An analysis of trends in drug advertising violations based on Warning letters & Untitled letters issued by the US FDA.

by

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Abstract

Introduction

The FDA Office of Prescription Drug Promotion (OPDP) reviews promotional material at the time of launch and after the product is marketed. The OPDP issues Warning Letters (WL) or Untitled Letters (UL) if the promotional material noncompliant with advertising regulations.

Objective

This study was designed to analyze the WL/UL issued by the OPDP from the period of January 2008 to August 2015. This study had two objectives: 1) Quantitative analysis of WL/UL and 2) Identification of major and minor violation types cited in the letters.

Methods

For analysis, the data compilation form was developed in MS Excel 2013™. Analysis variables were -Year of issuance of WL, Type of letter, Source of promotional material, Type of violation etc. Data analysis was performed with SAS 9.2™.

Results

During the seven-year period, out of 214 letters issued by the OPDP, 44 were WL and 170 were UL. The number of letters increased from 2008 (n= 20) to 2010 (n= 52). After 2011 (n=31), the number of letters decreased until 2015 (n= 9). Omission/minimization of risk information (n=179, 30%) was the most common violation cited followed by unsubstantiated claims of efficacy (n=108, 18%).

Conclusions

The total number of letters and WL gradually declined from 2011 to 2015. Forty-eight percent of the cited violations were related to the omission of risk information and overstatement of efficacy. This study highlighted the FDA's focus on truthful and balanced advertising as reflected from regulatory letters.

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Chapter 1: Introduction

The US FDA (United States Food and Drug Administration) is the federal government agency of the United States Department of Health and Human Services. One of the most important responsibilities of the FDA is regulation of the manufacturing and marketing of various pharmaceutical products (Food and Drug Administration 2015a, July 2).

The USA and New Zealand are only two countries which allow Direct to Consumer Advertising (DTCA) (Abel et al., 2006). Warning letters (WL) and Untitled letters (UL) are the tools of policy enforcement employed by the US FDA for the regulation of DTCA. All WL/UL issued by the FDA from 1998, are available on the FDA website (www.fda.gov) under the Freedom of Information Act (FOI) (Food and Drug Administration, 2015b).

DTCA has become the most prominent type of healthcare communication for consumers and prescribers alike (Kuehn, 2010). There are several methods used by companies to reach consumers and healthcare professionals. These methods range from simple reminder ads (advertisements) to complex scientific brochures (Ventola, 2011). All types of promotional materials are monitored by the FDA for different violations (Berry & Martin, 2008). For non-compliant promotional activities, the FDA issues WL or UL to pharmaceutical companies or distributors. Therefore, analysis of WL and UL was useful to gain insight into the FDA's perspective on advertising violations. Additionally, this was also important to identify the trends in different advertising violations.

Objective

According to the study by Nguyen et al. (2013), the FDA released 2,467 regulatory letters (WL and Notices of Violation) during the period of 1997 to 2011. The Division of Drug Marketing, Advertising and Communications (DDMAC) and the Office of Prescription Drug Promotion (OPDP) issued 850 regulatory letters, which amounted to 34.5% of all the regulatory letters. This was the highest number of letters issued by any FDA department during the period of 1997 to 2011. It was followed by the Office of Scientific Investigations, which issued 131 letters (5.3% of total).

These numbers suggested that advertising violations were most common to face regulatory intervention and the OPDP issued significantly more number of letters than any other FDA department. This study was designed to evaluate details in advertising violations through analyses of WL and UL issued by DDMAC and OPDP.

Specifically, this study had two objectives.

1. Quantitative analysis of WL/UL issued for drug advertising violations for the period of January 2008-August 2015.
2. Identify major and minor violation types cited in WL/UL to discover noncompliant advertising patterns used by different manufacturers.

Chapter 2: Background

The FDA

FDA (or "the agency") is the oldest comprehensive consumer protection agency in the US functioning under the Department of Health and Human Services (DHHS) of the federal government. It is responsible for safeguarding and promotion of public health through various means. The FDA is involved in the regulation of prescription and Over-the-Counter (OTC) drugs, dietary supplements, medical devices, biological, veterinary drugs, foods, etc. The agency is comprised of fourteen centers with headquarters located in Silver Spring, MD. The agency is headed by the Commissioner who is appointed by the President (Food and Drug Administration, 2015d). The overall cost of goods monitored by the FDA amounts to $1 trillion per year (U.S. Food and Drug Administration, 2015e).

The laws which have played an important role in the FDA regulations are, the Federal Food Drug, and Cosmetic Act, as amended (FDC Act, 1938), and the Public Health Service Act (1941). Various provisions in these laws have defined the depth and breadth of the FDA's jurisdiction (Food and Drug Administration, 2014a).

Within the process of federal rulemaking, proposed rules and notices are first published in the Federal Register (FR) for public comment. After finalization, the rules are published in the Code of Federal Regulations (CFR). CFR is codification of rules published in FR by different federal agencies. It is divided into 50 sections (Titles) which characterize wide areas subject to the federal regulations. Title 21 of the CFR comprises regulations for food and drugs (Food and Drug Administration, 2014b).

The history of drug advertising

The US federal government started regulating drugs in 1906 with the Pure Food and Drugs Act. Additional regulations were added in 1938 by the Food, Drug, and Cosmetic Act (FDC act). With this act, a new system of regulation was initiated which required manufacturers to establish safety for their products. The FDC act was later strengthened with the Kefauver-Harris amendments in 1962. This amendment mandated the demonstration of efficacy and greater drug safety (Food and Drug Administration, 2014a).

In 1941, the FDA designated few drugs as prescription only. Until 1960's, more than ninety percent of drug marketing was directed to health professionals. This trend of health professional directed advertising continued until 1980's (Hilts, 2003).

In 1981, the pharmaceutical industry raised questions on rationality of direct to consumer ads. In response to this, FDA commissioner Arthur Hull Hayes, Jr. asked for a brief voluntary moratorium on the DTC advertisements to enable the agency and other stakeholders to evaluate the effects of DTCA (Hunt, 1998). The FDA requested this moratorium on September 2, 1983 through a policy statement. During this period, the FDA conducted some studies to gain public perception of DTCA. These studies inferred that, DTCA could communicate both risks and benefits to consumers if they were conveyed in compliant manner. As a result, on September 9, 1985, the FDA removed the moratorium concluding that, appropriate regulatory measures were already in place for consumer protection (Food and Drug Administration, 2005).

By 1990, a few companies had started direct to consumer advertising. Slowly, DTCA took a larger form and culminated into a full-scale advertising by pharmaceutical companies that included many forms of promotion and marketing techniques. (Smeeding, 1990).

One of the factors that accelerated DTCA was the transition of prescription only drugs to over-the-counter (OTC) drugs. It was understood that, the drugs switching from prescription only to OTC had an advantage of brand recognition if they were advertised at the prescription stage. This, in turn created a long-term advantage for the manufacturer (Ling, Berndt & Kyle 2003).

In the early 1990's, the aging baby boomers were the larger part of the population. There was an increase in the attitude of active participation in making healthcare choices. Companies found this population to be more informed and could use more product information. Since then, DTCA has been a growing form of promotional tool for companies (Food and Drug Administration, n.d.).

In August 1999, the FDA released the first draft guidance for 'Consumer Directed Broadcast Advertisements'. This was the first step for the regulation of DTC advertising. This document outlined the "adequate provision requirement" which was an obligation to disseminate approved labeling information to the consumer. It was also mandated that the advertisement should include a "major statement" conveying the most important safety information about the product. The document also specified that instead of providing the summary information, the advertisement could refer consumers to other sources such as a toll free telephone number, a print ad (advertisement) a website, a pharmacist or a physician to get more information on the risks associated with the use of the product (Food and Drug Administration, 1999).

In August 2005, Pharmaceutical Research and Manufacturers of America (PhRMA) released its guiding principles on direct to consumer advertisements about prescription medicines. These guidelines had several recommendations for advertising, including submitting a television ad for a review to the FDA before broadcast (Pharmaceutical Research and Manufacturers of America, 2006).

In 2006, the FDA published the guidance for the format and content of prescription drug products for human use. According to this document, product labelling required highlights of prescribing information and a Table of Contents. This document was intended to enhance the safe and effective use of prescription drugs by minimizing medication errors (Food and Drug Administration, 2006).

Table 1 enlists all the guidance issued by the FDA for advertising regulations. The list includes draft and final guidance related to advertising (Food and Drug Administration, 2015c).

Table 1: The list of the advertising guidance issued by the FDA. Draft guidance represents a proposed version. Final guidance is an adopted regulation.

Title of FDA Guidance	Version	Date issued
Aerosol Steroid Product Safety Information in Prescription Drug Advertising and Promotional Labeling	Final Guidance	12/1/1997
Industry-Supported Scientific and Educational Activities	Final Guidance	12/3/1997
Consumer-Directed Broadcast Advertisements	Final Guidance	8/1/1999
Consumer-Directed Broadcast Advertisements Questions and Answers	Final Guidance	8/1/1999
Presenting Risk Information in Prescription Drug and Medical Device Promotion	Draft Guidance	5/27/2009
Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling-Final	Final Guidance	1/24/2012
Direct-to-Consumer Television Advertisements -FDAAA DTC Television Ad Pre-Dissemination Review Program	Draft Guidance	3/12/2012
Product Name Placement, Size, and Prominence in Advertising and Promotional Labeling	Draft Guidance	11/18/2013
Fulfilling Regulatory Requirements for Post marketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics	Draft Guidance	1/13/2014
Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation About Prescription Drugs and Medical Devices	Draft Guidance	6/17/2014
Internet/Social Media Platforms with Character Space Limitations— Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices	Draft Guidance	6/17/2014
Brief Summary and Adequate Directions for Use: Disclosing Risk Information in Consumer-Directed Print Advertisements and Promotional Labeling for Prescription Drugs	Draft Guidance, Revision II	8/5/2015

Source: (Food and Drug Administration, 2015c).

