agree that DTCA is not as educational as it should be and can cause misunderstanding among patients. According to an FDA survey, “75 percent of physicians surveyed believe that DTC ads cause patients to think that [a] drug is more effective than it truly is.”[9] The FDA survey also revealed that while “53% of physicians said DTC ads lead to "[b]etter discussion[s] with patients,” only 10% of those physicians believe that the advertisements had an educational or informational component for patients.[9] The authors of a *ScienceDirect* article discussed a report published by Aiken and colleagues that asked doctors about patients’ understanding of medicines presented in DTC advertisements.[52] The report revealed that “whilst 78% stated that they believed that the patient understood the benefits of the medication, only 40% believed that patients understood the risks and potential problems with the medications. Furthermore, 30% believed that patients understood drug efficacy information and 25% understood the type of people who should avoid this drug.”[52]

The fact that many DTC advertisements overemphasize benefits and minimize risk is a commonly cited argument against DTCA. From 1997 to 2006, nearly 84% of the regulatory letters for DTCPA cited ads for either minimizing risks (e.g., omitting information about side effects) or exaggerating a drug’s effectiveness (e.g., portraying the indication too broadly or making unsubstantiated claims of superiority over other drugs), or both.”[40] The risk portion the advertisements are often overlooked or ignored by consumers because they are generally displayed in very small print or recited very quickly at the end of a television commercial. Additionally, many advertisements make use of pleasant visual imagery while the narrator lists the serious side effects. According to Ventola, “research has shown that when visual and verbal messages are discordant, visual messages tend to predominate, which can result in insufficient

processing of verbally presented risk information."[40] Patients themselves have expressed concern about the lack of information about risks presented in the commercials. Friedman and Gould conducted a survey of 300 patients in 2005 to assess consumers perceptions of DTCA, and 46% of respondents agreed strongly that advertisements do not give enough information about the possible risks and negative side effects of using the drug and 23% agreed somewhat.[53] Evidence has shown that the majority of consumers don't have the expertise necessary to comprehensively evaluate the medical information presented in DTC advertisements, especially when deceptive techniques are used to minimize risk information. Encouraging consumers to take on this role and use the presented information to make their own health-care decisions causes a number of potential issues.

One of these potential issues is that DTCA puts strain on the doctor-patient relationship. When patients go into their doctors' offices and request a specific medication after seeing a DTC advertisement, it puts the physicians in an uncomfortable situation where they have to balance their desire to satisfy their patient with their obligation to uphold their expert medical opinion. According to a national survey cited by Ventola, "39% of physicians and 30% of patients felt that DTCPA interfered with the physician–patient relationship."[40] This negative impact has been well-documented. Ventola explains that "denial of a prescription request has been shown to decrease patient satisfaction and increase physician switching."[40] To support this claim, he cites a study that revealed that, "nearly half of the patients reported feeling disappointed about not receiving a requested medication. One-quarter of the patients said they would try to change their physician's mind or get the drug elsewhere, and 15% said they were considering switching physicians."[40] Many studies have revealed that doctors find it very

frustrating and challenging to convince patients of their medical opinion that contradicts with "evidence" the patients bring in from a DTC advertisement.[40] Because of these reasons, many doctors feel pressured to prescribe drugs requested on the basis of DTC advertisements. According to an FDA survey, "eight percent of physicians felt very pressured and 20 percent felt somewhat pressured to prescribe the specific brand name drug when the patient asked the physician to do so."[45]

When physicians feel pressured to prescribe medication requested by their patients, it may lead to inappropriate prescribing. This is another commonly cited argument of DTCA opponents. The authors of a *BMJ* article discussed a study that examined the impact of DTCA in the US compared with Canada by surveying patients and physicians.[46] The results revealed that, "patients in the US were more likely to request DTCA drugs, and physicians in both settings were more likely to acquiesce to these requests despite feeling ambivalent about the drug that was prescribed."[46] Additionally, "those who requested a specific DTCA drug were 16 times more likely to receive a drug than those who did not request a specific drug."[46] While this study did not address whether the prescriptions written were appropriate treatment options for particular patients' illnesses, it is clear that patient requests for DTCA drugs have the ability to encourage physicians to write prescriptions, in spite of potential uncertainty. Additionally, critics believe that DTCA can cause inappropriate prescribing because it may encourage consumers to "withhold information to fit a particular profile that they saw in DTC ads in an attempt to get the doctor to prescribe a drug they want but that might not be appropriate for them."[40] Only doctors have the knowledge and experience to make the difficult decision regarding diagnosis and treatment, and it is important that consumers continue to trust their

physicians to make the ultimate judgment, regardless of the information they find in pharmaceutical advertisements.

