Changes in the Rate of FDA Warning Letters and Untitled Letters Issued by CDER's OPDP

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Abstract

The Office of Prescription Drug Promotion (OPDP) is the office in the Center for Drug Evaluation and Research (CDER) that protects public health by reviewing promotional materials to assure truthful, and non-misleading drug information. Warning letters (WL) and Untitled letters (UL) are issued to drug companies by OPDP for off-label drug promotion. Overall 237 letters were studied from January 2008-October 2018, out of which warning letters and untitled letters accounts for 54 and 184 respectively. After 2011, court rulings provided more freedom to drug companies on first amendment grounds so that they could promote truthful and non-misleading off label uses. Since then, there has been a notable decrease in the rate of WL and UL issued by OPDP for promoting off-label drug promotion. The number of WL has remained under three till 2018 and a total number of letters issued has changed from double digits to single digits. However, OPDP is carefully observing promotional materials that are more serious rather than promotional materials that provide truthful and non-misleading information. The most common promotional violations found in this study were the omission and/or minimization of risk information (35%) and overstatement of efficacy claims (20%). This demonstrates that OPDP is more concerned about drugs safety and effectiveness that could impact public health.

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Introduction

OPDP

The Office of Prescription Drug Promotion (OPDP) is an office in the Center for Drug Evaluation and Research of the Food and Drug Administration (FDA). OPDP was previously known as Division of Drug Marketing, Advertising, and Communications (DDMAC) until November 2011. It is responsible for protecting and promoting public health by ensuring that truthful, balanced, and accurate information about the prescription drug is being promoted (Center for Drug Evaluation and Research, 2019). This protection is possible by handling promotional violations in a drug's labeling and promotional materials offered on social media, tv and radio advertisements, and conferences (Zegarelli, 2017). OPDP is responsible for sending Warning Letters (WL) and Untitled Letters (UL) to drug companies once off-label promotion is identified.

What is Off-label?

According to Mazina et al. (2017), off-label means when a physician prescribes a drug to be used for a disease or condition that is not approved by the FDA or not mentioned in approved labeling or packaging insert. This method of prescribing off-label drugs is very common and legal. The FDA does not control or interfere with medical practice. As a result, physicians are allowed to prescribe off-label drugs. For example, antiseizure drug topiramate is used off-label to treat alcohol dependence (Carr, 2016).

Prescribing off-label drugs is a recommended standard of care in medical practice guidelines. For instance, Mifepristone, previously approved dosage of 600mg was recently approved at a lower dosage of 200mg to induce abortions in women (Richardson, 2016). However, this seems to be standard medical practice for several years.

The physicians are not prohibited from prescribing off-label use, but drug companies are strictly prohibited from promoting and marketing off-label uses. Drug companies are responsible for promoting a drug so that it does not contain unapproved uses or has inadequate safety data for approved indications. In recent years, the FDA levied billions of dollars in fine for promoting drugs off-label. For example, in 2012, GlaxoSmithKline paid $3 billion for promoting an unapproved, off-label anti-depressant Paxil (paroxetine) in adolescents and children (Dennis, 2014; Richardson, 2016). Also, in 2013, Johnson & Johnson paid $2.2 billion or more for promoting off-label the antipsychotic Risperdal (risperidone) for an older population, children, and for patients with disorders such as anxiety, depression, and confusion.

Similarly, there are many other instances where the FDA levied criminal or civil fines to drug companies for promoting off-label use (See Table 1).

Drug company	Drug	Details	Settlement
Pfizer	Neurontin	Sales representative promoted off-label uses of Neurontin for bipolar disorder, ADHD, and other pain disorders.	$430 million (2004)
Intermune	Actimmune	Promotion of off-label uses in the treatment of Idiopathic pulmonary fibrosis.	$37 million (2006)
Jazz Pharmaceuticals	Xylem	Promotion of their drug for unapproved uses in treating bipolar disorders, fatigue, insomnia, and weight loss.	$20 million (2007)
Bristol-Myers Squibb and Otsuka American Pharmaceuticals	Abilify	Promotion of off-label uses of Abilify in treating dementia and schizophrenia.	$515 million (2008)
Pfizer	Bextra	Promotion of their drug for unapproved uses in treating acute and surgical pain.	$2.3 million (2009)
Astra Zeneca	Botox	Promotion of off-label uses in treating cerebral palsy.	$600 million (2010)
GlaxoSmithKline (GSK)	Paxil	GSK promoted Paxil for unapproved uses in the pediatric population.	$3 billion (2012)
Johnson & Johnson	Risperdal	Physicians were urged to prescribe off-label use of Risperdal in adults and children for dementia, anxiety, and depression.	$2.2 billion (2013)