The Office of Prescription Drug Promotion (OPDP)

The Office of Prescription Drug Promotion functions under the Office of Medical Policy which is in turn governed by the Center for Drug Evaluation and Research (CDER). This office came into existence on September 19, 2011. Previously, it was called as the Division of Drug Marketing, Advertising and Communications (DDMAC).

The OPDP has summarized its mission as follows:

"To protect the public health by ensuring that prescription drug information is truthful, balanced, and accurately communicated. This is accomplished through a comprehensive surveillance, enforcement, and education program, and by fostering better communication of labeling and promotional information to both healthcare professionals and consumers." (Food and Drug Administration, 2015f)

The OPDP regulates following types of promotion:

- TV and radio advertisements
- All written or printed prescription drug promotional materials
- Speaker program presentations
- Sales representative presentations
- Promotional content on the World Wide Web (Internet) and social media.

The OPDP does not regulate promotion following types of promotion:

- Over-the-Counter drugs (Regulated by Federal Trade Commission)
- Dietary supplements (Regulated by Federal Trade Commission)
- Medical devices (Regulated by the Office of Compliance within the Center for Devices and Radiological Health (CDRH)

Major responsibilities of the OPDP include:

- Strategy and guidance development
- Labeling assessments
- Core launch (initial promotional material) reviews and TV ad reviews
- Enforcement
- Training and communications

Some of the major responsibilities of the OPDP include policy enforcement and compliance monitoring. WL and UL are usually the first step of enforcement. Other enforcement tools used by the OPDP are as follows:

- Sanctions/Consent decree
- Confiscations/Criminal action
- Civil and monetary penalties

Risk based enforcement approach

The OPDP claims that its approach for enforcement is risk based. This means that, the higher level of importance and attention is given to the products that are potentially more harmful to consumers. Specifically, this includes:

1. Recently approved products
2. Products with demonstrated risks
3. Products with previous violations
4. Products with complaints
5. Products with larger dissemination etc.

This approach has helped the OPDP to allocate resources based on the risks and the repercussions on general public health (Abrams, 2014).

“Bad Ad” program

Traditionally, the OPDP was relying on promotional material submitted to the agency by manufacturing companies. To enhance its range and to broaden the process of advertisement monitoring, the OPDP has started “Bad ad” program in 2010. This program was intended for healthcare professionals to involve them in the monitoring process. Under this program, healthcare providers were educated to actively participate in the DTC advertisement monitoring and reporting of misleading information. Such "Bad Ads" can be reported through MedWatch website or by phone. The agency executed this program in phases. In the first phase, selected institutions and healthcare professionals were educated about the Bad Ad program and later phases were planned to include a wide variety of healthcare professionals (Food and Drug Administration, 2015g).

The FDA has classified drug advertisements into three different types as follows:

Product claim advertisements

These advertisements name the drug and present the benefits and risks. The manufacturers are required to include the name of the drug, at least one approved indication, and the most important risks associated with the product. The benefits and risks must be presented in the balanced fashion.

Print ads should also include a "brief summary" about the product presenting approved product information. These ads should include a standard statement directing consumers to the MedWatch website and a phone number to report any side effects to the FDA.

Broadcast product claim ads (TV, radio, telephone) must include a "major statement” mentioning most significant risks and either all other risks or a source where consumers can find all the prescribing information about the drug. This condition is called “adequate provision

requirement”. To direct the consumer to the prescribing information, a variety of sources can be used e.g. a healthcare provider, a toll free phone number, a print ad, or a website address (Food and Drug Administration, 2015c).

Reminder advertisements

Reminder ads only present the name of the drug assuming that, consumers already have the knowledge about the use. They do not contain risk information. However, the FDA does not allow reminder ads for certain prescription drugs who have significant safety concerns associated with them. Some drugs have a special warning called "boxed warning" in prescribing information. Due to safety risks associated with them, they must be accompanied by risk information (Food and Drug Administration, 2015c).

Help-seeking advertisements

These ads only describe the disease or health condition and do not mention the name of the drug. For example, conditions like diabetes, hypertension, etc. may be stated in the ad. The advertisement can mention various symptoms and can suggest consumers to talk to their healthcare provider. These ads can contain a company name or a telephone number for more information. Such type of advertisements are regulated by the Federal Trade Commission (Food and Drug Administration, 2015h).

Other product claim promotional materials

Other promotional materials include patient brochures, materials mailed to consumers, sales aids, banners, and other types of materials given out by drug companies. These materials are also called as promotional labeling. The product benefit information in these materials must be accompanied by safety information (Food and Drug Administration, 2015h)

FDA Form 2253

The FDA Form 2253 contains all the promotional material developed by the manufacturer in various forms. This is usually referred as the 'FDA Form 2253 submission'. It is mandatory to submit the FDA Form 2253 at the initial labeling dissemination and at the time of releasing the first product advertisement. The FDA Form 2253 can be submitted in eCTD (Electronic Common Technical Document) or paper format. The OPDP reviews all promotional materials submitted through the FDA Form 2253 and may provide advisory comments. The agency can enforce action for a promotional material at any time, even after the product is discontinued (Toscano, 2013). The volume of promotional materials can be very large. In 2013, the OPDP received approximately 85,000 promotional pieces (Abrams, 2014).

The warning letter

The FDA defines the warning letter as "A correspondence that notifies regulated industry about violations that FDA has documented during its inspections or investigations ". A warning letter notifies a manufacturer, or a responsible person about violation of different regulations. The FDA claims that a WL will be issued only for violations which have regulatory importance. Such violations can lead to enforcement actions if proper corrective and preventive actions are not taken by the manufacturer (Food and Drug Administration, 2012a). Necessary policies and legal procedures for WL are documented in Regulatory Procedures Manual (RPM) (Food and Drug Administration, 2012b).

The history of warning letters

Before 1991, the FDA issued “Notices of Advanced Findings” and “Regulatory Letters” to manufacturers for violating regulations. In 1991, the FDA began issuing Warning Letters and Untitled Letters as a new system of enforcement to establish consistency and compliance (Sampson, n.d.).

This system also empowered the FDA district offices to issue WL and UL. However, according to some opinions, this caused a spike in issuance of letters (Pilot, 2006). Due to this, the Department of Health and Human Services (DHHS) directed the FDA to restrict WL through enhanced scrutiny. Hence, in November 2001, an enforcement system was updated to mandate that all WL issued by district offices and other departments will be reviewed and cleared by the Office of Chief Counsel (OCC). Again, in 2009, this rule was amended to necessitate OCC review only for the letters that present substantial legal concerns for the FDA (Pilot, 2006).

A warning letter is one of the important tools the agency uses to enforce regulatory compliance. The receiving organization is mandated to reply to the letter within 15 working days with appropriate corrective actions. This response letter should contain each corrective action taken, the time within which the corrective action will be completed and the documentation necessary to prove that the correction has been done (Food and Drug Administration, 2012b).

The format of a warning letter

WL can vary in form, style and content, however following points are common:

1. It is titled as "Warning Letter"
2. Addressed to the highest known official of the facility
3. Clearly cites the violation of the law for which the letter is being issued
4. Acknowledges corrections during inspections

5. Requests for corrections with a written response within 15 working days
6. A warning statement that failure to comply can prompt for enforcement
7. An official's name – to whom the response should be addressed
8. Standard closing paragraph stating that, the letter is not all-inclusive and addressee is responsible for ensuring correction of all violations including not mentioned in the WL.

While referring to different product categories like drugs and biologics, WL/UL consider the product definitions as in the FDC act (Table 2) (U.S. Code Title 21, 2010).

Table 2: Products categories as defined in the FDC act. These legal definitions are used to designate appropriate product categories in WL/UL.

Drug
The FD&C Act defines drugs, in part, by their intended use, as "articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease" and "articles (other than food) intended to affect the structure or any function of the body of man or other animals" [FD&C Act, sec. 201(g)(1)].
Biological Product
The term "biological product" means a virus, therapeutic serum, toxin, antitoxin, vaccine, blood, blood component or derivative, allergenic product, protein (except any chemically synthesized polypeptide), or analogous product, or arsphenamine or derivative of arsphenamine (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of a disease or condition of human beings. 42 U.S.C. § 262(i)

Source: U.S. Code Title 21, 2010

Close out letter

In August 2009, the FDA announced that it would issue a close out letter if the organization's response to the WL was found to be adequate with corrective actions. Close out letters for a WL after September 2009, are posted on FDA website ("FDA commissioner sets out vision on enforcement to support public health," 2013).