The next widely discussed complaint about the practice of DTCA has to do with the timing of DTCA campaigns which this report previously discussed in the section on timing and trends. As mentioned earlier, the majority of DTC advertisements are published or aired within a year after FDA approval. According to Ventola, "clinical trials required for FDA approval are typically not designed to detect rare adverse effects, and current methods of postmarketing surveillance often fail to connect adverse events that have a high rate of background prevalence with the use of a particular drug."[40] Thus, the safety profile of a majority of the drugs being advertised is not fully known. One of the most commonly cited examples pertaining to this issue is the recall of Vioxx in 2004. From 1999 to 2004, Vioxx was one of the most heavily promoted pharmaceuticals, and during that time, the product manufacturer, Merck, spent over $100 million per year on marketing. Vioxx was used to treat osteoarthritis and widely prescribed among physicians.[9] An internal study conducted by Merck revealed that patients who took Vioxx had a five times increased risk of heart attack.[9] After withholding the data for years and sacrificing the lives of patients for profit, Merck voluntarily withdrew the product from the market on September 30, 2004.[9] The case of Vioxx is not unique. According to Ventola, "Other drugs that were heavily promoted to consumers have also been linked to safety advisories, FDA black-box warnings, and withdrawals from the market. These include benoxaprofen (Oraflex, Eli Lilly) for arthritis, troglitazone (Rezulin, Parke-Davis) for diabetes, cisapride (Propulsid, Janssen) for gastric reflux, cerivastatin (Baycol, Bayer) for high cholesterol, and tegaserod (Zelnorm, Novartis) for irritable bowel syndrome in women."[40] As this report

mentions previously, a number of parties within the medical community have come forward and called for regulation of the pharmaceutical industry's ability to market their products before their full safety profiles are known. Yet, no significant action has been taken to delay advertising for new products.

Additionally, a large amount of literature has discussed the "me-too" drug phenomenon. Critics argue that the pharmaceutical industry uses DTCA to promote expensive "copy-cat" drugs that might not offer any significant benefit over older, cheaper medication.[40] Connors notes that there is no universal definition of disease, and because of this, "manufacturers are free to 'sell expensive drugs with marginal benefits over older' and cheaper versions."[9] These drugs have been called "me-too" drugs. According to *The Truth about Drug Companies* from 1998 to 2002, "415 new drugs were approved by the Food and Drug Administration (FDA), of which only 14 percent were truly innovative. A further 9 percent were old drugs that had been changed in some way that made them, in the FDA's view, significant improvements."[4] Angell continues to explain that the remaining 77% were all me-too drugs, that were classified by the FDA "as being no better than drugs already on the market to treat the same condition."[4] Some of these me-too drugs had slightly different chemical compositions but the majority of them did not. The author explains that the manufacturing of these type of drugs is made possible by the fact that the FDA only requires that pharmaceutical companies show that the new drugs are "effective," not "more effective" than other existed drugs being used to treat the same condition.[4] Ventola gives specific examples of the promotion of expensive "me-too" drugs, explaining that "two heavily promoted diabetes treatments, rosiglitazone (Avandia, GlaxoSmithKline) and pioglitazone (Actos, Takeda), were found to be no

more effective—or safe—than older drugs, even though they were much more expensive."[40] Because the process of bringing a completely new drug to market is so costly and time-consuming and the probability of successfully developing a new drug is so rare, many pharmaceutical companies turn to "me-too" drugs to grow their profits.

