https://doi.org/10.7175/747.ch12

12. Pharmaceutical Market in the U.S: a Brief Treatise

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12.1 Introduction

Pharmaceutical manufacturing in the United States of America (U.S.) is and has been one of the most profitable industries overall during the past several decades. One reason for this fact may be that the U.S. is one of the few countries that do not have price controls on prescription drugs. Products are brought to market through a lengthy, expensive, clinical research process after approval by the FDA. The development, manufacture, and marketing of medications is now a trillion-dollar industry worldwide. Annual global revenues generated by the pharmaceutical industry exceeded one trillion U.S. dollars for the first time in 2014. The industry's revenues grew from approximately $ 390 billion dollars in 2001. This translates into a 250 percent growth over the past thirteen years [1]. The U.S. is the largest pharmaceutical market in the world with revenues valued at over $ 339.7 billion. This volume is more than 3.5 times larger than the second marketplace, Japan, at about $ 94 billion in annual revenue. America accounts for over 30 percent of the worldwide consumption of pharmaceutical products in terms of dollars [2].

The overall purpose of this work is to discuss pharmaceutical market access for the U.S. First, this chapter provides a brief history of the pharmaceutical industry in the U.S. Second, the structure of the highly successful American marketplace is explained along with how our capitalistic model of marketing has fostered the eminence growth of the pharmaceutical industry here. Third, unique characteristics of the well-developed marketing schema by the leading research-intensive manufacturers in the American market are described.

12.2 History and Development of the Pharmaceutical Industry Market in the U. S.

In the early 1900s, the American pharmaceutical was evolving from medicines prepared *secundum artem* on site by the pharmacist to a largely industrialized, technological operation. Ethical, responsible companies utilized botanists and other scientists to identify adulterated or impure crude products. Pharmaceutical research here was primarily limited to studying production problems. In 1912, Josiah K. Lilly, Sr, President of Eli

Lilly and Company, prophetically said that synthetic, active ingredients and biologicals would replace natural, crude products. "Punishing the stomach with large, frequent and nauseous doses is bound to give way where possible to more refined and direct methods. Medicine will become less empirical and more and more rigid demands will be made upon the manufacturer [...]" [3].

By the beginning of World War I, Germany dominated the pharmaceutical and fine chemical industries using a research-based model that helped propel the country's economic growth and industrialization. It was able to export complex, organic chemical intermediates as "raw materials" to the U.S. duty-free, thus inhibiting the American production of synthetic chemicals at a time where their importance was growing internationally and domestically. German-owned patents and German-owned companies controlled much of what was manufactured here. For the most part, the American pharmaceutical manufacturers were merely part of the producer-goods industry.

One hundred years ago, during the summer of 1917 (just a few months after the U.S. declared war on Germany), the Council on National Defense deliberated with 250 American Manufacturers regarding how to put the pharmaceutical industry, among others, on wartime footing. The Federal Trade Commission sanctioned the issuing of non-inclusive licenses to domestic companies to manufacture medicines formerly protected by German-owned patents. The most important after-effects of these events were that the American pharmaceutical manufacturers were able to commandeer economic power and control over their own science and technology [4].

Post World War II, the American pharmaceutical industry began to invest seriously in research and development and to produce highly differentiated consumer goods that were exclusively distributed via community and institutional pharmacies. By the 1960s, drugs had become «social goods [...] goods that are so important in the contemporary social milieu that they lose much of their private commercial character and become closely integrated within the public, and thereby, political sector» [4]. The 1962 Kefauver-Harris Amendment to the Federal Food Drug and Cosmetic Act was enacted, in part, to expand Federal regulation of medical experimentation on humans. The law also required that manufacturers prove drug effectiveness as a condition of gaining marketing approval, as well as requiring promotional activities to disclose accurate side-effect information [5].