Untitled letter

An Untitled Letter is an initial correspondence which cites violations that do not meet the threshold of a Warning Letter. Some of the distinguishing characteristics of an Untitled Letter from the Warning Letter are:

1. It is not titled
2. It doesn't include a statement about the agency's advice to other federal agencies to take notice of that letter while awarding contracts
3. UL doesn't include a warning about enforcement action
4. UL doesn't induce mandated district follow-up
5. In the letter, a written response is requested rather than required (Food and Drug Administration, 2012b).

A WL and an UL are called as advisory actions by the FDA (Food and Drug Administration, 2015i).

Cyber letter

These letters are sent electronically through the Internet. In 2000, the FDA started issuing cyber letters to websites who sell prescription drugs online (Food and Drug Administration, 2015j).

FDA District offices

The FDA has five regional offices classified into Northeast, Central, Southeast, Southwest, and Pacific covering 20 district offices serving specific territory across the country (Food and Drug Administration, 2015d). Since 1991, District Offices have started issuing WL/UL for violations which are not specifically covered by any other FDA division (Pilot, 2006).

Chapter 3: Methods

Sample size and duration of analysis

For the purpose of analysis, the letters issued by the DDMAC and the OPDP were considered. To include letters by the DDMAC and the OPDP both and to have sufficient data for analysis, the duration of the study was selected from January 2008 to August 2015. Considering this, 214 letters were selected for analysis (Sample size, N=214). One letter had an inactive hyperlink on the FDA website and it was excluded from the study.

Data collection

General strategy employed for data collection in this study was to analyze the content of WL/UL and systematically categorize the information into an analysis ready database. The source for the data was WL/UL published by the FDA on their website.

The FDA website contains regulatory letters categorized by issuing office and subject. This also includes the letters issued by district offices. On the FDA website (www.fda.gov), these letters can be found under the section of drugs > Guidance, compliance & regulatory information > Enforcement activities by the FDA.

For this study, all letters from the DDMAC and the OPDP issued during the period of January 2008 to August 2015 were selected. Letters issued by the District Offices were not considered for analysis. All the letters issued by the DDMAC & the OPDP were for prescription drug advertising violations.

Frequently, a single letter was found to contain multiple types of violation. Hence, the number of violations listed in the analysis were more than the number of WL analyzed. In the letters, each violation was mentioned under the heading of a specific violation category. In this

study, these violations were categorized according to this heading mentioned in the letter e.g. overstatement of efficacy, omission of risk etc. It was found that, the violation categories cited in letters from 2008 to 2015, were in consistent format throughout this period.

After considering the general structure of a warning letter and variables required for analysis within the scope of the study, the data compilation form was developed in MS Excel 2013™. The final data form contained numbered list of rows, naming each letter, with a hyperlink to the original letter to the FDA website.

All letters were also downloaded and converted into PDF (Portable Document Format) for future data search and analysis. Along with analysis, the content of the letters was also analyzed to suit study objectives.

Analysis variables

Different variables listed in the data compilation form were – name of the company, year of issuance of WL, issuing office, type of the letter, drug type (marketed drug/biologic), hyperlink to the letter on the website, source of the promotional material (website/poster etc.), type of a violation, a violation code based on the United States Code (USC) and the CFR, etc.

Data compilation

Each WL/UL was read and carefully analyzed to find type of violations and other related analysis variables. The information was entered in the MS Excel 2013™ data compilation form. Data was sorted and filtered according to the requirement, to permit analysis of different variables. This information served as a source data for all analyses.

WL often cite more than one violation in a particular category. For example, there can be multiple labeling violations cited. In this case, the letter was counted in a category for labelling violation for once only.

Data analysis

Collected data was converted into SAS™datasets (.sas7bdat format) for analysis and organization purpose. Descriptive statistics and other statistical analyses were performed using SAS™ version 9.2. Within the scope of study, violations were analyzed and contributing factors were identified. Violations were also categorized according to the USC and the CFR. This study included WL/UL for marketed drugs, investigational drugs, and biological products.

Chapter 4: Results

For the duration January 2008 to August 2015, there were 215 letters posted on the FDA website for prescription drug advertising violations. Out of this, 214 letters (N=214) were included in the analysis for this study. One letter had inactive hyperlink and was excluded from analysis. The distribution of letters is illustrated in Table 3. Overall, UL were in majority with the count of 170 (79%) and WL were 44 (21%).

Table 3: The total number of letters analyzed for the duration of January 2008 to August 2015. Percentages were based on the total count of letters during this period.

Type of letter	**N**	**Percentage**
Warning Letters	44	21%
Untitled Letters	170	79%
Total	**214**	

Figure 1: The distribution by type of letters. The counts represent number of letters in each type.

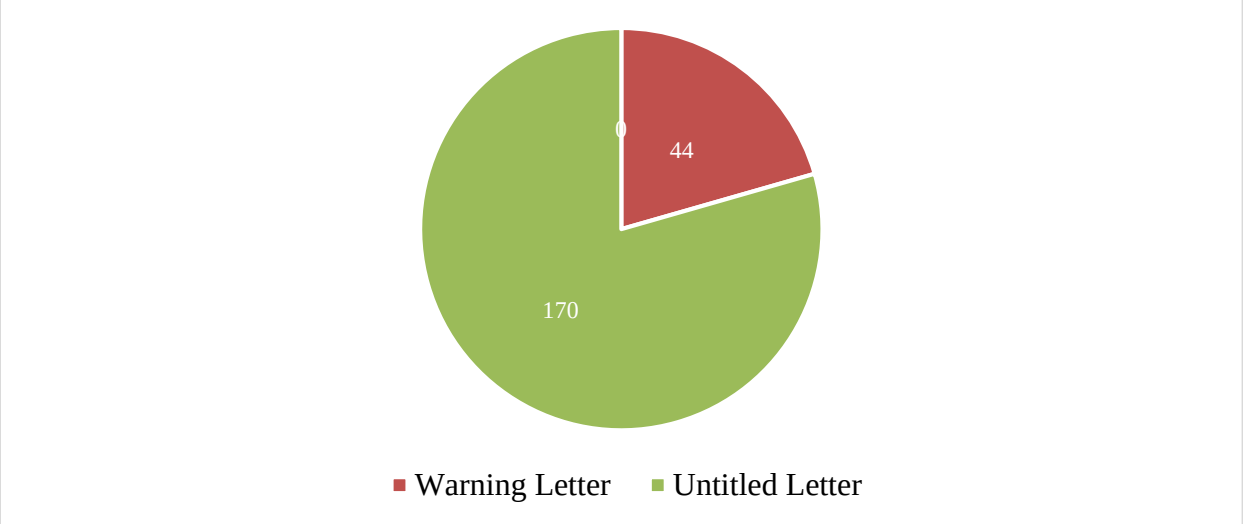


Table 4 represents total number of letters issued by the OPDP by year. On an average, 27 letters were issued per year.

Table 4: The distribution of letters by year. The duration was from January 2008 to August 2015. Total letters included Warning Letters and Untitled Letters.

Year of issuance	Total letters issued
2008	20
2009	41
2010	52
2011	31
2012	28
2013	24
2014	9
2015	9
Total	**214**

Figure 2: The total number of letters issued by year from January 2008 to August 2015. There was a steady decline in total number of letters after 2010.

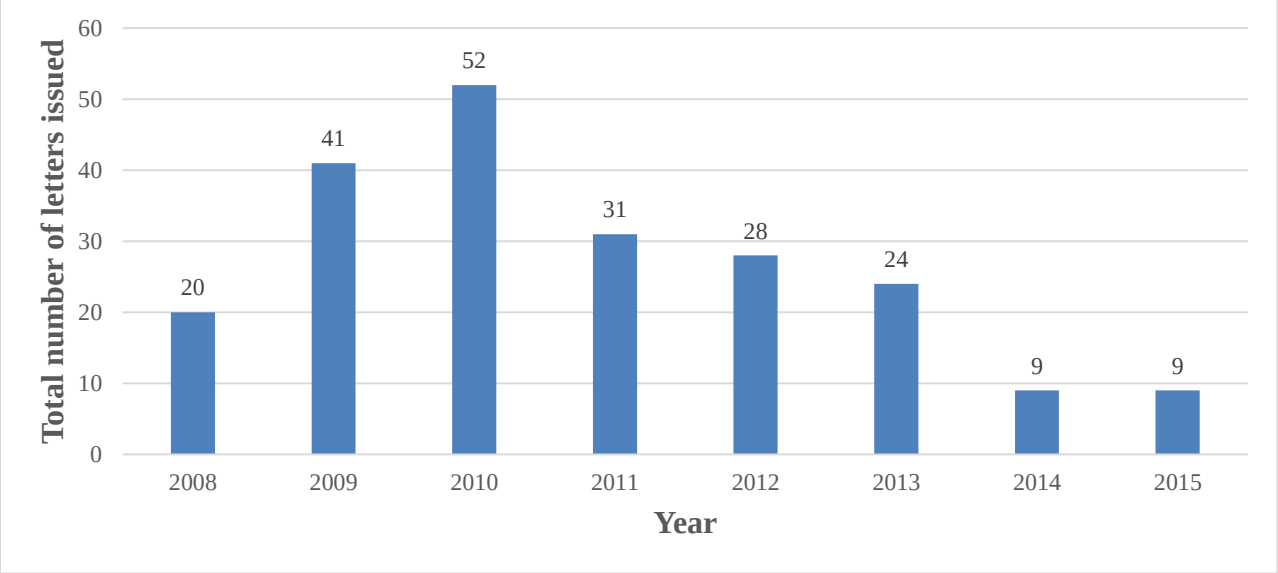


Figure 2, depicts the graphical distribution of letters by year. In the year 2014 and 2015, lowest number of letters were issued (n=9).