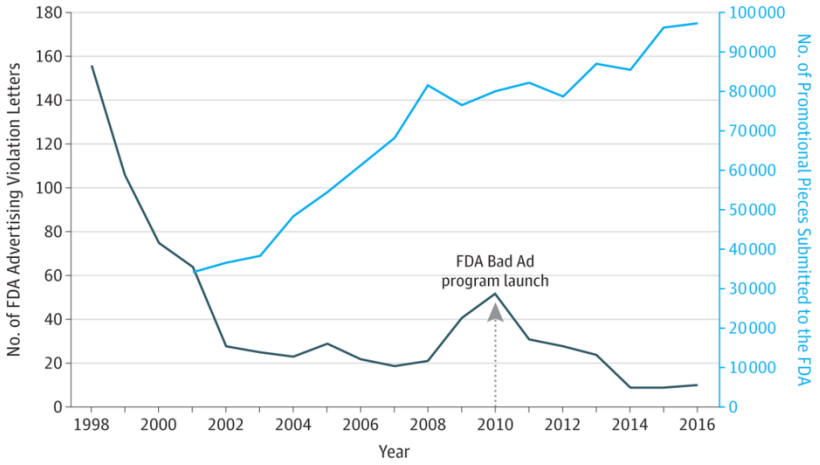
The last major argument used in the case against DTCA is the idea that the pharmaceutical industry is using these advertisements to "manufacture diseases." Some refer to this practice as "disease mongering" and define it as the "phenomenon wherein drug developers create a new disease state as part of a carefully planned marketing campaign to sell their latest drug of choice."[52] In less extreme terms, many claim that the pharmaceutical industry uses DTCA to "reframe and medicalize human traits to create a need for the drug."[26] Before seeing these advertisements, patients may view their conditions a natural, trivial ailments that are inherent to the human condition. Pharmaceutical companies market these commonly experienced ailments as "conditions" or "diseases" that can be treated with their products in order to create markets which did not previously exist and drive demand. Connors additionally discusses this issue, and refers to this tactic as the targeting of "lifestyle diseases" in order to "widen their productivity net."[9] A large volume of literature exists on this issue, and a number of authors cite a variety of examples of the pharmaceutical practice of "disease manufacturing." Both Connors and Ventola use the example of erectile dysfunction (ED) drugs which target men who may experience normal variations in sexual performance.[9,40] According to both of these authors, "only 10% of American men experience total inability to achieve an erection."[40] Therefore, many of the men who take ED drugs may actually be experiencing "normal" issues, but are using the drug to treat a "socially-constructed" disease. Connors also

notes that the more anxiety pharmaceutical companies can create in their advertisements of ED, the larger the market, as worrying about ED may in fact cause ED.[9] In this discussion, Connors also used the advertisement of Paxil as an example of the pharmaceutical company GlaxoSmithKline (GSK) marketing a "lifestyle disease."[9] Paxil was an antidepressant used to treat social phobia, a disease that affected only a small percent of the population. Connors explains that, "GSK extended the definition of social phobia to include 'shyness' and played upon people's fears in order to enlarge its market. Only a month after 9/11, GSK aired 'an advertisement of a woman walking on a crowded street, her face strained, in a crowd otherwise blurred. The caption read '[m]illions suffer from chronic anxiety. Millions could be helped.'"[9] The author discusses the notion that this advertisement took advantage of the fear felt by the entire US population after the 9/11 attacks, and tried to convince consumers that this fear and additionally their potential shyness could be treated with Paxil. Authors list a number of other drugs that have been marketed to treat natural or trivial conditions such as bladder medication (Detrol), baldness medication (Rogaine and Propecia), low testosterone medication, and more.[9,26,40,46] Many feel that the practice of "disease manufacturing" exacerbates unhappiness about normal experiences and has created an over-medicated society. From 2000 to 2012, the proportion of Americans taking five or more medications nearly doubled, jumping from 8.2% to 15%.[57] The United States holds the position of the most medicated country in the world, but whether this is caused by the practice of disease manufacturing remains unclear. Additionally, many feel that the development of drugs to treat natural, trivial conditions is time wasted not spent on developing drugs to treat more serious, life-threatening conditions.

A Call for More Stringent Regulation

Given all of the previously discussed negative ramifications of DTCA, a number of individuals have called for increased regulation of the pharmaceutical marketing practice. Despite the growing number of complaints, the FDA has done little to heighten the requirements for DTCA. Not only do people feel that there is not enough regulation in place, but they also feel that the FDA is doing an insufficient job of enforcing the current regulation. As mentioned previously in this report, pharmaceutical companies must submit their advertisements to the agency before airing or publishing, but they do not have to obtain official approval before doing so. If the FDA finds that a DTC pharmaceutical advertisement violates the rules set forth, they respond by issuing violation letters, which are no more than a warning. This regulatory process is supposed to protect consumers and hold drug companies accountable for the information they distribute. But are they really being held accountable? As the number of DTC advertisements has increased exponentially in recent years, one would logically expect that the number of violation letters would increase as well. But this isn't the case. From 1997 to 2016, number of DTC advertisements increased from 79,000 to 4.6 million ads while the number of letters of violation issued fell from 142 to 11.[56] Figure 10, taken from *Medical Marketing in the United States*, illustrates this trend.