Table 1. Settlements drug companies paid for promoting off-label use:
Source: Richardson & Carr, 2016

History of Off-label Promotion

The Pure Food and Drugs Act (1906) required that the drugs should meet strength and purity standards. It also prohibited misbranded, adulterated foods, drinks, and drugs shipments for sale in the United States (Meadows, 2006; Ventola, 2011). Moreover, submission of any other information to the FDA before marketing was not required except that drugs meet official standards of strength and purity. It was the FDA's responsibility to show if any drug's labeling was false or misleading for a drug to be off-market.

For instance, in 1910, the FDA seized a substantial amount of Johnson's Mild Combination Treatment for cancer after finding that the drug's label featured false claims for effectiveness (Meadows, 2006). However, the court ruled against the FDA that the act did prohibit false or misleading labeling, but not false therapeutic claims. Therefore, in 1912, Congress passed the Sherley amendment to prohibit product labeling with false therapeutic claims (Donohue, 2006).

In 1938, the Food Drug and Cosmetics Act (FDCA) required that drug companies obtain the FDA's approval before marketing their product. This act was passed after the sulfanilamide tragedy that killed 107 patients due to a toxic ingredient in a sulfanilamide elixir. As a result, adulterated or misbranded drugs were prohibited into interstate commerce (Donohue & Meadows, 2006). In the light of sulfanilamide tragedy, FDCA extended its requirements of drug labeling to include a list of ingredients, adequate directions for use and warnings (Meadows, 2006). These had to appear on the drug package in a way that it was readable and understandable by the lay-person.

Moreover, in 1951, the Durham Humphrey amendment was passed. With this act, it was required that certain drugs must be labeled for sale by prescription only. In 1957, Thalidomide was marketed as a safe drug to treat morning sickness in pregnant women; it was later determined that the drug induced a serious birth defect, phocomelia, a deformity with short hands and limbs (Meadows, 2006; Ventola, 2011). In response to the thalidomide tragedy, the Kefauver-Harris amendment was passed in 1962 that, amongst other major changes, strictly prohibited off-label promotion of drugs. This amendment mandated the drug companies show substantial evidence of effectiveness for the drug's intended use.

Until 1962, the FDA did not regulate pharmaceutical drug advertising because physicians were deemed capable of verifying the accuracy of drug advertisements (Meadows, 2006; Ventola, 2011). But as noted above, after the thalidomide tragedy, the FDA regulated the advertising of pharmaceutical drugs. This revision to the FDCA required drug advertisements to include a drug's brand and generic name, list of the ingredients, side effects, contraindications, and more. It was also required inclusion of a summary of side effects, contraindications, and warnings (Donohue, 2006). Therefore, the goal was to ensure that advertising and promotion included all necessary information on the drug product that was supported by substantial evidence.

According to Ventola (2011), drug companies were allowed to disseminate peer-reviewed or scientific journals about off-label promotion under the Food and Drug Administration Modernization Act (FDAMA) of 1997. Section 401 of FDAMA provided certain requirements for drug companies who choose to promote off-label uses of their approved drug. If a drug company complied with all the requirements stated in Section 401, the FDA would not consider this activity as an intent to promote off-label uses of the drug. Therefore, the Section 401 provision was provided as a safe harbor to promote off-label uses. However, this practice had certain limitations. In 2009, new guidance permitted drug companies to distribute-peer reviewed journals and texts but were more restrictive than before as it did not include the previous safe harbor provision. It further extended FDAMA interpretation to include non-peer-reviewed journals that included off-label indications.

Although the FDA has issued multiple guidance documents regarding off-label promotion and communication (see Table 2), some drug companies may still violate the regulations. Some have challenged the FDA in federal court.