Table 5 shows the distribution of letters by year.

Table 5: The number of letters issued by the DDMAC/OPDP in each year. Duration was from January 2008 to August 2015

Year of issuance	Warning Letters	Untitled Letters
2008	10	10
2009	11	30
2010	13	39
2011	3	28
2012	3	25
2013	2	22
2014	0	9
2015	2	7
Total	**44**	**170**

Figure 3 represents the number of each type of letter over the years from 2008.

Figure 3: The type of letters issued by the DDMAC/OPDP in each year. There were no WL issued in 2014.

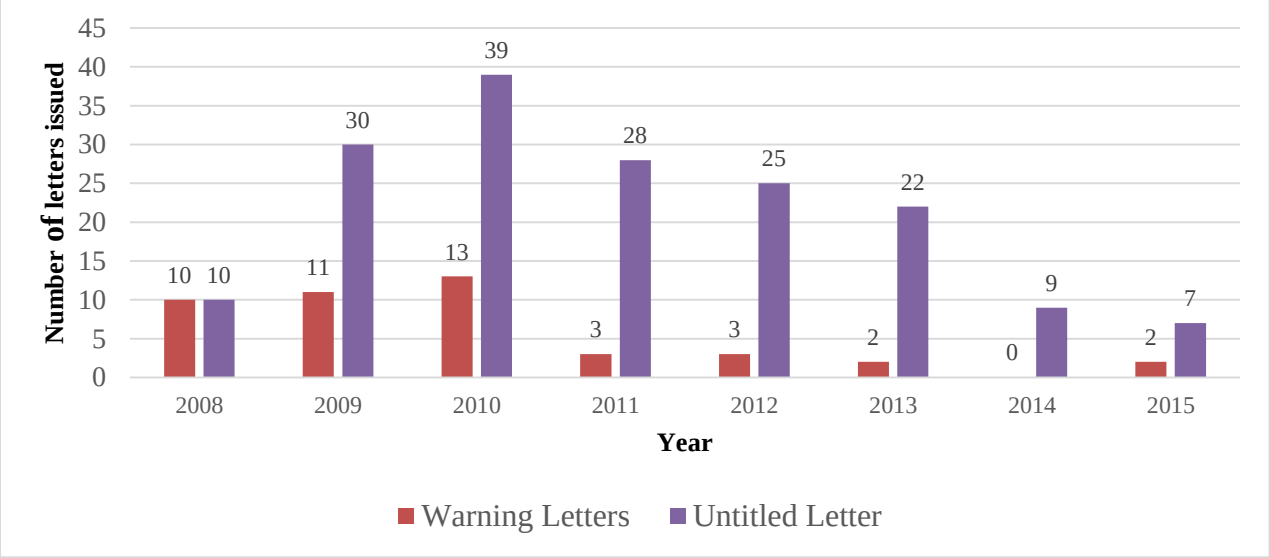
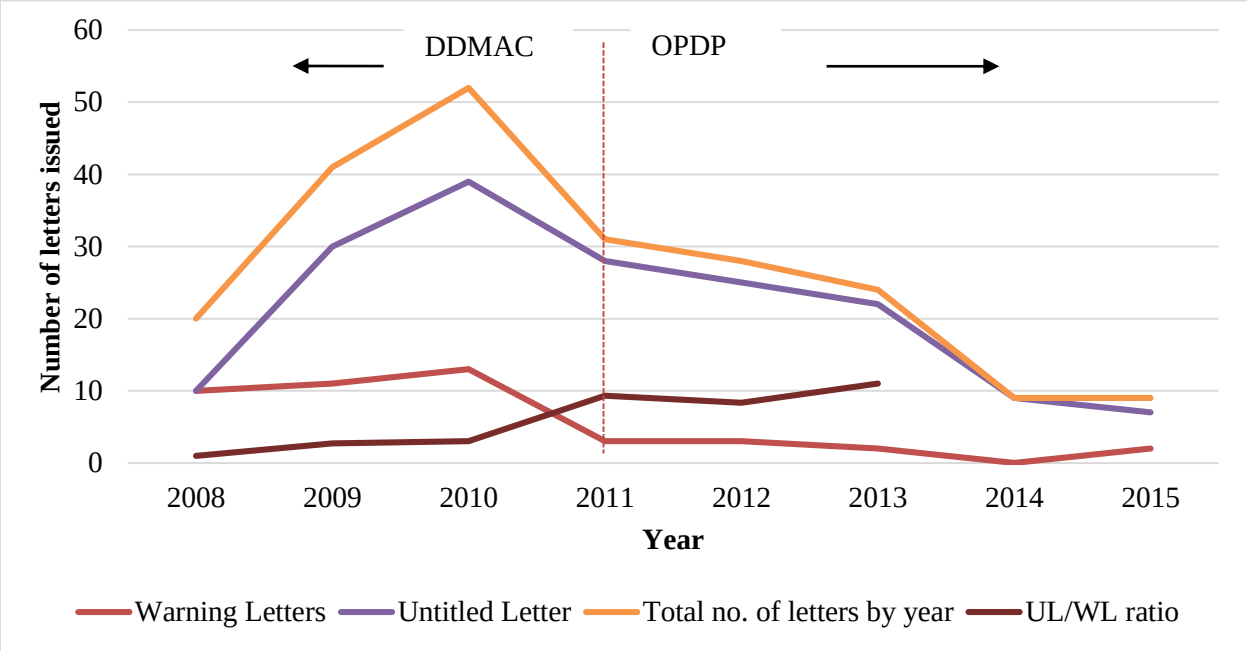


Figure 4 : Overall trends in letters. The graph depicts correlation in total letters, individual numbers of WL/UL and UL/WL ratio. The dotted vertical line represents establishment year of the OPDP in the year of 2011. The DDMAC was active from 2008 to September 2011. Two horizontal arrows denote respective periods for issuing offices on both sides of the vertical line.



From figure 3 and 4, it was evident that, the overall number of letters have steadily declined after reaching its peak in 2010. UL/ WL ratio shows an increasing trend suggesting that more number of UL were issued compared to WL in each year.

Figure 5: The percentage of WL out of total letters issued over the period of January 2008 to August 2015. There was a steady decline in percentage of WL until 2014. There were no WL issued by the OPDP in 2014.

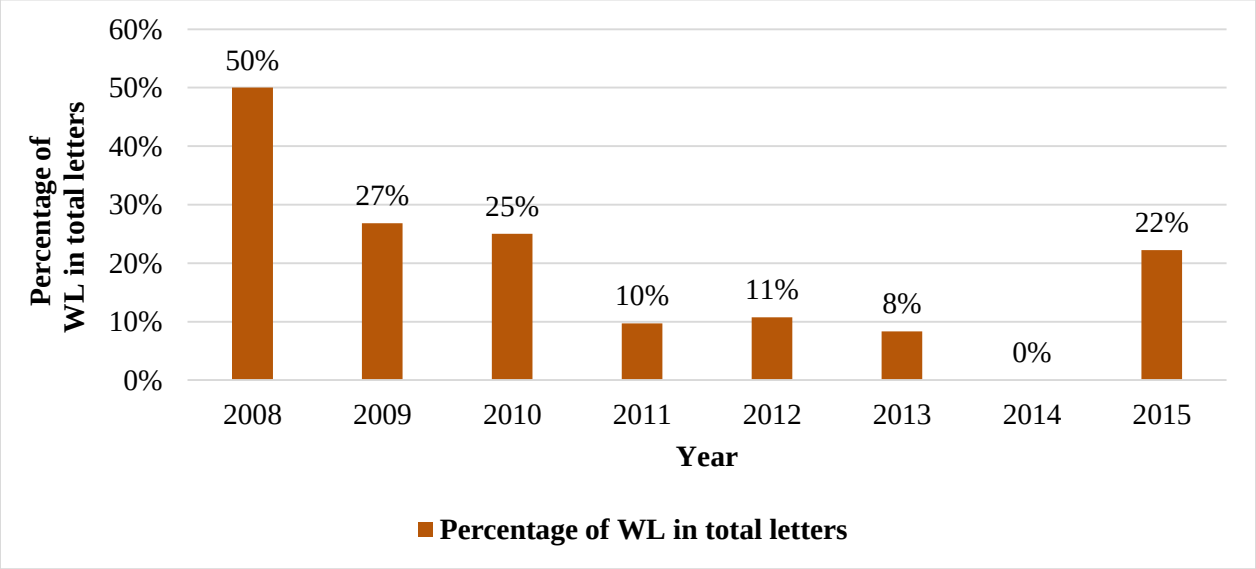


Figure 5 shows the percentage of WL by year. The percentage of WL declined from 2008. In 2014, no WL was issued by the OPDP. For the year 2015, until August, two WL were issued and it accounted for 22% of total letters.

Sources of violations

Table 6 shows different sources of violation cited in the letters by the OPDP for the initial dissemination materials, which were submitted under the FDA Form 2253. Patient information materials like brochures and patient guides had the largest number of violations (n=17), followed by sales aids (n=14).

Table 6: Sources of violations in the FDA Form 2253 submission. Sources were cited in WL/UL filed under FDA Form 2253. One letter could have multiple sources.