Two dynamics have been mostly responsible for fueling the incredible growth of the American pharmaceutical industry. First, Research & Development has evolved into a highly sophisticated spectrum of processes and specialties, including molecular modeling, pharmacogenomics, proteinomics, clinical applications, biologic preparation, pharmacogenetics, packaging, marketing, to name a few. All of which have contributed to unique types of medicines, dosage forms, and distribution systems available in the marketplace. In 2015, the U.S. Food and Drug Administration approved forty-five New Chemical Entities (NCEs) for marketing. Thirty-nine percent (39%) of these approvals were for biologic agents, which were up from twenty-two percent in 2013 (a 77% increase). By 2016, the percentage of approved NCEs that are considered as biologics rose to 59%; thus, signaling a huge shift in the origins of products which are being approved. Effectively, we now have shifted from the synthetic chemical era of medicines to the new epoch of biologic-based drug products [6].

The second parameter that has fueled the pharmaceutical industry tremendous growth is marketing, which has become increasingly more sophisticated, cutting-edge, targeted, and successful. This topic is the subject matter for the rest of the chapter. Marketing processes are very important to the overall economy. They are even more critical to the high degree of success enjoyed by the research-intensive pharmaceutical industry and the considerable profits gleaned by it.

Overall, this chapter highlights the evolution of marketing and promotion and explains the current position of the pharmaceutical marketplace, from the manufacturer's vantage point and, to a lesser degree, the practical standpoint. In the next section, marketing basics as they relate to the U.S. pharmaceutical manufacturing industry and to the practice of pharmacy will be discussed, followed by a focus on the current practices of promotional activities for prescription drug products.

12.3 Pharmaceutical Market Structure

Pharmaceutical marketing is defined as "the sum of all the activities that facilitate the flow of prescription drug products (goods, services, or information) from their origination point (manufacturer, importer, service provider, or information source) to the ultimate consumer (patient)". Marketing processes include shipping systems, channels of

Box 1. Universality of Marketing Functions. Modified from [7]

Assembling functions
- Marshalling sufficient raw materials
- Functioning distribution networks
- Selecting appropriate product mix (including different strengths and dosage forms, where applicable)
- Managing resources
- Gathering production and distribution information

Distribution functions
- Setting and following production schedules
- Timing logistics
- Transportation (among all three function types)
- Storage of material and products

Administrative functions
- Risk bearing (for everything throughout all operations)
- Quality control (continuous quality improvement)
- Financing (who pays for what, when)
- Selling (product must be sold)
- Buying (product must be purchased)
- Marketing research on end users and operations

distribution, product and consumer research (economic, social, and behavioral), quality control, merchandising considerations, product promotional practices, pricing strategies, financial risk bearing, planning and logistics, among other things [7].

In a normal marketplace, the market for the producers (sellers) is usually the prospective ultimate user (patients). The prescription drug market is not a normal one; it is a directed market where prescribers direct the purchase by the patient. Either way, it is the marketer's job to persuade consumers to buy or utilize their products. Whomever the producer (supplier) is, numerous operations (tasks) must be executed for the product to be able to reach the correct person in a timely manner. These collective tasks are known as the Universality of Marketing Functions (Box 1); all operations must be performed for the marketing process to work efficiently. A failure of any of these operations leads to problems at the patient end of the supply chain such as wrong item, poor-quality, insufficient quantity, or too many products being delivered. When any part of this system of marketing functions fails, numerous problems arise. The American system excels in all marketing function aspects; these operations are the key to the excellence it enjoys as a leader in marketing pharmaceuticals. If a supplier cannot meet the demand needs of the end-user, then the producer will go out of business (even if it is a government). These facts also apply to health care delivery systems.

Levels of Distribution

In the pharmaceutical/healthcare marketplace, there are many distinct categories of end-users. As a result, there are various levels of distribution (Table 1). Each type of product has similar, yet unique levels. In complex economies, this hierarchy may not be an exact representation and there may be interfaces among the horizontal planes. In the U.S., there is usually a wholesale level (for prescription drugs) or a central office (for service providers) that functions as an intermediary between producer and the place where the patient either purchases or receives their product. This middleman in the marketing process places a critical role in terms of efficiency.