Figure 10. FDA Prescription Drug Advertising Violation Letters and Promotional Materials Submitted to the FDA[1]



A study from *The New England Journal of Medicine* examined these violation letters from 1997 to 2006.[47] During this period, they found that the proportion of violation letters citing problems with Direct to Consumer Advertisements increased from 15.5% to 33.3%.[47] Additionally, they revealed that "nearly 84% of regulatory letters regarding direct-to-consumer advertising cited advertisements for either minimizing risks (e.g., minimizing or omitting information on side effects), exaggerating effectiveness (e.g., portraying the indication too broadly or making unsubstantiated claims of superiority over other drugs), or both."[47]

One argument might be that pharmaceutical industry compliance with regulations has increased over the years, but many believe that the enormous overflow of DTC advertisements has led to worsening FDA oversight. The authors of *The New England Journal of Medicine* article discuss possible reasons for the weakening of advertising regulations. They note that "in 2002 the Secretary of Health and Human Services began requiring that all draft FDA regulatory

letters, including letters related to advertising violations, be reviewed and approved by the FDA's Office of Chief Counsel before they are issued."[47] A report prepared by the U.S. Government Accountability office revealed that "this legal review has led to a reduction in the number of letters issued, as well as to delays such that FDA warning letters are frequently sent out long after the false or misleading advertising campaign has run its course."[47] These authors additionally note that the number of FDA officials responsible for reviewing DTCA has remained stable over the years as the number of advertisements have grown exponentially and speculate that a shortage of staff may be contributing to worsening oversight.[47] Lastly the authors note that "the proportion of broadcast advertisements that underwent FDA review before airing declined from 64% in 1999 to only 32% in 2004."[47] They argue that this evidence supports their hypothesis that staffing has not kept pace with the growing number of advertisements, leading to a decrease in review.

Regardless of the arguments for or against DTCA, advertisements for prescription medication have the potential to impact the consumers health and well-being and should be carefully reviewed and strictly regulated. The numbers are clear—regulatory action taken by the FDA regarding pharmaceutical marketing of prescription drugs has dramatically declined in recent years. This is particularly concerning when considering the evidence presented in numerous studies that indicates DTCA advertisements are continuing to present confusing and misleading information and minimize risks. The growing number of advertisements should not present an excuse for more laxed regulation, but rather a need more heightened oversight than ever before.

Part IV: DTPP and DTCA

While multiple studies have examined the impact of DTPP and DTCA individually, fewer studies have examined the impact of using both DTPP and DTCA together to market a pharmaceutical product. It appears that DTPP in itself is more effective in driving prescription sales than DTCA, but employing DTCA in combination with DTPP can further drive sales. In a 2014 article from the *National Bureau of Economic Research*, Datta and Dave discuss a study that examined interactions between marketing elements.[17] The study was conducted by Narayanan, Desiraju, and Chintagunta who utilized monthly data on three branded second generation anti-histamines from 1993-2002.[17] The researchers found that "detailing primarily and positively affects brand share, whereas DTCA has a significant positive effect on both brand shares and class sales."[17] They also found that DTPP generates a much larger ROI than DTCA, and explained that this was most likely due to the fact that DTPP is much more targeted. This study also revealed "synergy" between the two marketing tactics. Datta and Dave note that "a sales call to a physician's office has a higher marginal impact on brand share when combined with DTCA."[17] After a comprehensive literature search, I was unable to find additional studies that examined the impact of combining DTPP and DTCA for a particular pharmaceutical product, but it seems reasonable to postulate that utilizing these two individually powerful techniques together would be effective. DTCA encourages consumers to see their doctors and request the advertised medication, and DTPP employs detailing, sampling, and other tactics to encourage and incentivize physicians to acquiesce to those patient requests. The pharmaceutical industry has discovered how to effectively advertise to all of the parties involved in the sale of prescription medication, both on the demand and the supply side.

Conclusion

While pharmaceutical companies are in the business of developing life-saving drugs, they are also in the business of making money. The market for pharmaceuticals is worth over a trillion dollars. The massive success of the pharmaceutical industry cannot be simply attributed to the inherent demand for their products. Through marketing, the pharmaceutical industry has conditioned both physicians and patients to believe that their products are the answer to any and all ailments. America has become the most medicated country in the world, and while there are likely a number of different reasons for this, pharmaceutical marketing plays a major role.