Source of violation in FDA Form 2253	Frequency
Patient brochure/Brochure/Notebook/Patient guide	17
Professional Sales Aid/Detail aid	14
Webpage	10
Journal advertisement/Launch journal	10
Mailer	8
Flash card/File card/Professional slide deck/Slide presentation	7
Video/Promotional DVD	6
Convention panels/Exhibit panel/Convention graphic	6
Television advertisement	4
Sales sheet/ Key fact sheet	4
Patient profile	3
Print advertisement	3
Visual aids	3
Announcing letter/Intro letter/Physician letter	3
Rebate card /Tent card/Postcard	3
Email/Sponsored links	3
Article detailer/Case highlights/Professional reprint carrier	3
Online banners	2
News ad/Press release	2
Professional card /Pocket dosing card	2
Flyer/Leave behind	2
Branded story	1
Dosing sheet	1
Medical exam light case	1
Professional telephone script	1
Waiting room sign	1
Total	120

Table 7 shows sources of violations which did not come under the FDA Form 2253 submission. In this category, the largest source was webpage (n=26) followed by sponsored links (n=14).

Table 7: Sources of violations other than the FDA Form 2253 submission. Sources were mentioned in WL/UL. One letter could have multiple sources.

Source of violation (Non-FDA Form 2253 submission)	**Frequency**
Webpage	26
Sponsored link	14
"Bad Ad" Program	9
Video/Patient Testimonial Videos/Video News Releases/ Television Interview	8
Oral statements made by a representative	7
Sales aid /Pharmacology aid	7
Brochure/Patient brochure	4
Print ad	3
Facebook/Social media post	3
Flash card/Leave behind sheet/White paper	3
Pharmacy printouts/labeling piece/Product sheet	3
Exhibit banner/Professional table top panels	2
Podcast/Webcast	2
Direct mail/Letter	2
Book	1
Clinical meeting	1
Email	1
Live consumer-directed program	1
Professional journal advertisement	1
Promotional statements	1
WebMD little blue book	1
Total	100

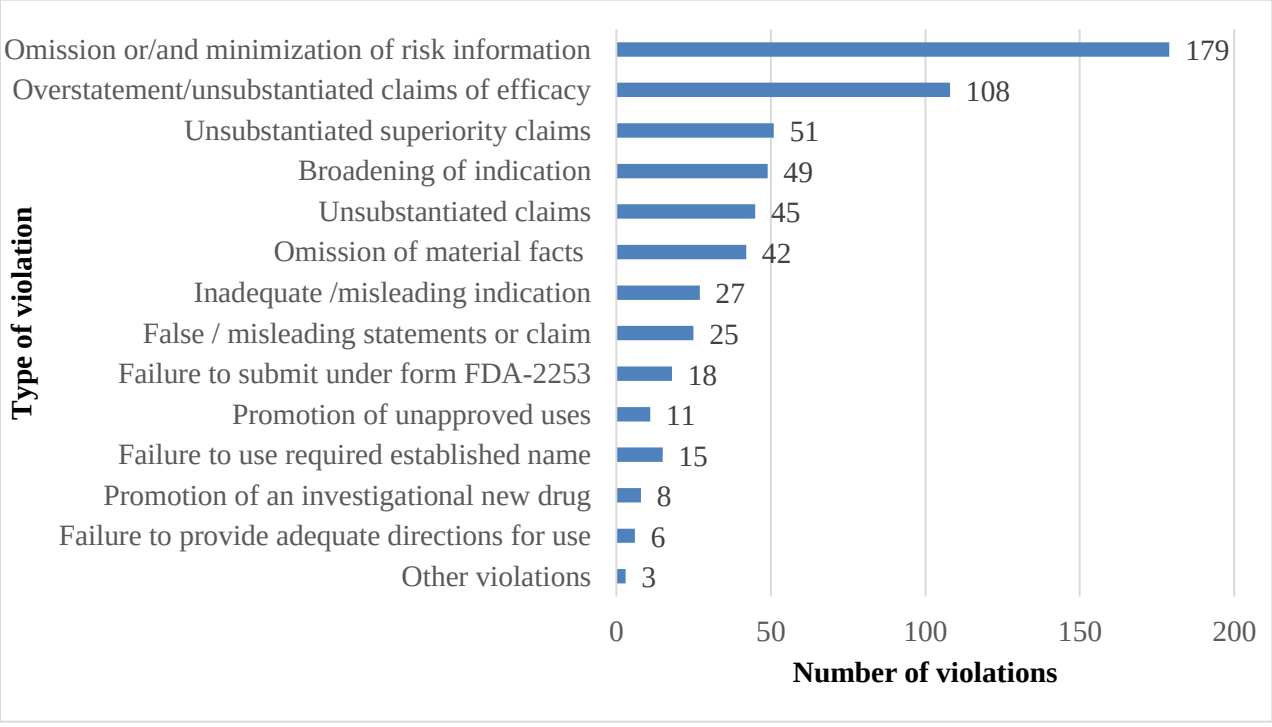
Table 7 shows that, within the category of non-FDA Form 2253 submissions, the highest cited source for violations was website (n=26 or 26%) and sponsored links (n=14 or 14%). The OPDP also considered the oral statements made by company representatives (n=7 or 7%). Patient brochure and sales aid which were on top in the FDA Form 2253 submissions merely contributed 1% in the non-FDA Form 2253 submissions.

Types of violations

Figure 6 depicts all types of violations cited in WL/UL during the period of January 2008 to August 2015. In total, there were 587 violations cited in these letters. Overall, the categories mentioned were kept same as they were cited in the FDA issued letters. However, some categories were consolidated to keep consistency in content and meaning. The similar type of violations were grouped together. For example, 'failure to state full indication', 'inadequate indication', 'misleading indication', and 'omission of indication' were grouped under the category of 'inadequate or misleading indication'. Some violations which had relatively less citations, were grouped into the category of "other violations" as mentioned in Table 8.

Omission/minimization of risk information was the most commonly observed type of violation (n=179) followed by overstatement or unsubstantiated claims of efficacy (n=86).

Figure 6: Types of violations mentioned in WL/UL. A letter could have multiple types of violations.



Following section describes each type of violation in detail.

1. **Omission or/and minimization of risk information (n=179, 30%)**

This was the most common violation type observed. It was found in the FDA Form 2253 submission, as well as non-FDA Form 2253 submissions. Many letters, citing this type of violation had the standard text specifying, "promotional materials are misleading if they fail to reveal facts that are substantial in light of the representations made by the materials or with respect to consequences that may result from the use of the drug as recommended or suggested by the materials".

According to 21 CFR 202.1(e) (5), an advertisement should present "true statement" of information. It should also completely reveal all contraindications, side effects with fair balance. The advertisements lacking this information were considered misleading and violative. Special statements like "boxed warnings" should be prominently displayed to catch the attention of patients and healthcare providers. The OPDP has also paid close attention to where these special statements were placed within the advertisement. In addition, stating only the links for the sections of warnings and contraindications or referring to another section was not accepted.

Thus, any advertisement that lacked risk information was deemed as misleading and cited as a violation in the letter. The regulatory codes cited for this type of violations were section 21 U.S.C. 352(a), 321(n) and 21 CFR 202.1(e) (5).

2. **Overstatement or unsubstantiated claims of efficacy (n=108, 18%)**

Letters citing this violation stated that, promotional materials were misleading if they suggested that the drug was better or more effective without presenting any demonstrated evidence from clinical trials or clinical experience.

Advertisements had different types of efficacy claims as below

1. The drug cured specific condition to a great extent
2. Extended survival
3. The drug provided statistics for better efficacy
4. Provided additional benefits etc.

However, underlying data from clinical trials did not support these claims. Hence, these advertisements were deemed as misleading and violative of 21 CFR 202.1 (e) (6) (i), (e)(7)(i), (iii), (e)(7)(viii).

3. Unsubstantiated superiority claims (n =51, 9%)

If an advertisement claimed that a particular drug was safer or more efficacious than any other drug and if this claim was not substantiated by placebo controlled, randomized trials comparing both drugs, then it was deemed as unsubstantiated superiority claim.

Letters cited different forms of unsubstantiated superiority claims as below:

1. Safer (than other drug) and more efficacious
2. More potent
3. Longer half life
4. Superior pharmacokinetic and pharmacodynamics parameters
5. Superior dosing regimens etc.

These claims were found to be in violation of 21 CFR 202.1(e) (5) (i), (iii), (e)(6)(i), (ii), (xviii).

4. Broadening of the indication (n=49, 8%)

Some advertisements suggested that the drug could be used in a broad range of conditions or patients. However, if it was not demonstrated by substantial evidence from clinical trial data or clinical experience then it was considered as broadening of indication. This type of

advertisements were also deemed as misleading. Some of the advertisements in this category failed to appropriately define the patient population. Some advertisements did not mention conditions of use of the drug.

This was cited as violation of 21 CFR 202.1(e)(6)(i).

5. **Unsubstantiated claims (n=45, 8%)**

This category grouped together all types of unsubstantiated claims made in the advertisements including claims for safety and efficacy. The OPDP treated promotional materials as misleading if they suggested that the drug was efficacious or safer than it was demonstrated in clinical trials or clinical experience.