Intrinsic role of the middleman

It is important to note that for each marketing tier, value must be added to the product. If value is not added, then that level will cease to function in an efficient marketplace. "There is a value added to the overall distribution process using wholesalers characterized

Prescription drugs (good)	Health care services	Information
Manufacturer	Health care service originator	Information creator
Wholesaler	Health care service Distributor	Information distributor
Pharmacy	Health care Provider	Information provider
Consumer	Patient	Client

Table 1. Distribution levels for prescription drugs and related products. Modified from [7]

through the concepts of appropriate order quantity, utility of time, place and access. This type of operation is even more important in the efficient and effective distribution system for pharmaceutical products than for general consumer goods" [8].

A wholesaler is defined as "an entity that purchases manufacturers' goods, resells them to others, and that operates one or more facilities where these goods are received, stored and reshipped" [8]. The question is "Why not cut out the wholesaler intermediary and save money by removing a level of marketing?" Certain benefits (such as the minimum number of transactions, sorting, and proximity) accrue to society because of the unique role of the middleman. A discussion of these advantages follows.

Minimum Number of Transactions. The first benefit that accrues to the marketing system and society is that the overall total of monthly exchanges/transactions is minimized. Without pharmaceutical wholesalers, each pharmacy would have to order from the different manufacturers. Below is an example of what the overall number of monthly transactions would be in this scenario (numbers used are not an exact representation):

50,000 (pharmacies)	**x**	**250** (manufacturers)	**x**	**4** (weekly orders)	**=**	**50,000,000** (monthly transactions)

According to this estimation, if each of the 50,000 pharmacies in the U.S. ordered weekly (which would be a low estimate) from each of the 250 manufacturers, the total would be about 50 million transactions monthly. On the other hand, the current system uses the pharmaceutical wholesaler, thereby radically reducing the calculated number of monthly transactions.

250 (manufacturers)	**x**	**50** (wholesalers)	**x**	**4** (orders/month)	**=**	**50,000**
50 (wholesalers)	**x**	**1,000** (pharmacies per wholesaler)	**x**	**22** (order days per month)	**=**	**1,100,000**
				Grand total	**=**	**1,150,000**

In the above, closer-to-what-really-happens scenario, each pharmacy (estimating 1,000 pharmacies per wholesaler) receives twenty-two (22) deliveries per month from their wholesaler and each wholesaler orders four times monthly from the manufacturers. When these two calculations are added, the sum is 1,150,000 transactions. This 97.7% reduction in the total number of transactions is accompanied with a similar, large decrease in ordering, shipping, packing, invoicing and other affiliate costs (e.g., holding and interest), as well as the greatly diminished likelihood of errors being committed. Thereby, adding significant value to the overall marketing process.

The overall advantages illustrated above with the current distribution network are further supplemented by the other services offered by most wholesalers to manufacturers and pharmacies. This well-structured, strategic system is responsible for the economic, precise, efficient, and resource-sparing delivery of prescription drugs to their intended end-point of distribution.

Sorting. The second accrued benefit is essentially the definition of what a pharmaceutical wholesaler does. As a marketing concept, sorting has two discrete, but related actions – concentration and dispersion. Concentration – the wholesaler buys from many manufacturers in much larger quantities than an individual retail could, earning substantial discounts typical of such purchases. Consequently, the per-unit and overall total costs are lower. Dispersion – a specific product is shipped simultaneously to a pharmacy after an order has been placed and it is combined with products for that outlet and with requests from other outlets nearby. This process economizes the overall cost of distribution; a key component of marketing.

Proximity. In general, wholesalers are closer to the final marketplace than manufactures. As a result, distributions that are more frequent can be made, sometimes multiple times per day. The idea is "providing the right good at the right time to the right person at the right place" [9].

12.4 Accessing the American Pharmaceutical Market

Gaining access to the pharmaceutical marketplace in the United States requires expensive and highly sophisticated strategies and tactics. However, it can be a very lucrative proposition for those who succeed. This section of the chapter will describe some of the approaches used by current leaders in the industry. Figure 1 depicts many of the methods the pharmaceutical industry uses to build and protect their product's place in the market.