This report describes in detail the marketing activities used by pharmaceutical companies to target both physicians and consumers directly. The most influential DTPP activities appear to be detailing, sampling, and "educational" activities. All of these promotional efforts share the underlying aim of creating favorable, reciprocal relationships between the industry and physicians. DTCA appears to be primarily distributed through television and increasingly online. Consumer targeted ads have proven to be highly effective in encouraging viewers (and readers) to request the advertised medication from their doctors. All of these activities, both individually and in combination, appear to have a significant influence on both physician and consumer behavior and result in a considerable increase in prescription sales. The pharmaceutical industry asserts that DTPP and DTCA create a number of benefits for both physicians and patients, but over the years, doctors, patients, and organizations within the medical community have grown increasingly concerned about the ethicality of industry influence. This report describes both the positive and negative impacts of pharmaceutical

promotion, but after conducting a comprehensive analysis of literature on the subject, the present nature of the practice may be creating more harm than good.

While there are many issues with the current practice of pharmaceutical marketing, it should not be considered as "evil." Pharmaceutical marketing has a number of positive impacts. Physicians and patients benefit from increased access to information about health conditions and treatment options. However, given the evidence presented in the large volume of literature written on the negative ramifications of pharmaceutical marketing, it is clear that the current nature of the practice is flawed. It is May of the year 2020, and we are living in unprecedented times. Our world is in the midst of a pandemic as the coronavirus outbreak began just four months ago. As of April 21, 2020, 2.5 million people throughout the world have been diagnosed with a never-before-seen virus, and 171,718 of those people have lost their lives.[59] The health of not only our nation, but the world has never been more at risk and in need of life-saving pharmaceutical efforts. Now, more than ever there is a need to reevaluate the business practices of the pharmaceutical industry. It is not necessary for doctors to be flown to Hawaii to learn about the latest advances in medicine, and patient's do not need to be distracted with charming visuals while listening to serious risk information associated with their potential treatment option. The world is in need of life-saving medication and education about treatment options stripped of the biased frills interwoven into pharmaceutical promotional content. Patient care must be prioritized over profit and education must be prioritized over promotion.

REFERENCES

1. Schwartz LM, Woloshin S. Medical Marketing in the United States, 1997-2016. *JAMA*. 2019;321(1):80. doi:10.1001/jama.2018.19320.
2. Carr T. Too Many Meds? America's Love Affair with Prescription Medication. *Consumer Reports*. https://www.consumerreports.org/prescription-drugs/too-many-meds-americas-love-affair-with-prescription-medication/. Published August 3, 2017. Accessed March 23, 2020.
3. Emanuel EJ. Big Pharma's Go-To Defense of Soaring Drug Prices Doesn't Add Up. *The Atlantic*. https://www.theatlantic.com/health/archive/2019/03/drug-prices-high-cost-research-and-development/585253/. Published March 23, 2019. Accessed March 18, 2020.
4. Angell M. *The Truth About the Drug Companies: How They Deceive Us and What to Do About It*. Melbourne: Scribe; 2006.
5. Tamimi NA, Ellis P. Drug Development: From Concept to Marketing! *Nephron Clinical Practice*. 2009;113(3):c125-c131. doi:10.1159/000232592.
6. Pharma R&D Annual Review 2019. Pharmaprojects. https://pharmaintelligence.informa.com/~/media/informa-shop-window/pharma/2019/files/whitepapers/pharma-rd-review-2019-whitepaper.pdf. Published February 2019. Accessed April 1, 2020.
7. Anderson R. Pharmaceutical Industry Gets High on Fat Profits. BBC News. https://www.bbc.com/news/business-28212223. Published November 6, 2014. Accessed March 23, 2020.
8. Gagnon M-A, Lexchin J. The Cost of Pushing Pills: A New Estimate of Pharmaceutical Promotion Expenditures in the United States. *PLoS Medicine*. 2008;5(1). doi:10.1371/journal.pmed.0050001.
9. Connors AL. Big Bad Pharma: An Ethical Analysis of Physician-directed and Consumer-directed Marketing Tactics. *Albany Law Review*. 2009;73(1):243-282.
10. Persuading the Prescribers: Pharmaceutical Industry Marketing and its Influence on Physicians and Patients. The Pew Charitable Trusts. https://www.pewtrusts.org/en/research-and-analysis/fact-sheets/2013/11/11/persuading-the-prescribers-pharmaceutical-industry-marketing-and-its-influence-on-physicians-and-patients. Published November 11, 2013. Accessed March 23, 2020.
11. Wazana A. Physicians and the Pharmaceutical Industry: Is a Gift Ever Just a Gift? *Obstetrical & Gynecological Survey*. 2000;55(8):483-484. doi:10.1097/00006254-200008000-00012.
12. Agrawal S, Brennan N, Budetti P. The Sunshine Act — Effects on Physicians. *New England Journal of Medicine*. 2013;368(22):2054-2057. doi:10.1056/nejmp1303523.
13. Marwah U, Huettenmoser D, Patel S. Prescription Drug Advertising and Promotion Regulations and Enforcement in Select Global Markets. Food and Drug Law Institute (FDLI). https://www.fdli.org/2017/08/prescription-drug-advertising-promotion-regulations-enforcement-select-global-markets/. Published February 26, 2018. Accessed March 23, 2020.