This category included the following types of claims

1. Unsubstantiated comparative claim
2. Unsubstantiated compliance claim
3. Unsubstantiated mechanism of action claims
4. Misleading superiority claims
5. Unsubstantiated dosing claims
6. Unsubstantiated claims of safety

The OPDP has viewed such type of claims in totality and their general impression on readers. These claims were in violation of 21 CFR 202.1(e)(7)(i), (iii).

6. **Omission of material facts (n=42, 7%)**

This type of violation was comprehensive and cited for exclusion of any important information from the advertisement.

Some of the examples of omission were as follows:

1. Omission of approved indications
2. Omission of comprehensive treatment programs
3. Omission of contraindications
4. Omission of approved treatment phase and duration
5. Omission of severe symptoms
6. Omission of statement about the adjuvant treatment
7. Omission of dosing information
8. Omission of precautions while administering drugs

The relevant CFR code cited for this violation was 21 CFR 202.1(e) (5).

7. Inadequate / misleading indication (n=27, 5%)

This violation was cited for failure to state full indication, inadequate communication of indication or misleading representation of indication.

The FDA approves some drugs only for the specific type of indication or they can be used only at the particular stage of disease. An advertisement should include all these conditions while presenting the approved indication. Some advertisements present an indication in highly complex medical terms, which cannot be understood by a nonprofessional. In this case, this violation was quoted.

CFR code cited for this violation was 21 CFR 202.1(e) (3) (ii)

8. False / misleading statements or claim (n=25, 4%)

This violation was cited if the information presented in the advertisement directly or indirectly contradicted package insert or full prescribing information. For example, if the drug had potentially serious adverse effects and the advertisement claimed the drug to be safe, then

this violation was cited in letters. Some advertisements claimed that the drug had expanded access (for compassionate use) while the approval for expanded access had not been granted by the FDA. In this case, the advertisement was cited for a false and misleading claim. This was considered as violation of 21 CFR 312.300, 21 CFR 202.1(e)(3)(iii).

9. Failure to submit under the FDA Form 2253 (n=18, 3%)

All companies are required to submit all kind of promotional material at the time of launch and at the first publication of the advertisement for all prescription drugs. Each submission should be accompanied by the FDA Form 2253 (Transmittal of advertisements and promotional labeling for drugs for human use). This is required by 21 CFR 314.81(b) (3)(i).The advertisements which failed to submit the initial copy of advertisement for the FDA review were cited with for this type of violation.

10. Failure to use required established name (n=15, 3%)

The advertisements which failed to present full established name as required by 21 CFR 201.10(g) (1) were cited with this violation.

Particularly, 14 letters issued in 2009 for sponsored links in the web search engine have cited this violation. An inadequate presentation of established name was also cited as a violation under this category.

11. Promotion of unapproved uses (n=16, 3%)

Some advertisements were found to promote the drug for unapproved use. Hence, this violation was cited in 16 letters according to 21 CFR 201 (e) (6)(i).

In this violation category, oral statements made by company representatives was a common cause. Some company representatives told prescribers that the drug was approved in other countries for another use. However, it was not approved in the US for that indication. Hence, some letters made it clear that, though the drug was approved in other territories, it was not legal to promote it in the US for that unapproved use even through verbal means.

12. Promotion of an investigational new drug (n=8, 1%)

According to 21 C.F.R. § 312.7(a), an investigational drug cannot be presented in the promotional context implying that it is safe and effective to use. However, the information exchange about the investigational drug can be limited to scientific purposes.

Since investigational product's indication(s), warnings, precautions, adverse reactions, dosage and administration could not be established until approval, it could not be considered as safe for use in general population. Hence, commercial advertising of an investigational drug was prohibited in any form.

13. Failure to provide adequate directions for use (n=6, 1%)

This violation was cited when an advertisement claimed use of the drug in conditions other than approved labeling. Eventually the product failed to provide adequate directions for use.

For example, if a product was approved only for the treatment of a condition and an advertisement claimed that it was useful also for prevention. In this scenario, the use of drug for preventive use should be approved by the FDA and it should also have complete prescribing information.

This was in violation of CFR 201.5, 201.100.

14. Other violations (n=3, 1%)

Under this category, relatively low frequency violations were included as shown in Table 8.

Table 8: Other violations. Violations with relatively low frequency were grouped under this category.

Other types of violations	Frequency
Failure to fulfill "adequate provision" requirement	1
Failure to submit during the preapproval review period	1
Inappropriate reminder labeling	1

a) Failure to fulfill the "adequate provision" requirement (n=1)

The "adequate provision" requirement is the condition to disseminate sufficient approved labeling information to the consumer. According to 21 CFR 202.1(e) (1), the advertisement should mention a brief summary of side effects, contraindications etc. This violation was cited in one letter with missing "adequate provision" requirement.

b) Failure to submit during the preapproval review period (n=1)

If any biologic was approved under 21 CFR 601.41, the FDA mandated that companies should submit all copies of all promotional materials including labeling information within 120 days of market approval. One letter was issued failing to fulfill this requirement.

c) Inappropriate reminder labeling (n=1)

Reminder labeling should only mention the name of the drug according to 21 CFR 201.100(f). One letter was issued for an advertisement, which included only the drug name but had graphical representations that implied indication.

Chapter 5: Discussion

Number of letters over the years

This study found that a total 214 letters were issued. Out of that, 44 were WL and 170 were UL. The two most visible patterns emerged from the analysis were decrease in overall number of letters for advertising violations (Figure 2) as well as the decrease in number of WL in each year after 2010 (Figure 3). In addition, the most common type of violations were related to safety and efficacy information, which contributed to 48% of overall violations (Figure 7).

There was a spike in overall letters issued in 2009 and 2010 (41 and 52 letters respectively). These letters were issued by the DDMAC. Out of 41 letters issued in 2009, 14 UL were issued for a single source of sponsored links, which were used for online advertisements. In addition, there was a decline in number of WL after 2010. From 13 WL in 2010 to 3 WL in 2011 describes approximately 77% decline in these two years. After 2010, the WL count has remained less than three until 2015. In the year of 2014, there was no WL issued by the OPDP.

As shown in Figure 4, the vertical line represents the year 2011 when the DDMAC transitioned to the OPDP. This line divides the graph in two sections to represent the tenure of the DDMAC on the left side and the OPDP on the right side of the graph. There was a sharp drop in number of letters issued in 2011. The decline in letters continued until 2015. This decline was observed in total number of letters and individual WL/UL numbers. However, UL/WL ratio increased from 2011 suggesting that more number of UL were issued compared to WL after 2011. Figure 5 depicts the percentage of WL issued each year. It is clear from the graph that the percentage of WL has steadily decreased from 2008. The lowest point was in 2014, when no WL were issued. However, in 2015 two WL were issued with seven UL. Hence, this year the percentage of WL spiked to 22%.

The downward trend in overall letters (Figure 2) may be ascribed to several factors like evolution of guidance over the years, evolution of FDA policies, and better compliance for promotional activities by pharmaceutical companies.

Evolution of the FDA guidance documents

Until 2009, only four guidance were available regarding advertising regulations. However, since 2009, the FDA has issued eight more advertising guidance (final or drafts) which averaged to about one guidance per year (Food and Drug Administration, 2015c). There was increasing use of Internet and social media for advertising since 2008. Hence, in 2014, the FDA issued its first draft guidance directed at third party misinformation on Internet/Social Media platforms. This evolution of guidance documents may have helped manufactures to design and present online advertisements in a more compliant manner.

Evolution of the FDA policies

The two major factors that may have contributed to the reduction of letters are risk-based approach in enforcement and assessment of WL by the Office of Chief Counsel. Risk based approach may have enabled the FDA to focus on most significant violations in consideration of public safety. The OCC review may have helped in filtering of letters only with stellar legal base.

To improve policies, the FDA also takes some initiatives. It conducts various studies and research programs to understand industry trends and their repercussions on public health. This has helped to keep the FDA policies current with industry trends (Woodcock, 2009).

Improvement in compliance to advertising regulations

Increased information dissemination to public through Internet and Social media may have prompted companies to be more cautious about regulatory letters from the FDA.

Additionally, there are other tools available for the industry to achieve better compliance for advertisements. The FDA staff participates in industry outreach programs such as panel discussions and presentations across the pharmaceutical industry and law firms. These programs are part of the FDA's continuous effort to disseminate better understanding of regulations (Woodcock, 2009).

All these reasons may have encouraged pharmaceutical companies to take a more responsible approach in product advertising.

Types of violations

To analyze the types of violations was another objective of this study. In total, 587 violations were cited in letters issued from January 2008 to August 2015. As described in Figure 6, the most common type of violation was the minimization or omission of risk information (n=179, 30%). This finding was also consistent with another study conducted in the past (Chang, Noormohamed, & Nadal, 2010). The second type of violation was overstatement of efficacy(n=108, 18%). These two categories account for 48% of overall violations. This shows that the FDA was concerned more about safety and efficacy information in the advertisements.

Companies engage in misleading advertisements to gain competitive advantage in the market (Benson & Alfors, 2007). Additionally, consumers are more receptive to such convincing claims rather than information based product advertising (Holmes & Desselle 2004). Hence, the FDA concentrated more risk and efficacy information. In case of "minimization of risk information" letters explicitly state that all major risk related information should be mentioned. The letters also illustrate increased importance given to the location where the risk related warnings appear. It is the FDA's clear stand that, important messages such as "Boxed Warnings" should be prominently displayed on the promotional material to catch the attention of

the consumer or prescriber. To address this important issue, the FDA has released a separate draft guidance in 2009 for presenting risk information in prescription drugs and medical device promotions (Table 1). Another draft guidance was recently released in 2015 regarding brief summary and adequate directions for use in promotional materials.