Sampling

A successful tactic used to increase product demand is the use of samples (actual product available in a patient-convenient package). Sampling, as a strategy, is designed to permit prescribers to "test drive" the product in order to learn more about the effectiveness and safety profile of the product at no expense to the patient. Samples are also used as "starter packages" so that patients can initiate their therapy immediately. The professional sales representative furnishes these items to the clinician upon the written request of a prescriber to the manufacturer. These samples are also used to provide medication to those patients who cannot afford to pay for their therapy. Samples can be in the form of an actual product or as a coupon. These vouchers are then presented to the pharmacist to be dispensed. The pharmacist submits these forms to the manufacturer or an intermediary for reimbursement.

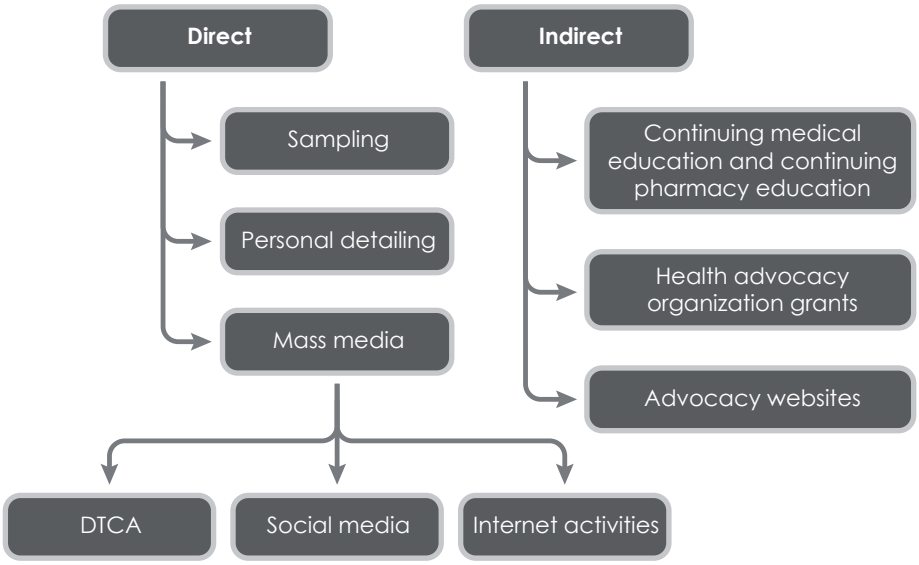

Figure 1. Types of pharmaceutical marketing
DTCA = Direct-To-Consumer Advertising

Personal Detailing

Pharmaceutical companies still engage in in-person visits to prescribers. This high-labor cost strategy is effective in reaching practitioners. Creative methods for accessing hard-to-reach physicians are used by professional representatives such as spicy food catering and ice cream parlor service in-office. These imaginative strategies are successful in promoting prescription products to those who are responsible for their use. Personal detailing has evolved over the years as a lucrative means to grow market share. Due to the high-labor costs, this approach is decreasing as a percentage of the overall promotional effort and is being supplanted by direct-to-consumer advertising (discussed later).

Continuing Professional Education

Pharmaceutical Research and Manufacturers of America (PhRMA) is the organization that represents the leading biomedical research companies in this country. PhRMA established guidelines on engagement with health professionals. These rules include specifics such as the maximum value of gifts and meals that can be provided to prescribers and pharmacists. It also established rules regarding the content and conduct of Continuing Medical Education and Continuing Pharmacy Education programs. In order to circumvent these policies, companies contract with third-party vendors to offer a non-accredit-

ed "information session" on a specific product featuring a physician testimonial at a high-end restaurant that would draw the desired audience.