Drug advertising and promotion guidance issued by the FDA	
Guidance	**Issued date**
Aerosol Steroid Product Safety Information in Prescription Drug Advertising and Promotional Labeling	12/1/97
Consumer-Directed Broadcast Advertisements	8/1/99
Presenting Risk Information in Prescription Drug and Medical Device Promotion	5/27/09
Responding to Unsolicited Requests for Off-Label Information about Prescription Drugs and Medical Devices	12/27/11
Direct-to-Consumer Television Advertisements- FDAAA DTC Television Ad Pre-Dissemination Review Program	3/12/12
Fulfilling Regulatory Requirements for Post Marketing Submissions of Interactive Promotional Media for Prescription Human and Animal Drugs and Biologics	1/13/14
Distributing Scientific and Medical Publications on Risk Information for Approved Prescription Drugs and Biological Products-Recommended Practices	2/28/14
Internet/Social Media Platforms with Character Space Limitations-Presenting Risk and Benefit Information for Prescription Drugs and Medical Devices	6/17/14
Internet/Social Media Platforms: Correcting Independent Third-Party Misinformation about Prescription Drugs and Medical Devices	6/17/14
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Product Name, Placement, Size, and Prominence in Advertising and Promotional Labeling	12/11/17
Presenting Quantitative Efficacy and Risk Information in Direct-to-Consumer Promotional Labeling and Advertisements Guidance for Industry	10/6/18

Table 2. Drug advertising and promotion guidances issued by FDA
Source: Center for Drug Evaluation and Research, 2019

Court's Rulings and First Amendment Issues

For years, drug companies have paid billions of dollars to resolve settlements regarding off-label promotion (See Table 3). Janet Woodcock, Director of the Center for Drug Evaluation and Research (CDER), stated that this trend seems to be changing as a result of recent court rulings (Osborn & Gingery, 2018). In cases like Sorrell v. IMS Health, U.S v. Caronia, and U.S. v. Amarin Pharma (See Table 3), the Federal District Court stated that on the basis of the First Amendment, a protection that protects the free expression of ideas such as the freedom of speech

or of the press, the FDA cannot restrict drug companies from promoting off-label uses of their drugs as long as truthful and non-misleading information was being provided (Silverman, 2015, Mazer and Curfman, 2016; Henning and Thomas, 2017). These rulings seem to have affected the FDA's authority to regulate prescription drug advertising and promotion. However, despite these rulings, OPDP continues to take action upon finding any misleading off-label promotion.

Year	Case	Court's Rulings
1999	Nonprofit Washington Legal Foundation	The U.S. District Court decided that the FDA's policy of restricting the distribution of scientific and medical journal articles describing off-label uses was an unconstitutional restriction of free speech. On appeal, it was agreed that drug companies do have First Amendment rights.
2011	Sorrell v. IMS Health	The U.S. Supreme Court held that truthful speech used in drug marketing or off-label promotion is protected under First Amendment.
2012	US v. Caronia	The Federal Second Circuit Court upturned the conviction of sale representative who promoted off-label uses of Xyrem. The court concluded that the FDA cannot prosecute drug companies and their sales representatives under the Food, Drug, and Cosmetic Act for speech promoting truthful and non-misleading off-label uses.
2015	US v. Amarin	The U.S. District Court in New York ruled out that the FDA cannot restrict truthful, off-label marketing. After the agreement, Amarin was allowed to promote one specific off-label use of Vascepa, a cardiovascular drug approved for lowering triglycerides.

Table 3. Court's role in changing the FDA's method of regulating off-label promotion
Source: Silverman, 2015; Mazer & Curfman, 2016; Henning & Thomas, 2017.

Purpose and Objective

According to Zegarelli et al. (2017), recent court rulings have played a major role in changing the FDA's enforcement focus to promotional violations that challenge serious health concerns such as the omission or/and minimization of risk information. They also found that the FDA is focusing more on drug labels with boxed warnings and less on communications conveying off-label information that could be truthful and non-misleading. For instance, OPDP Director Thomas Abrams issued a WL to Amherst Pharmaceuticals for Zolpimist (zolpidem

tartrate) for omitting important risk information and labeled warnings on the drug's website (Center for Drug Evaluation and Research, 2018). Therefore, it appears that the rate of WL and UL issued by the CDER's OPDP has likely been affected due to the Courts' rulings on First Amendment rights. This was the primary area of interest for this study.