In case of efficacy claims, promotional materials not adhering to approved indications and prescribing information were cited. The superiority claims (n=51, 9%) and broadening of indication claims (n=49, 8%) were cited for lack of evidence from appropriate clinical trials or clinical experience. The omission of material facts was cited for 42 times due to exclusion of important information like contraindications and dosing information.

Warning letter vs. Untitled letter:

Issuance of either WL or UL was an important consideration for the DDMAC/ OPDP. It was observed that, WL were issued for repeat violations and for the breach of some important regulations like the omission of risk information.

The number of violations were seen to be a determining factor in differentiating WL to UL. On an average, WL were found to have three violations in different categories. Some WL were also issued for a single violation of omission of risk information. Therefore, it can be concluded that the FDA decision to issue WL or UL was a combination of frequency and relative severity of different violations. This was consistent with the senate committee statement provided by CDER director Janet Woodcock about regulation of prescription drug promotion (Woodcock, 2003). This trend was also visible for letters issued until 2015.

The knowledge obtained from this study could be helpful for consumers, prescribers, industry and government. This study could help consumers to have a better understanding of DTCA and its impact. Prescribers could assess advertisements more objectively and make

informed choices among available drugs. Pharmaceutical industry could present their product information in a compliant way. Governmental agencies could assess trends in advertising violations and design efficient processes for reducing advertising violations.

Overall, the findings from this study highlighted the cause of providing clear, substantiated and scientifically validated information to consumers and promote transparent advertising practices. All letters indicate clear focus of the FDA on dissemination of substantiated scientific information and consumer safety.

Study limitations

The results from this study were based on letters posted on the FDA website. Therefore, the conclusions from this study are pertinent to the number of letters and their content posted by the FDA.

Though the categories of violations presented in this study were based on the categories cited in letters, some WL/UL had overlapping categories and the decision to include the violation in a particular category was taken based on content of the letter and subjective judgment.

Finally, duration of analysis was from January 2008 to August 2015. Hence, the findings from this study can be generalized only to this period.

Chapter 6: Conclusions

Analysis of WL/UL from this study served as an insight to the diverse nature of advertising violations by pharmaceutical manufactures. It was also helpful in interpreting the FDA perspective on violations in different formats of advertising.

Though the number of letters for advertising violations have declined since 2011, the categories with most common violations remain same. Omission of risk information and unsubstantiated efficacy claims still form a major cause of violations. This calls for a clear definition of safety and efficacy information to be included in advertisements. Going forward, a well-defined standard framework can be developed by regulatory agencies to avoid repetitions of these violations in promotional materials.

Prescription drug advertising, if done right, can serve as an important informative link of communication between manufacturers, prescribers and consumers. To maintain this valuable link, manufacturers and the FDA can effectively work together to generate truthful and compliant advertisements and ultimately enhance public health. The goal of DTCA is to enable consumers and prescribers to make more informed decisions about their healthcare choices and this can be served only with truthful and balanced prescription drug advertising.

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Appendix

List of warning letters analyzed

No.	Year	Company	Letter type	Hyperlink
1	2015	Duchesnay, Inc.	Warning	http://www.
2	2015	ECR Pharmaceuticals	Warning	http://www.
3	2015	ASCEND Therapeutics	Untitled Letter	http://www.
4	2015	Actavis Laboratories	Untitled Letter	http://www.
5	2015	Oak Pharmaceuticals, Inc.	Untitled Letter	http://www.
6	2015	Otsuka Pharmaceutical	Untitled Letter	http://www.
7	2015	Discovery Laboratories, Inc	Untitled Letter	http://www.
8	2015	UCLA	Untitled Letter	http://www.
9	2015	Luitpold Pharmaceuticals, Inc.	Untitled Letter	http://www.
10	2014	Sunovion Pharmaceuticals, Inc.	Untitled Letter	http://www.
11	2014	Sciecure Pharma	Untitled Letter	http://www.
12	2014	Cipher Pharmaceuticals Inc	Untitled Letter	http://www.
13	2014	Concordia Pharmaceuticals Inc	Untitled Letter	http://www.
14	2014	Gilead Sciences	Untitled Letter	http://www.
15	2014	Citius Pharmaceuticals, LLC	Untitled Letter	http://www.
16	2014	Alvogen, Inc	Untitled Letter	http://www.
17	2014	Institut Biochimique SA	Untitled Letter	http://www.
18	2014	Assurance Mission Pharmacal Company	Untitled Letter	http://www.
19	2013	DaraBiosciences, Inc.	Untitled Letter	http://www.
20	2013	Pernix Therapeutics Holdings, Inc.	Untitled Letter	http://www.
21	2013	Amarin Pharmaceuticals Ireland LTD	Untitled Letter	http://www.
22	2013	Covis Pharmaceuticals	Untitled Letter	http://www.
23	2013	Amgen,	Untitled Letter	http://www.
24	2013	Kadmon Pharmaceuticals	Warning	http://www.
25	2013	Duchesnay,	Untitled Letter	http://www.
26	2013	US WorldMeds, LLC	Untitled Letter	http://www.
27	2013	Aegerion	Untitled Letter	http://www.
28	2013	Daiichi Sankyo, Inc.	Untitled Letter	http://www.
29	2013	Sunovion	Untitled Letter	http://www.
30	2013	Merz Pharmaceuticals	Untitled Letter	http://www.
31	2013	Acorda Therapeutics	Warning	http://www.
32	2013	Spectrum Pharmaceuticals	Untitled Letter	http://www.
33	2013	Johnson & Johnson International,	Untitled Letter	http://www.
34	2013	Janssen Biotech Products	Untitled Letter	http://www.
35	2013	Sigma-tau Pharmaceuticals	Untitled Letter	http://www.
36	2013	Validus	Untitled Letter	http://www.

37	2013	Mobius Therapeutics	Untitled Letter	http://www.
38	2013	CBA Research	Untitled Letter	http://www.
39	2013	Teva Neuroscience	Untitled Letter	http://www.
40	2013	Omission of Material Fact/Minimization of	Untitled Letter	http://www.
41	2013	ParaPRO,	Untitled Letter	http://www.
42	2013	Alcon Research	Untitled Letter	http://www.
43	2012	Salix Pharmaceuticals	Untitled Letter	http://www.
44	2012	Alcon Research	Untitled Letter	http://www.
45	2012	Cornerstone	Untitled Letter	http://www.
46	2012	ONY,	Untitled Letter	http://www.
47	2012	Burzynski	Untitled Letter	http://www.
48	2012	Genentech,	Untitled Letter	http://www.
49	2012	Endo	Untitled Letter	http://www.
50	2012	Jazz	Warning	http://www.
51	2012	Eli Lilly	Untitled Letter	http://www.
52	2012	Forest	Untitled Letter	http://www.
53	2012	Valeant	Untitled Letter	http://www.
54	2012	Bristol-Myers Squibb	Untitled Letter	http://www.
55	2012	Validus	Untitled Letter	http://www.
56	2012	Acorda	Untitled Letter	http://www.
57	2012	Valeant	Untitled Letter	http://www.
58	2012	Pfizer	Untitled Letter	http://www.
59	2012	Quintiles,	Untitled Letter	http://www.
60	2012	Watson	Untitled Letter	http://www.
61	2012	Vertex	Untitled Letter	http://www.
62	2012	Pfizer	Warning	http://www.
63	2012	Meda	Untitled Letter	http://www.
64	2012	The Medicines Company	Untitled Letter	http://www.
65	2012	Ferring	Untitled Letter	http://www.
66	2012	Biogen	Untitled Letter	http://www.
67	2012	Teva	Warning	http://www.
68	2012	Dow	Untitled Letter	http://www.
69	2012	Merck	Untitled Letter	http://www.
70	2012	Novartis	Untitled Letter	http://www.
71	2011	Celgene	Untitled Letter	Untitled
72	2011	Dr. Reddy's	Untitled Letter	Untitled
73	2011	Mutual	Untitled Letter	Untitled
74	2011	Sunovion	Untitled Letter	Untitled
75	2011	NeurogesX,	Untitled Letter	Untitled
76	2011	EUSA	Untitled Letter	Untitled
77	2011	Lantheus	Untitled Letter	Untitled
78	2011	Otsuka	Untitled Letter	Untitled
79	2011	Alcon	Untitled Letter	Untitled
80	2011	Pfizer	Untitled Letter	Untitled