14. Richardson E. The Physician Payments Sunshine Act. The Physician Payments Sunshine Act | *Health Affairs*. https://www.healthaffairs.org/do/10.1377/hpb20141002.272302/full/. Published October 2, 2014. Accessed March 23, 2020.
15. Fugh-Berman A, Ahari S. Following the Script: How Drug Reps Make Friends and Influence Doctors. *PLoS Medicine*. 2007;4(4). doi:10.1371/journal.pmed.0040150.
16. Winston Burton. 2018 Pharmaceutical Sales Salary Report. PhRMA. https://www.pharmaopportunities.com/articles/pharmaceutical-sales-salary-report. Published July 30, 2018. Accessed March 23, 2020.
17. Datta A, Dave D. Effects of Physician-Directed Pharmaceutical Promotion on Prescription Behaviors: Longitudinal Evidence. *Health Economics*. 2014;26. doi:10.3386/w19592.
18. Fickweiler F, Fickweiler W, Urbach E. Interactions between Physicians and the Pharmaceutical Industry Generally and Sales Representatives Specifically and Their Association with Physicians' Attitudes and Prescribing Habits: A Systematic Review. *BMJ Open*. 2017;7(9). doi:10.1136/bmjopen-2017-016408.
19. Manchanda P, Honka E. The Effects and Role of Direct-to-Physician Marketing in the Pharmaceutical Industry: An Integrative Review. *Yale Journal of Health Policy, Law, and Ethics*. 2005;5(2). https://digitalcommons.law.yale.edu/yjhple/vol5/iss2/8/?utm_source=digitalcommons.law.yale.edu/yjhple/vol5/iss2/8&utm_medium=PDF&utm_campaign=PDFCoverPages.
20. Ahari S. Here's How Pharma Companies Pushed Opioids When I Was a Drug Rep. *The Eagle*. https://www.theeagle.com/opinion/columnists/here-s-how-pharma-companies-pushed-opioids-when-i-was/article_34ee7710-8edf-508d-93fd-035b8df380fb.html. Published November 26, 2019. Accessed March 23, 2020.
21. Mello MM, Messing NA. Restrictions on the Use of Prescribing Data for Drug Promotion. *New England Journal of Medicine*. 2011;365(13):1248-1254. doi:10.1056/nejmhle1107678.
22. Brennan TA, Rothman DJ, Blank L, et al. Health Industry Practices That Create Conflicts of Interest: A Policy Proposal for Academic Medical Centers. *JAMA*. 2006;295(4):429-433. doi:10.1001/jama.295.4.429.
23. Spurling GK, Mansfield PR, Montgomery BD, et al. Information from Pharmaceutical Companies and the Quality, Quantity, and Cost of Physicians Prescribing: A Systematic Review. *PLoS Medicine*. 2010;7(10). doi:10.1371/journal.pmed.1000352.
24. Chimonas S, Kassirer JP. No More Free Drug Samples? *PLoS Medicine*. 2009;6(5). doi:10.1371/journal.pmed.1000074.
25. Lahey T. The High Costs of "Free" Drug Samples. *Clinical and Translational Gastroenterology* . 2014;5(12). doi:10.1038/ctg.2014.16.
26. Kessel M. Restoring the Pharmaceutical Industry's Reputation. *Nature Biotechnology* . 2014;32:983-990. doi:https://doi.org/10.1038/nbt.3036.
27. Ornstein C. Doctors Dine on Drug Companies' Dime. ProPublica. https://www.propublica.org/article/doctors-dine-on-drug-companies-dime. Published September 7, 2011. Accessed March 23, 2020.