Direct-to-Consumer Advertising (DTCA)

Historically, the preponderance of prescription drug marketing information was targeted directly towards prescribers. In 1981, an advertisement appeared in *Reader's Digest* magazine, a publication for the general public, for Pneumovax® (pneumococcal polysaccharide vaccine) from Merck & Co., Inc. Soon thereafter, print ads in other magazines also ran for Zovirax® (acyclovir) by Burroughs Wellcome & Company (now GlaxoSmithKline). These commercial messages were created to inform the laity that specific prescription medications were available and suggested that they seek advice from physicians about whether this product would work for them. The first broadcast advertisement of a prescription drug to the masses was aired on television May 19, 1983. A commercial was shown for Rufen® (ibuprofen) manufactured by Boots Pharmaceuticals was shown on a major network in Florida [10].

New Zealand and the United States are currently the only two countries that permit direct-to-consumer advertising for prescription drugs. The use of DTCA is controversial; this is why there are so few countries that permit it. Among the advantages of DTCA are that the public has an increased awareness of and is better informed about available treatments, and, therefore, empowers them to be a better partner in their own healthcare. Another advantage is that patients could benefit from having more than one information source about pharmaceuticals and treatment regimens. Additionally, the ads encourage a patient to contact their primary care clinician and promote a more-informed dialogue

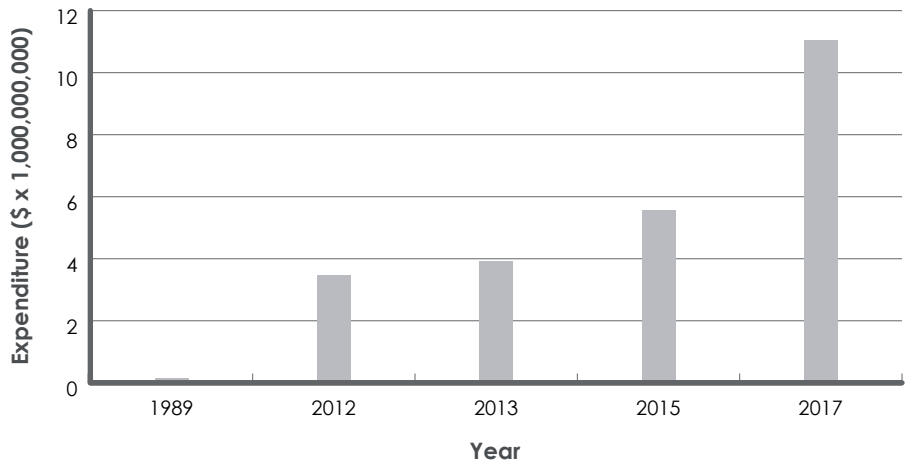

Figure 2. DTCA expenditures in the U.S. [13,14]

between patient and practitioner. Possibly the best public health benefit is that these ads may reduce the stigma associated with the conditions the promoted drugs treat. Research has consistently shown that customers who request a prescription from their practitioner after viewing a DTCA were among the most adherent outpatients [11].

Some of the arguments in opposition to DTCA are:

- the ads may misinform by omitting key information;
- patients lack the analytical skills to assess the provided information;
- the ads rarely focus on non-therapeutic options such as diet, exercise, and other lifestyle changes; and
- they may encourage patients to take too many drugs and will favor the more heavily advertised products.

These ads also promote new products before a comprehensive safety profile can be ascertained in the general population [11]. The American Medical Association adopted a policy in 2015 that calls for a ban on DTCA because of «concerns that a growing proliferation of ads is driving demand for expensive treatments despite the clinical effectiveness of less costly alternatives» [12].

DTCA is now the most prominent mode of health communication that is encountered by the American public [11]. Figure 2 presents the amount expended on DTCA in the U.S. for select years.

