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YAM B. LIMBU, CHRISTOPHER MCKINLEY, AND VALERIO TEMPERINI

A Longitudinal Examination of FDA Warning and Untitled Letters Issued to Pharmaceutical Companies for Violations in Drug Promotion Standards

This study examined over-time differences in the nature and frequency of Food and Drug Administration warning and untitled letters issued to pharmaceutical companies. Across a 12-year time frame, results indicate that frequency of letters and specific violations rose steadily from 2005 to 2010 but have since fallen dramatically. When infractions do occur, they continue to result from the omission or lack of risk information, misleading/false claims, omission of material facts, and labeling issues. In addition, the findings show that violations occur most frequently on brochures, sales aids, corporate websites, and print ads, with the proportion of violations on Internet media rising consistently over-time. Overall, while these findings offer encouragement to those wary of deceptive marketing practices, given the increased proportion of violations within digital marketing platforms coupled with the rare, yet consistent tendency of companies to misrepresent product risk and/or efficacy information, continued focus must be given to consumer education initiatives.

By 2015, the US pharmaceutical market was estimated at roughly $440 billion, representing one of the two largest world markets for prescription drugs (the other being China; Daemmrich and Mohanty 2014). The rising demand for these products can partially be linked to the significant investment pharmaceutical companies have made in advertising and promotion. While traditional promotional strategies, such as detailing (promotions to physicians) and medical journal advertising are still commonly utilized to market products, direct-to-consumer advertising (DTCA) and electronic forms of DTCA (eDTCA) are quickly becoming central components of advertising spending. DTCA and eDTCA strategies provide information

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about these pharmaceuticals and, more importantly, can influence US consumers' preventive health and treatment decisions by encouraging individuals to demand physicians prescribe the advertised drugs (Huhmann and Limbu 2016; Liang and Mackey 2011a). In 2014, DTCA spending in the United States was estimated to be $4.53 billion, about 18% more than in 2013 (Koons 2015). Furthermore, DTCA spending increased more rapidly than spending on promotion to physicians or research and development of new drugs. With the rapid growth of eDTCA, the Food and Drug Administration (FDA) has faced a serious challenge to its ability to produce guidelines that keep up with the changing media landscape. Although the FDA recently (2014) released three draft guidances involving suggestions and comments linked to eDTCA, a major obstacle has been the delay in issuance of final guidelines and lack of clarity in regulatory requirements as recommended by the draft guidelines.

The explosive growth of DTCA has led to increased FDA concern over deceptive or incomplete information. Proponents of DTCA argue that these ads help educate consumers, ultimately increasingly understanding of possible conditions and treatments (Calfee 2002; Holmer 1999; Pines 2000). Furthermore, recent data suggest that DTCA may reduce optimistic bias among consumers (Park et al. 2014; Park and Ju 2016), eventually promoting increased health information seeking. In contrast, opponents argue that advertisements fail to offer balanced information on effectiveness and safety (Coney 2002; Wolfe 2002). Ultimately, a DTCA that typically contains emotion-rousing messages (Wolfe 2002) may lead misinformed consumers to develop unrealistic treatment expectations (Pinto et al. 1998).

The FDA's Office of Prescription Drug Promotion (OPDP)—formerly known as the Division of Drug Marketing, Advertising and Communications (DDMAC)—monitors and reviews pharmaceutical product labeling, advertising, and promotional materials to ensure advertisements are truthful, balanced, and accurately communicated. All pharmaceutical promotional materials distributed in the United States must be submitted to the OPDP at the time of initial dissemination. Significant regulatory infractions frequently result in companies being issued "Warning Letters" and "Untitled Letters." A "Warning Letter" is issued for significant regulatory violations that may lead to enforcement action if they are not promptly and adequately corrected, but an "Untitled Letter" is issued for violations that are not as significant as those that trigger warning letters. Untitled letters cite enforcement violations and serve as an initial notification to firms. Importantly, failure to address concerns raised in the letters may result in recalls, seizures, injunctions, administrative detention, and criminal prosecution.

Despite the FDA's increased regulations, pharmaceutical companies have continued to violate industry standards. Given the expanding marketing presence of pharmaceutical products in newer media platforms, coupled with greater FDA concerns over misleading promotional activities, it is critical to address: (1) the nature and extent of violations mentioned in regulatory letters, and (2) whether industry marketing tactics comply with appropriate regulatory requirements. This longitudinal study is important as it allows us to see how effectively enforcement procedures implemented by the FDA influence pharmaceutical promotion over time.

SIGNIFICANCE OF FDA WARNING LETTERS

To date, there have been numerous investigations addressing the nature and prevalence of FDA warning letters, the majority of which involved samples prior to 2006 (Benson and Alfors 2007; Kamal et al. 2009; Salas et al. 2008; Stewart and Neumann 2002). Rather than providing a comprehensive evaluation of warning letter features, prior analyses have typically examined distinct qualities of regulatory letters (Benson and Alfors 2007; Kim 2015). For example, Kim (2015) examined only letters related to online promotion of prescription drugs advertised directly to consumers. Other investigations have evaluated ethical issues contained in warning letters (Bramstedt 2004; Bramstedt and Kassimatis 2004). In one study, researchers explored warning letters issued to clinical researchers by the FDA (Bramstedt 2004). Another investigation assessed ethical issues contained in warning letters issued to institutional review boards by the US FDA (Bramstedt and Kassimatis 2004).