81	2011	Ortho-McNeil-Janssen	Untitled Letter	Untitled
82	2011	CEL-SCI Corporation	Untitled Letter	Warning
83	2011	Valeant Pharmaceuticals	Untitled Letter	Untitled
84	2011	ISTA	Untitled Letter	Warning
85	2011	AOI	Untitled Letter	Untitled
86	2011	Cephalon,	Untitled Letter	Untitled
87	2011	Nycomed	Untitled Letter	Untitled
88	2011	Dow	Untitled Letter	Untitled
89	2011	Novartis	Untitled Letter	Untitled
90	2011	Noven	Untitled Letter	Untitled
91	2011	Shire	Warning	Warning
92	2011	Warner	Untitled Letter	Untitled
93	2011	ChemGenex	Untitled Letter	Untitled
94	2011	Forest	Untitled Letter	Untitled
95	2011	Arbor	Untitled Letter	Untitled
96	2011	Inspire	Untitled Letter	Untitled
97	2011	Three Rivers	Warning	Warning
98	2011	Taro	Untitled Letter	Untitled
99	2011	AMAG	Untitled Letter	Untitled
100	2011	Genentech,	Untitled Letter	Untitled
101	2011	DENTSPLY	Warning	Warning
102	2010	Hill Dermaceuticals, Inc.	Warning	Warning
103	2010	Watson Pharmaceuticals, Inc.	Untitled Letter	Warning
104	2010	Allergan Inc.	Untitled Letter	DDMAC
105	2010	Alkermes Inc.	Untitled Letter	Warning
106	2010	Tercica Inc.	Warning	DDMAC
107	2010	AMAG Pharmaceuticals, Inc.	Warning	DDMAC
108	2010	Alcon Research Ltd.	Untitled Letter	DDMAC
109	2010	Wyeth Pharmaceuticals, Inc.	Untitled Letter	DDMAC
110	2010	Allergan, Inc.	Untitled Letter	DDMAC
111	2010	Novartis Pharmaceuticals Corporation	Untitled Letter	Warning
112	2010	Novartis Pharmaceuticals Corporation	Untitled Letter	DDMAC
113	2010	AstraZeneca LP	Untitled Letter	DDMAC
114	2010	Axcan Pharma, Inc.	Warning	DDMAC
115	2010	Jazz Pharmaceuticals	Warning	DDMAC
116	2010	Cornerstone Therapeutics, Inc.	Warning	DDMAC
117	2010	Shire Development, Inc.	Untitled Letter	DDMAC
118	2010	Cumberland Pharmaceuticals, Inc.	Untitled Letter	DDMAC
119	2010	Auxilium Pharmaceuticals, Inc.	Untitled Letter	DDMAC
120	2010	Sepracor, Inc.	Untitled Letter	DDMAC
121	2010	Eisai Corporation of North America	Untitled Letter	Warning
122	2010	Amgen, Inc.	Untitled Letter	Warning
123	2010	Genentech, Inc.	Untitled Letter	DDMAC
124	2010	Shire Development, Inc.	Untitled Letter	DDMAC

125	2010	Shire Development, Inc.	Untitled Letter	DDMAC
126	2010	Novartis Oncology	Warning	DDMAC
127	2010	Adolor Corporation	Untitled Letter	DDMAC
128	2010	Sanofi-Aventis U.S., Inc.	Untitled Letter	DDMAC
129	2010	GlaxoSmithKline	Warning	Warning
130	2010	GlaxoSmithKline	Untitled Letter	DDMAC
131	2010	Novartis Consumer Health, Inc.	Untitled Letter	DDMAC
132	2010	Astellas Pharma US, Inc.	Untitled Letter	Warning
133	2010	Luitpold Pharmaceuticals, Inc.	Untitled Letter	DDMAC
134	2010	Aton Pharma, Inc.	Untitled Letter	DDMAC
135	2010	Hoffman-La Roche Inc	Untitled Letter	DDMAC
136	2010	Gilead Sciences, Inc.	Untitled Letter	DDMAC
137	2010	Genentech, Inc.	Untitled Letter	DDMAC
138	2010	Biogen Idec, Inc.	Untitled Letter	DDMAC
139	2010	Slate Pharmaceuticals, Inc.	Warning	DDMAC
140	2010	Salix Pharmaceuticals, Inc.	Warning	DDMAC
141	2010	ISTA Pharmaceuticals, Inc.	Warning	DDMAC
142	2010	Actavis US	Warning	DDMAC
143	2010	Sirion Therapeutics, Inc.	Warning	Warning
144	2010	Eisai Medical Research Inc.	Untitled Letter	DDMAC
145	2010	Takeda Pharmaceuticals North America, Inc.	Untitled Letter	DDMAC
146	2010	Lilly Corporate Center	Untitled Letter	DDMAC
147	2010	Meda Pharmaceuticals, Inc.	Untitled Letter	DDMAC
148	2010	sanofi-aventis U.S. LLC	Untitled Letter	DDMAC
149	2010	Novalar Pharmaceuticals, Inc.	Untitled Letter	Warning
150	2010	Baumann Cosmetic and Research Institute	Untitled Letter	DDMAC
151	2010	Bracco Diagnostics Inc.	Untitled Letter	Warning
152	2010	GE Healthcare	Untitled Letter	Warning
153	2010	Eli Lilly and Company	Untitled Letter	Warning
154	2009	Bayer HealthCare Pharmaceuticals Inc.	Untitled Letter	DDMAC
155	2009	Amylin Pharmaceuticals, Inc.	Untitled Letter	DDMAC
156	2009	Cephalon, Inc.	Untitled Letter	DDMAC
157	2009	Iroko Pharmaceuticals, LLC	Untitled Letter	DDMAC
158	2009	Eisai, Inc.	Warning	Warning
159	2009	Shire Development Inc	Warning	Warning
160	2009	Sanofi-Aventis U.S. LLC	Untitled Letter	DDMAC
161	2009	King Pharmaceuticals, Inc.	Warning	Letter (PDF
162	2009	Bioniche Pharma	Warning	Letter56
163	2009	Allergan, Inc.	Untitled Letter	DDMAC
164	2009	Johnson & Johnson, Consumer & Personal	Untitled Letter	ERTACZO
165	2009	Pedinol Pharmacal, Inc.	Warning	Nalfon®
166	2009	Galderma Laboratories	Untitled Letter	Tri-Luma®
167	2009	Allergan, Inc.	Untitled Letter	ACZONE®
168	2009	Abbott Laboratories	Warning	NDA #s 21-

169	2009	Alaven Pharmaceutical LLC	Warning	NDA #19-
170	2009	Millennium Pharmaceuticals, Inc.	Untitled Letter	Velcade
171	2009	Romark Laboratories, L.C.	Warning	Alinia
172	2009	Dexcel Pharma Technologies Ltd.	Warning	PerioChip
173	2009	Cornerstone Therapeutics, Inc.	Warning	Spectracef
174	2009	Johnson & Johnson	Warning	ULTRAM
175	2009	sanofi-aventis	Untitled Letter	Taxotere
176	2009	Biogen Idec	Untitled Letter	FDA/DDM
177	2009	Sanofi Aventis, U.S.	Untitled Letter	FDA/DDM
178	2009	Bayer Healthcare Pharmaceuticals, Inc.	Untitled Letter	FDA/DDM
179	2009	GlaxoSmithKline	Untitled Letter	FDA/DDM
180	2009	Forest Laboratories, Inc.	Untitled Letter	FDA/DDM
181	2009	Cephalon, Inc.	Untitled Letter	FDA/DDM
182	2009	Johnson & Johnson Pharmaceutical Services	Untitled Letter	FDA/DDM
183	2009	Pfizer, Inc.	Untitled Letter	FDA/DDM
184	2009	Novartis Pharmaceuticals Corp.	Untitled Letter	FDA/DDM
185	2009	Genentech, Inc.	Untitled Letter	FDA/DDM
186	2009	Boehringer Ingelheim Pharmaceuticals, Inc.	Untitled Letter	FDA/DDM
187	2009	Merck & Co., Inc.	Untitled Letter	FDA/DDM
188	2009	Hoffman-LaRoche, Inc.	Untitled Letter	FDA/DDM
189	2009	Eli Lilly and Co.	Untitled Letter	FDA/DDM
190	2009	GlaxoSmithKline	Untitled Letter	FDA/DDM
191	2009	GlaxoSmithKline	Untitled Letter	Avodart
192	2009	Gilead Sciences, Inc.	Untitled Letter	Letairis
193	2009	Abbott Laboratories	Untitled Letter	Depakote
194	2009	Indevus Pharmaceuticals, Inc.	Untitled Letter	Sanctura
195	2008	Abbott Laboratories	Untitled Letter	HUMIRA
196	2008	AstraZeneca	Untitled Letter	Seroquel
197	2008	Victory Pharma, Inc.	Untitled Letter	Xodol
198	2008	Shionogi USA, Inc.	Warning	Cedax
199	2008	Actelion Pharmaceuticals US, Inc.	Warning	Tracleer
200	2008	Protherics, Inc.	Untitled Letter	Voraxaze12
201	2008	Amgen	Untitled Letter	Sensipar
202	2008	Bayer HealthCare Pharmaceuticals, Inc.	Warning	YAZ
203	2008	Shire Development	Warning	Adderall XR
204	2008	Johnson & Johnson	Untitled Letter	Concerta
205	2008	Novartis Pharmaceuticals	Untitled Letter	Focalin XR
206	2008	Mallinckrodt Inc.	Untitled Letter	Methylin
207	2008	Boehringer-Ingelheim	Warning	Mirapex
208	2008	Eli Lilly & Company	Warning	Strattera
209	2008	Forest Laboratories, Inc.	Warning	Bystolic
210	2008	Novartis Pharmaceuticals	Untitled Letter	Diovan
211	2008	Shire Development, Inc.	Untitled Letter	Fosrenol47
212	2008	Zila Pharmaceuticals, Inc.	Warning	Peridex52

213	2008	Pfizer, Inc.	Warning	Viagra54
214	2008	King Pharmaceuticals, Inc.	Warning	Avinza55