The primary objective of this study was to evaluate whether the rate of FDA Warning Letters (WL) and Untitled Letters (UL) from CDER's OPDP has changed since the Courts' rulings on First Amendment rights.

The secondary objective was to evaluate whether the violations that were cited were more serious because of these rulings.

Methods

The total number of WL and UL issued by the OPDP and the DDMAC were evaluated. The period from January 2008 to October 2018 was selected to evaluate whether there was a change in the total number of letters (WL or UL) due to Courts' rulings on First Amendment rights. In the first step, the WL/UL were downloaded and converted to pdf format from the FDA website (Enforcement Activities by FDA, 2019). The total number of letters (WL/UL) were calculated and formatted to tables using MS Excel 2016.

In the second step, WL and UL were reviewed for promotional violations such as the omission or minimization of risk information, the omission of material facts, etc. A table was created to include promotional violations, Code of Federal Regulations (CFR) section, total number. of. violations and percentages of each violation type. After doing a thorough review, promotional violations were grouped by the CFR section that drug companies violated, and the table was updated. The current electronic version of the CFR was retrieved from the Government Publishing Office website (https://www.ecfr.gov). Next, clicking on "Title 21-Food and Drugs" from the drop-down list displays further details on parts 200-299 and 300-499. After clicking on the part, "200-299" from the Chapter I (Food and Drug Administrations) Subchapter C (Drugs; General), section §201.1 for "Labeling" and §202.1 for "Prescription Drug Advertising" was searched. Similarly, clicking on part 300-499 from Subchapter D (Drugs for Human Use), Section §312.7 for "Promotion of Investigational Drugs," §312.300 for "General Requirements for the Use of Investigational New Drugs," and §314.81 for "Other Post marketing Reports" were searched.

Results

Overall, a total of 53 (22%) WL and 184 (77%) UL from January 2008 to October 2018 were published on the FDA webpage (see Table 5). A total number of 237 letters were considered for this study (see Tables 4 and 5). These letters were cited for promoting false and misleading prescription drug information.

Year	Warning Letters	Untitled Letters	Total
2008	10	10	**20**
2009	11	30	**41**
2010	13	39	**52**
2011	3	28	**31**
2012	3	25	**28**
2013	3	21	**24**
2014	0	9	**9**
2015	2	7	**9**
2016	3	8	**11**
2017	3	2	**5**
2018	2	5	**7**

Table 4. Total Letters Issued by DDMAC/OPDP from January 2008-October 2018

Type of letters issued	Number	Percentage
WL letters issued	53	22%
UL letters issued	184	77%

Table 5. Summary of the Type of Letters Issued by DDMAC/OPDP

The total number of letters

Table 4 indicates an apparent decrease in the total number of letters through the study period. In 2010, 52 WL and UL were issued by OPDP, but then in 2013, it further decreased to 24 letters, which is less than fifty percent seen in 2010. In 2014 and 2015, OPDP issued only 9 letters. However, in 2016 it slightly increased to 11 letters. Again in 2017 and 2018, it decreased to 5 and 7 letters, which is the least number of letters seen since 2010.

Warning Letters

There was a sharp decline in the total number of WL from 13 in 2010 to only 3 in 2011 (see Table 4). In 2014, there were no WL issued by OPDP. From 2015 to 2018 only 10 (WL) were issued.

Table 6 shows promotional violations from January 2008 to October 2018. Overall, a total of 635 violations were cited in WL and UL. The most common violations are discussed below.

Promotional violations	Code of Federal Regulations (CFR.)	Total no. of. violations (N= 635)	Percentages of violations (%)
Omission or/and minimization of risk information	21CFR202.1(e)(5)	223	*35%*
Unsubstantiated/overstatement of efficacy claims	21CFR202.1(e)(6)(i), (e)(7)(i), (iii), (e)(7)(viii)	135	*20%*
Unsubstantiated superiority claims	21CFR202.1(e)(5)(i), (iii), (e)(6)(i), (ii), (xviii)	51	*8%*
Unsubstantiated claims	21CFR202.1(e)(7)(i), (iii)	49	*8%*
Omission of material facts	21CFR202.1(e)(5)	46	*8%*
Broadening of patient population/indication	21CFR202.1(e)(6)(i)	45	*7%*
False/misleading statements or claims	21CFR312.300, 21CFR202.1(e)(3)(iii)	25	*4%*
Failure to submit under the FDA form 2253	21CFR314.81(b)(3)(i)	22	*4%*
Failure to use the required established name	21CFR201.10(g)(1)	15	*2%*
Promotion of unapproved uses	21CFR201(e)(6)(i)	8	*1%*
Promotion of investigational new drug	21CFR312.7(a)	8	*1%*
Lack of/inadequate directions for use	21CFR201.5; 201.100	8	*1%*