Furthermore, many studies analyzed enforcement letters over a "relatively" short period of time (Benson and Alfors 2007; Kamal et al. 2009; Nguyen et al. 2013). For example, Benson and Alfors (2007) analyzed the themes and trends of 30 warning letters issued from January 2001 through June 2005, while Stewart and Neumann (2002) assessed the number and frequency of economic and quality-of-life claims violations between 1997 and 2001.

Given the limited time-frame and focus of prior investigations, it remains unclear what distinct characteristics reflect typical FDA notices of violation as well as what longitudinal changes, if any, have occurred in the nature and frequency of warning letters (Kamal et al. 2009; Salas et al. 2008). The current investigation is unique in two ways. First, this study encompasses a longitudinal (12-year period) evaluation of FDA letters issued through 2016. Second, it offers a comprehensive analysis of regulatory violations by time-frame, types of letters, and media platforms.

CURRENT STUDY AND RESEARCH QUESTIONS

The main purpose of this longitudinal descriptive study is to content-analyze regulatory violations cited in all FDA warning and untitled letters issued to pharmaceutical firms over a 12-year (2005-2016) period. This study will offer further insights and understanding on how well pharmaceutical marketers comply with FDA guidelines. These analyses provide insight on frequency of enforcement letters, the most common violations, types of letters, and media platforms (traditional and online), and the nature and presence of FDA's recommendations to firms.

Results from this investigation can assist consumers, regulators, and policymakers in identifying current trends in pharmaceutical advertising violations. By highlighting common infractions and current problematic marketing tactics, regulators may draw insight into the effectiveness of current guidelines and ways to enhance consumer protection strategies. In addition, this analysis provides pharmaceutical companies with critical information on common advertising infractions to avoid, and may help encourage these corporations to utilize alternative ways to promote products through non-misleading information.

In sum, this study addresses the following main research questions:

RQ1. What is the prevalence of pharmaceutical promotion-related regulatory letters issued by the FDA from 2005 to 2016?

RQ2. What type of regulatory letter (warning or untitled) were issued most frequently from 2005 to 2016?

RQ3a. What violations occurred most frequently from 2005 to 2016?

RQ3b. Do the number of violations across time period differ by letter type (warning vs. untitled)?

RQ3c. Does the ratio of violations to regulatory letters differ over the study period?

RQ4. Are there differences across pharmaceutical marketing media platform (traditional vs. online) in regulatory letters received from the FDA?

RQ5a. What is the nature of FDA recommendations provided in regulatory letters?

RQ5b. Do FDA recommendations vary over the study period?

RQ5c. Does FDA recommendation vary by types of letters (warning vs. untitled)?

METHODS

Data Collection

A content analysis technique was used to explore the frequency and nature of all warning and untitled letters issued to pharmaceutical companies by the OPDP for advertising and promotional violations over a 12-year

period (2005–2016). The year 2005 was chosen as the initial data point due to the fact that in 2005 controversy surrounding DTCA intensified, leading to calls for robust regulations from various stakeholders. Furthermore, that same year, the FDA held public hearings to review DTCA, and the Pharmaceutical Research and Manufacturers of America approved to adopt an industry-wide voluntary code governing DTCA. The regulatory letters are publicly available on the FDA webpage. Researchers extensively trained two independent coders to review the letters and extract information related to five broad categories as discussed below—related to company, nature of letter, violations, media platforms, and FDA's recommendations to firms.

All warning letters were reviewed independently by two different coders who were assistant professors of marketing at a major university. Each coder completed extensive training in utilizing the coding scheme. The intercoder reliability was assessed using Holsti's (1969) method. Since Holsti's index does not account for chance agreement and is subject to overestimation of agreement, the literature recommends adopting higher critical values for accepting data (Lombard et al. 2002, p. 593). In the current study, the average reliability was more than 90% for each variable, which showed a high level of agreement between the two coders, and disagreements in coding were resolved through discussion and consensus.

Company Information

Coders assessed various information about firms that received warning and untitled letters. They include: (1) company name, (2) brand or product name, and (3) company type (e.g., US-based, international, private, public, full-service pharmaceutical company or research and development or marketing, sales and distribution-only).

Types of FDA Letter

Judges coded an FDA letter either as a "Warning Letter" that prompted compliance with the FDA guidelines (such letter is titled "Warning Letter" by DDMAC) or as an "Untitled Letter" that did not include a title and a warning statement.

Media Platforms

Coders identified whether media outlets fall under "traditional" (e.g., TV ad, Print ad, Radio ad, Brochures, Sales Aids) category or "online" (e.g., corporate website, Facebook, Twitter, YouTube, corporate blogs, independent third-party blogs, online advertisement, online discussion forums) category. Some letters cited multiple media platforms.