28. Ornstein C, Nguyen D, Weber T. Piercing the Veil, More Drug Companies Reveal Payments to Doctors. ProPublica. https://www.propublica.org/article/piercing-the-veil-more-drug-companies-reveal-payments-to-doctors. Published September 7, 2011. Accessed March 23, 2020.
29. Schofferman J. Industry-Funded Continuing Medical Education: The Potential for Bias. *Pain Medicine*. 2015;16(7):1252-1253. doi:10.1111/pme.12828_1.
30. Kerridge I. Pharmaceutical Industry Support for Continuing Medical Education: Is It Time to Disengage? *Journal of Pediatrics and Child Health*. 2011;47(10):690-692. doi:10.1111/j.1440-1754.2011.02191.x.
31. Goold S, Campbell E. Industry Support of Continuing Medical Education: Evidence and Arguments. *The Hastings Center Report*. 2008;38. doi:10.1353/hcr.0.0084.
32. Sitthikul NC. Senate Finance Committee Releases Report on Drug Industry CME Grants. FDA Law Blog. http://www.fdalawblog.net/2007/05/senate_finance_/ Published May 8, 2007. Accessed March 23, 2020.
33. Sullivan T. Future Directions in Industry Funding of Continuing Medical Education or A Rejection of Innovation? Policy & Medicine. https://www.policymed.com/2011/02/future-directions-in-industry-funding-of-continuing-medical-education-or-a-rejection-of-innovation.html. Published May 5, 2018. Accessed March 23, 2020.
34. Marco CA, Moskop JC, Solomon RC, Geiderman JM, Larkin GL. Gifts to Physicians from the Pharmaceutical Industry: An Ethical Analysis. *Annals of Emergency Medicine*. 2006;48(5):513-521. doi:10.1016/j.annemergmed.2005.12.013.
35. Austad KE, Avorn J, Franklin JM, Kowal MK, Campbell EG, Kesselheim AS. Changing Interactions Between Physician Trainees and the Pharmaceutical Industry: A National Survey. *Journal of General Internal Medicine*. 2013;28(8):1064-1071. doi:10.1007/s11606-013-2361-0.
36. Sinha MS, Kesselheim AS, Darrow JJ. Pharmaceutical Advertising in Medical Journals. *Chest*. 2018;153(1):9-11. doi:10.1016/j.chest.2017.09.048.
37. Fugh-Berman A, Alladin K, Chow J. Advertising in Medical Journals: Should Current Practices Change? *PLoS Medicine*. 2006;3(6). doi:10.1371/journal.pmed.0030130.
38. Wilkes MS, Doblin BH, Shapiro MF. Pharmaceutical Advertisements in Leading Medical Journals: Experts Assessments. *Annals of Internal Medicine*. 1992;116(11):912. doi:10.7326/0003-4819-116-11-912.
39. Cardarelli R, Licciardone JC, Taylor LG. A Cross-sectional Evidence-based Review of Pharmaceutical Promotional Marketing Brochures and Their Underlying Studies: Is What They Tell Us Important and True? *BMC Family Practice*. 2006;7(1). doi:10.1186/1471-2296-7-13.
40. Ventola CL. Direct-to-Consumer Pharmaceutical Advertising: Therapeutic or Toxic? *P T*. 2011;36(10):669–684.
41. Basics of Drug Ads. U.S. Food and Drug Administration. https://www.fda.gov/drugs/prescription-drug-advertising/basics-drug-ads. Published June 19, 2015. Accessed March 23, 2020.
42. American College of Physicians. Direct-to-Consumer Prescription Drug Advertising. Philadelphia: American College of Physicians; 2006: Position Paper. (Available from