Table 6. Promotional violations from January 2008 to October 2018

Omission or/and minimization of risk information (n=223, 35%). This type of violation states that "promotional materials are misleading if they fail to reveal facts that are important in light of the representations with respect to consequences that may result from the use of the drug as suggested or recommended in the materials". As an example, in a 2017 WL, OPDP alleged that a professional detail aid omitted important risk information regarding the use of ConZip, a drug used in the treatment of severe pain (Center for Drug Evaluation and Research, 2018 & Chavan, 2016). Although the detail aid made suggestions or recommendations

about the efficacy of the drug, it failed to provide information about the serious side effects from the use of the drug. Regulation 21CFR202.1(e)(5) states that an advertisement must present "true statement of information" including a fair balance between all contraindications and side effects. Such advertisements were held misleading and violative upon omitting or minimizing or failing to reveal important risk information resulting from the use of the drug as described in the materials.

Unsubstantiated/overstatement of efficacy claims (n=135, 20%). The promotional materials suggested statements that a drug had long term survival rates provided treatment for certain conditions with additional benefits or was safer and more effective than was demonstrated from clinical trials. For instance, one of the brochures in a 2012 UL implied that Vantas (histrelin acetate) would improve particular individual systems in patients with treatment-resistant schizophrenia (Center for Drug Evaluation and Research, 2012). However, OPDP stated that the drug's clinical trial or clinical experience does not prove such an effect. Therefore, the brochure overstated the efficacy.

Unsubstantiated superiority claims (n=51, 8%). This type of promotional violation focuses on unsubstantiated claims, which suggested that a drug was superior, safer, more efficacious, and more potent to any other drug when this was not demonstrated. For example, OPDP highlighted to claim on ONY, Inc.'s webpages and Infasurf Feature and Benefits Video that addressed the Infasurf (calfactant) superiority to animal-derived products in treating respiratory distress syndrome (RDS), referencing an observational study (Center for Drug Evaluation and Research, 2012). However, this study did not support the efficacy claims described.

Unsubstantiated claims (n=49, 8). According to this violation, promotional materials were deemed misleading and violative if they implied that the drug is safer or more efficacious for outcomes which had not been demonstrated. For instance, ECR Pharmaceuticals posted professional sales aid about TussiCaps dosage form that suggested that patients had preferred capsules over oral formulations than it was demonstrated in clinical trials (Center for Drug Evaluation and Research, 2015). Therefore, such materials were held misleading and violative.

The omission of material facts (n=46, 8%). Promotional materials of forty-six letters omitted material facts. This type of violations omitted information such as:

a) The intended patient population
b) Dosing parameters
c) Contraindications and precautions
d) Approved indications and treatments

For example, in 2016, a promotional detail aid failed to provide ConZip's full approved indications with its important limitations of use that involved serious risks to public health. The following information was summarized in the 2016 warning letter:

> "Because of the risks of addiction, abuse, and misuse with opioids, even at recommended doses, and because of the greater risks of overdose and death with extended-release/long-acting opioid formulations, reserve CONZIP for use in patients from whom alternative options are ineffective, not tolerated, or otherwise inadequate to provide sufficient management of pain" (Center for Drug Evaluation and Research, 2017).

Therefore, such materials were deemed misleading and violative if they omitted any important information.

Broadening of the patient population (n=45, 8%). According to 21CFR202.1(e)(6)(i), a drug being used in different patient population or different indications should be supported by adequate safety and efficacy data from clinical trials or clinical experiences. However, some of the promotional materials suggested that a drug can be useful in a specific patient population/indication that was demonstrated in clinical trials or clinical experiences. For example, in 2013 WL, OPDP criticized Kadmon Pharmaceuticals, LLC for submitting a RibaPak Introduction letter that stated Ribasphere Ribapak (ribavirin, USP) tablets might help improve patient adherence to Hepatitis C virus medication, leading to improved rates of systemic vascular resistance (Center for Drug Evaluation and Research, Benson & Alfors, 2018). This letter was false or misleading, as it suggested that a drug could be used as monotherapy for treating Hepatitis C patients.