Figure 2 presents a vivid picture of the rapid growth of this promotional strategy. DTCA spending has increased from $ 12 million in 1989 to a projected $ 11 billion in 2017 [13,14]. This massive, approximately 916% increase in expenditures on DTCA demonstrates the necessity of engaging in this stratagem to stay competitive. Over 69% of

Type of advertisement	Description	Brief listing of requirements
Product claim	Only type that uses a drug name, its uses, and presents its risks and benefits using understandable language	Specific items must be in the main part of the ad: • Generic and brand name • An FDA-approved indication • Most significant risks via audio
Reminder	Mentions the drug name and maybe its cost, but not its indications Ads not permitted to be used for drugs classified as having serious risks (black boxed warnings)	Cannot imply in audio or visual about drug's uses or safety profile
Help-seeking	Ads that promote a disease or condition and suggest that patients talk with their doctor or pharmacist about it, but do not recommend a specific product	May include the pharmaceutical manufacturer's name

Table 2. FDA regulatory requirements for different types of direct-to-consumer TV ads [17]

the overall spending on DTCA was devoted to television ads in 2016 [15]. The products that had the most money spent on them in 2016 were Lyrica® (pregabalin) at $ 313 million, Humira® (adalimumab) at $ 303 million, and Eliquis® (apixaban) at $ 186 million [16].

The U.S. Food and Drug Administration regulates the content of DTCA. Table 2 presents a brief description of the basic guidelines for the different categories of these ads. These "fair and balance" rules make it more imperative that DTCA be visually mesmerizing to smother the warnings.

Companies have also experimented with DTCA ads shown on social media. In August 2015, the FDA reprimanded Duchesnay USA for a paid message presented on Instagram. Kim Kardashian West, a high-profile celebrity who had just given birth, was a compensated spokesperson. As such, she posted a testimonial about the effectiveness of this **antinauseant** drug and picture of herself holding a bottle Diclegis® (doxylamine succinate and pyridoxine hydrochloride delayed release). This experiment was highly successful in that over 40 million people had access to the ad and 464,000 people "liked it" [18].

12.5 In Summary

Many and significant changes have occurred in the American prescription drug marketplace since 2000. Previously "unthinkable" therapeutic categories, new research methods and capabilities, high-tech dosage forms, robotic biomedical and point-of-care diagnostic devices, innovative practice approaches, big data analysis, and persuasive promotional campaigns are among the transformations that have transpired. The fundamental tenets of the industry are transforming due to marketplace, financial, and regulatory forces.

Understanding the magnitude of the many, dynamic forces impacting access to the prescription drug marketplace in the United States is impossible without first comprehending the critical part that promotion by the industry plays. It is highly sophisticated and has evolved to be successful in maintaining or increasing market position. The U.S. pharmaceutical industry has been and still is very clever and creative. «Pharmaceutical manufacturers can be thought of as compounders of various marketing parameters that are concocted skillfully and dispensed to form the company's unique (at least from the business' point-of-view) offerings in the marketplace» [10]. For prescription drugs, the market place in the U. S. is significantly different from for other traditional consumer products in that patients (the end-users) do not have direct access to purchase these items. From a marketing point-of-view, this "directed market" has the distinct advantage that a limited number of prescribers control access to a large end-user patient population exceeding 350,000,000. This scenario provides a dream opportunity to focus marketing efforts on a limited number of people and gain widespread return on investment.

The American pharmaceutical marketplace, because of its high-level of profitability, is able to experiment with unique and innovative promotional ideas that other markets just could not sustain. As a result, many endeavors are tried to promote specific products or

to improve (or maintain) market share or an image. It is possible to concentrate marketing efforts on a few to receive widespread benefits.

In the future, I expect more ingenuity and inventiveness in how companies position their products and themselves. High drug prices are a volatile, emotion, and political issue right now. The high cost of marketing is thought to add to the high price charged for prescription drugs. Other significant issues of growing concern within the U.S. are drug shortages (due to limited production facilities, raw material shortages, etc.), drug importation, and counterfeit products. Addressing some or all of these concerns as part of a push to enter or expand a company's market position would be met with an enthusiastic acceptance.