American College of Physicians, 190 N. Independence Mall West, Philadelphia, PA 19106.)
43. Rosenthal MB, Berndt ER, Donohue JM, Epstein AM, Frank RG. Demand Effects of Recent Changes in Prescription Drug Promotion. *Forum for Health Economics & Policy*. 2003;6(1). doi:10.2202/1558-9544.1044.
44. Tsai WH, Lancaster AR. Message Strategies in Direct-to-Consumer Pharmaceutical Advertising: A Content Analysis Using Taylors Six-Segment Message Strategy Wheel. *Health Marketing Quarterly*. 2012;29(3):239-255. doi:10.1080/07359683.2012.705708.
45. Das R. Are Direct-To-Consumer Ads for Drugs Doing More Harm than Good? Forbes. https://www.forbes.com/sites/reenitadas/2019/05/14/direct-to-consumer-drug-ads-are-they-doing-more-harm-than-good/#1a0150514dfc. Published May 14, 2019. Accessed March 23, 2020.
46. Gilbody S, Wilson P, Watt I. Benefits and Harms of Direct to Consumer Advertising: A Systematic Review. *Quality and Safety in Health Care*. 2005;14(4):246-250. doi:10.1136/qshc.2004.012781.
47. Donohue JM, Cevasco M, Rosenthal MB. A Decade of Direct-to-Consumer Advertising of Prescription Drugs. *New England Journal of Medicine*. 2007;357(7):673-681. doi:10.1056/nejmsa070502.
48. Applequist J, Ball JG. An Updated Analysis of Direct-to-Consumer Television Advertisements for Prescription Drugs. *The Annals of Family Medicine*. 2018;16(3):211-216. doi:10.1370/afm.2220.
49. Carpentier FRDCRD. Considering the Future of Pharmaceutical Promotions in Social Media. *International Journal of Health Policy and Management*. 2016;5(4):283-285. doi:10.15171/ijhpm.2016.15.
50. Celia F. Pharma Ups the Ante on DTC Advertising. *Pharmaceutical Commerce*. https://pharmaceuticalcommerce.com/brand-marketing-communications/pharma-ups-ante-dtc-advertising/. Published April 4, 2017. Accessed March 23, 2020.
51. Preechavuthinant S, Willis W, Coustasse A. Trends and Effects of Pharmaceutical DTCA. *International Journal of Pharmaceutical and Healthcare Marketing*. 2018;12(1):61-70. doi:10.1108/ijphm-04-2017-0019.
52. Babar Z-U-D, Siraj AM, Curley L. A Review of DTCA Techniques: Appraising Their Success and Potential Impact on Medication Users. *Research in Social and Administrative Pharmacy*. 2018;14(3):218-227. doi:10.1016/j.sapharm.2017.04.005.
53. Friedman M, Gould J. Consumer Attitudes and Behaviors Associated with Direct-to-Consumer Prescription Drug Marketing. *Journal of Consumer Marketing*. 2007;24(2):100-109. doi:10.1108/07363760710737102.
54. Weinmeyer R. Direct-to-Consumer Advertising of Drugs. *American Medical Association Journal of Ethics*. 2013;15(11). doi: 10.1001/virtualmentor.2013.15.11.hlaw1-1311.
55. Brown JL. Physician Exposure to Direct-to-Consumer Pharmaceutical Marketing: Potential for Creating Prescribing Bias. *The American Journal of Medicine*. 2017;130(6). doi:10.1016/j.amjmed.2016.12.023.

56. Center for Drug Evaluation and Research. Warning Letters 2016. U.S. Food and Drug Administration. https://www.fda.gov/drugs/warning-letters-and-notice-violation-letters-pharmaceutical-companies/warning-letters-2016. Published January 30, 2018. Accessed March 23, 2020.
57. Brownlee S, Garber J, Brownlee S, et al. Overprescribed: High Cost Isn't America's Only Drug Problem. STAT. https://www.statnews.com/2019/04/02/overprescribed-americas-other-drug-problem/. Published April 1, 2019. Accessed April 1, 2020.
58. Suchotliff S, Evan H. The Changing Landscape of DTC Spending in Pharma. ZS. https://www.zs.com/publications/articles/the-changing-landscape-of-dtc-spending-in-pharma. Published 2018. Accessed April 1, 2020.
59. Portz G. COVID-19 Update: U.S. Distancing Guidance Ends; Unsafe Sanitizers; Tracking COVID in Sewage. Medical News and Free CME Online. https://www.medpagetoday.com/infectiousdisease/covid19/86229?xid=nl_popmed_2020-04-30&eun=g727597d0r&utm_source=Sailthru&utm_medium=email&utm_campaign=CoronaBreak_043020&utm_term=NL_Daily_Breaking_News_Active. Published April 30, 2020. Accessed April 30, 2020.

BIOGRAPHY

Caroline C. Jones was born in Dallas Texas on April 4, 1997. She attended and graduated from the Episcopal School of Dallas and enrolled in the Plan II Honors program at the University of Texas at Austin in 2015. In addition to earning her Bachelor of Arts in Plan II Honors, Caroline also earned her Bachelor of Business Administration in Management Information Systems through the McCombs School of Business. After graduation from the undergraduate school at UT in May 2020, she will begin working as a Junior Rotational Program participant at the National Football League in New York.