False or misleading claims (n=45, 4%). Twenty-five of total violations cited that promotional materials are false or misleading if they directly or indirectly contradicted full prescribing information or package inserts and represented that the drug had unapproved expanded access for use. For example, In April 2015, a pharmacy aid for Abilify (aripiprazole) submitted by Otsuka Pharmaceutical Development & Commercialization, Inc. was false or misleading as it implied that the drug had more advantages over other available treatments for bipolar disorder (Center for Drug Evaluation and Research, 2015).

Failure to submit under the FDA Form 2253 (n=22, 4%). This violation states that regulations require drug companies to submit all labeling or promotional materials at the time of launch and initial publication of the advertisement for prescription drugs. For instance, in November 2017, Amherst Pharmaceuticals, LLC webpage and Magna Pharmaceuticals Inc.'s

exhibit panel for Zolpimist was not submitted under this form at the time of launch and initial publication (Center for Drug Evaluation and Research, 2017).

Failure to use required the established name (n=15, 2%). Promotional materials of this violation failed to use the required established name. For instance, in June 2014, Gilead Sciences Incorporated a sponsored link on Google.com for Viread that failed to use the required established name (Center for Drug Evaluation and Research, 2014).

Promotion of unapproved uses (n=8, 1%). Promotional materials that were found to promote unapproved uses. For example, sales representative of Amarin Pharmaceuticals made oral statements that the Vascepa was approved to lower triglycerides levels (Thomas, 2016).

Promotion of an investigational new drug (n=8, 1%). Promotional materials that imply an investigational new drug (IND) is safe and effective to use. For example, in February 2015, the Taumark Better Brain Diagnostics website suggested that investigational FDDNP was safe and effective in diagnosing brain injuries and Alzheimer's disease (Center for Drug Evaluation and Research, 2015).

Lack of adequate directions for use (n=8, 1%). Promotional materials that claimed the use of the drug in unapproved conditions and that failed to provide adequate directions for use. For instance, In October 2018, an Eisai Inc. sales representative made statements that Fycompa (perampanel) tablets were intended for uses in the treatment of types of seizures in a pediatric population for which it lacked approval and failed to provide adequate directions for use (Center for Drug Evaluation and Research, 2018).

Discussion

A total of 237 letters issued by DDMAC/OPDP was analyzed for this study. The notable decrease in the total number of WL and UL was likely due to courts' rulings on First Amendment issues. Dr. Woodcock also reported that a decrease in the total number of WL/UL was primarily due to the First Amendment issues that were raised in the court's rulings (Osborn & Gingery, 2018). This change seemed inevitable following the recent court's rulings, particularly on U.S v. Caronia (2012) and U.S v. Amarin (2015) (See Table 3). In U.S v. Caronia, a sales representative, was convicted for promoting Xyrem for insomnia, fibromyalgia and Parkinson's disease in patients under the age of sixteen, for which it lacked FDA approval. The FDA prosecuted Alfred Caronia for his promotional speech as he intended that the Xyrem could be used for purposes that are not approved by the FDA. In this case, the federal court overturned the conviction and concluded that the FDA could not prosecute drug companies and their sales representatives for speech promoting truthful and non-misleading information, because by doing so the FDA would violate their First Amendment rights.

Also, in U.S v. Amarin, the federal court held that the FDA could not prohibit Amarin from promoting off-label use of a drug based on their truthful and non-misleading promotional speech. In response to this federal court ruling, the FDA allowed Amarin to promote off-label use of Vascepa in patients with high levels of triglycerides. Again in 2014, the FDA issued WL to Pacira Pharmaceuticals, Inc. for promoting off-label use of an Exparel (bupivacaine liposome suspension) in surgical procedures (Mazer & Curfman, 2016). After receiving a WL, Pacira sued the FDA because they were promoting their drug based on truthful and non-misleading off-label uses. Considering recent judgments, the FDA withdrew WL against Pacira Pharmaceuticals, Inc. As a result, in the year 2014, there were no WL issued. As compared with a total of 196 WL (43)