12.6 References

1. Statista: The Statistics Portal. Leading countries in global pharmaceutical mergers and acquisitions. Available at https://www.statista.com/statistics/398229/leading-countries-by-pharmaceutical-industry-mergers-and-acquisitions/ (last accessed August 2017)
2. WorldAtlas. Biggest Pharmaceutical Markets in the World by Country. http://www.worldatlas.com/articles/countries-with-the-biggest-global-pharmaceutical-markets-in-the-world.html (last accessed August 2017)
3. Lilly JK. The Pharmaceutical Era. 1912; 45: 449-52; 513-7
4. Vogt DD, Montagne M. The process of drug development: I. Historical interplay of political economics, research and regulation. *Clin Res Pr Drug Regul Aff* 1983; 1: 1-18
5. Drug Amendments Act of 1962. An act to protect the public health by amending the Federal Food, Drug, and Cosmetic Act to assure the safety, effectiveness, and reliability of drugs, authorize standardization of drug names, and clarify and strengthen existing inspection authority; and for other purposes. Public Law 87-781, 76 STAT 780. Available at http://uscode.house.gov/statutes/pl/87/781.pdf (last accessed August 2017)
6. U.S. Food and Drug Administration. Novel Drug Approvals for 2016. Available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/DrugInnovation/ucm483775.htm (last accessed August 2017)
7. Bleidt B. Marketing activities: The keystone of capitalism, increasing the availability of prescription drugs through pharmaceutical promotion. *J Drug Issues* 1992; 22
8. Bleidt B, Clouse E, Nichols A. How to Develop a Successful Retail Pharmacy Marketing Mix. In: NARD, AACP, NACDS, Glaxo (eds.). Retail Pharmacy Practice Management. Chapel Hill, North Carolina: Health Sciences Consortium, 1990
9. Smith HA. Principles and Methods of Pharmacy Management. Philadelphia, Pennsylvania: Lea & Febiger: 1986

10. PharmaVOICE. How 5/19 changed the industry forever. Available at http://www.pharmavoice.com/article/1232/ (last accessed August 2017)
11. Ventola CL. Direct-to-consumer pharmaceutical advertising: therapeutic or toxic? *P T* 2011; 36: 669-84
12. American Medical Association. AMA calls for ban on DTC ads of prescription drugs and medical devices. Press Release 17 November 2015. Available at https://www.ama-assn.org/content/ama-calls-ban-direct-consumer-advertising-prescription-drugs-and-medical-devices (last accessed August 2017)
13. Millman J. It's True: Drug Companies Are Bombarding Your TV with More Ads than Ever. The Washington Post. March 23, 2015. Available at https://www.washingtonpost.com/news/wonk/wp/2015/03/23/yes-drug-companies-are-bombarding-your-tv-with-more-ads-than-ever/?utm_term=.769b7d135e7b (last accessed August 2017)
14. Global Industry Analysts, Inc. The US Direct-to-Consumer (DTC) Advertising in Pharmaceuticals to Reach US$11.4 Billion by 2017. Available at http://www.prweb.com/releases/direct_to_consumer_dtc/pharma_advertising/prweb8831454.htm (last accessed August 2017)
15. Pharmalive: The Pulse of Pharmaceutical Industry. DTC Ad Spend by Media Type in 2015. Available at http://www.pharmalive.com/dtc-ad-spend-by-media-type-in-2015/ (last accessed August 2017)
16. Horovitz B, Appleby J. Prescription drug costs are up; so are TV ads promoting them. USA Today. March 16, 2017. Available at https://www.usatoday.com/story/money/2017/03/16/prescription-drug-costs-up-tv-ads/99203878 (last accessed August 2017)
17. U.S. Food and Drug Administration. Basics of Drug Ads. Available at https://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072077.htm (last accessed August 2017)
18. Kroll D. FDA admonishes drug maker over Kim Kardashian Instagram endorsement. Forbes August 11, 2015. Available at https://www.forbes.com/sites/davidkroll/2015/08/11/fda-spanks-drug-maker-over-kim-kardashian-instagram-endorsement/#526dbfa3587b (accessed 15 August 2017)
19. Bleidt B. Recent issues and concerns about pharmaceutical industry promotional efforts. *Journal of Drug Issues J Drug Issues* 1992; 22