and UL (153) issued during years 2008-2013, there has been a remarkable decrease in the total number of WL and UL issued during 2014-2018. The total number of letters is down to only 41 WL (10) and UL (31), and it appears that the decrease in letters is mainly due to courts' rulings on First Amendment. Also, a downward trend was seen in the total number of off-label violations such as unsubstantiated superiority claims and unsubstantiated claims, broadening of patient population or indication and failure to provide adequate labeling. The average number of off-label violations has decreased from 70% to only 20% during the years 2008-2018. In comparison with other violations such as omission or minimization of risk information and overstatement of efficacy claims, they account for 8% of total violations. Since the First Amendment cases, the FDA has been focusing more on promotional violations that raise safety issues and promote false or misleading information as compared to violations that involve truthful or non-misleading off-label uses (Osborn & Gingery, 2018). So, in 2015, OPDP issued 7 UL letters for violations such as omission of risk information, omission of material facts and false or misleading statements and issued only 2 WL for unsubstantiated superiority claims and inadequate directions for use claims. As per the evaluation done in this study, there was a decrease in total number of off-label violations such as unsubstantiated superiority claims (8%), unsubstantiated claims (8%), and broadening of patient population or indication (7%) whereas other violations that remained consistent were omission of risk information (35%) and overstatement of efficacy claims (20%).

In light of these First Amendment cases, drug companies requested the FDA to provide clarification on off-label communications. In response, the FDA issued a draft guidance document in 2017 to clarify views on off-label communications and the First Amendment. It was indicated in the guidance that a drug company would not be exposed to enforcement action if

their promotional materials are “consistent with the FDA required labeling” (Food, Drugs and Devices, 2017). The FDA would evaluate such promotional materials based on three factors:

a) Any representations regarding drug use in treating or diagnosing a disease or condition in a patient population other than approved
b) Any representations that drug used as monotherapy in conjunction with other therapies other than approved
c) Any representations that drug used in different dosage, strength, or route of administration other than approved.

These are the major categories that demonstrate the FDA’s intent to initiate enforcement actions against off-label drug communications (FDA Health care & Compliance, 2015 & Zegarelli, 2017)

Also, in 2017, the FDA issued a partially amended final rule as a potential approach to off- label drug promotion. The previous “intended use” definition that focused on “knowledge of facts that would provide manufacturers” with off-label purposes was amended with “totality of the evidence” concept. According to this concept, “if the totality of the evidence establishes that a drug manufacturer objectively intends that a drug introduced into interstate commerce by him is to be used for conditions, purposes, or uses other than ones for which it has been approved, he is required to provide adequate labeling with respect to all intended uses of drug” (FDA Health care & Compliance, 2015; Barlas, 2017 & Gingery, 2018). Using this approach, the FDA is most likely to consider any relevant indirect or direct source of evidence as evidence of intended use against drug companies that engage in off-label drug promotion.

Conclusion

The total number of WL/UL has consistently been decreasing for the past few years, likely due to recent courts' rulings on First Amendment issues. Since 2014, there has been a remarkable decrease in off-label promotional violations such as unsubstantiated claims and superiority claims, broadening of patient population or indication and failure to provide adequate directions for use. However, promotional violations that raise safety issues such as omission of risk information and overstatement of efficacy claims remain consistent from 2008 to 2018. These data support the idea that OPDP is concerned about promotional violations that are more serious rather than violations that promote truthful and non-misleading off-label uses. As a result, there is a decrease in the total number of off-label promotional violations as well as a decrease in the total number of WL/UL from 2014-2018 as compared to 2008-2013. However, there is a need to strengthen off-label promotion regulations further so that drug companies are careful and stay within the requirements while promoting off-label uses because any false or misleading information of a drug could increase risks to public health and safety.

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Appendix

Acronyms Used

ADHD: Attention Deficit Hyperactivity Disorder

CDER: The Center for Drug Evaluation and Research

CFR: Code of Federal Regulations

DDMAC: Division of Drug Marketing, Advertising, and Communications

FDA: Food Drug and Administration

FDCA: The Food Drug and Cosmetic Act

FDAMA: FDA Modernization Act

IND: Investigational New Drug

OPDP: The Office of Prescription Drug Promotion

WL: Warning Letter

UL: Untitled Letter