Violations

Judges evaluated FDA warning letters to identify explanations for these notifications. The violations were classified into 15 categories in line with the violation headings cited in the FDA letters. This includes: *omission or lack of risk information* (promotional materials omitted facts about the consequences that may result from the use of the drug as recommended or suggested by the material), *inadequate or minimization of risk information* (promotional materials failed to present risk information with a prominence and readability reasonably comparable with the presentation of information relating to the effectiveness of the drug, taking into account all techniques apt to achieve emphasis), *misleading claims of drug efficacy* (promotional materials misinformed about the efficacy of drug), *misleading superiority claims* (promotional materials suggested that a drug is more effective than has been demonstrated by substantial evidence or substantial clinical experience), *unsubstantiated claims* (promotion of drugs that were not supported by substantial clinical evidence or substantial clinical experience), *broadening of indication* (promotional materials that suggested that a drug was useful in a broader range of conditions or patients than had been demonstrated by substantial evidence or substantial clinical experience), *off-label use* (promotion of a drug that was promoted without following the FDA's approved packaging label), *labeling issues* (firms used label with inadequate directions for use, dosage etc.), *comparative advertising* (promotional materials that persuaded consumers that a drug is safer and more effective than the drug it was being compared to), *failure to submit under form FDA-2253* (firms failed to submit Form FDA-2253 to the agency), *lack of fair balance* (promotional materials that lacked of a fair balance of information about drug risks as compared with information about drug benefits), *promotion of an investigational new drug* (firms promoted an investigational new drug that was prohibited under FDA), *omission of material facts* (promotional materials that omitted important information such as product's FDA-approved indication), *inadequate presentation of established name* (promotional materials failed to present the established name in direct conjunction with the proprietary name) and "Other violations."

FDA's Recommendations to Firms

FDA's recommendations or suggestions to firms were coded from warning and untitled letters. The following three categories of recommendations were created:

$1 = A$, $2 = A + B$, and $3 = A + B + C$.

where,

"A" refers to "immediately cease the dissemination of violative promotional materials" and "submit a written response to this letter to DDMAC stating whether you intend to comply with this request."

"B" refers to "submit a plan of action to discontinue use of such materials."

"C" refers to "review your promotional materials for the other prescription drug products that your company promotes in the United States."

RESULTS

Planned Analyses

Coded data were analyzed using IBM SPSS Statistics 20. Descriptive statistics were used to report frequency and means of letters, violations, media outlets, and FDA's recommendations to firms. Cross-tabulations with chi-square were employed to explore the relationship between FDA recommendations and letter type and time period. Pearson's correlations were performed to estimate the correlations between the frequency of violations on traditional media and the frequency of violations on online media and between the frequency of letters and frequency of violations. One-way analyses of variance were performed to determine the differences between average number of violations per letter and time period and type of letter.

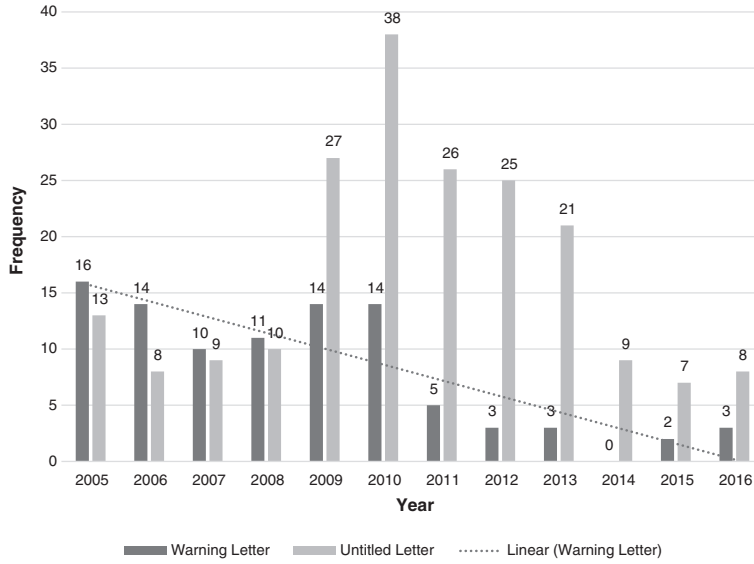
FDA Letters by Years

As shown in Figure 1, the US FDA issued 296 regulatory letters to firms involved in research, development, manufacturing, marketing, and sales of finished pharmaceuticals or active ingredients from 2005 to 2016. This reflects an average of over 25 letters per year. The greatest number of letters were issued in 2010 ($n = 52$) followed by 2009 ($n = 41$) and 2011 ($n = 31$). Results show that the frequency of letters issued remained fairly consistent between 2005 and 2008, then increased substantially in 2009. However, after peaking in 2010, the number of letters issued has trended downward dramatically. From 2014 to 2016, a total of only 29 letters were issued ([2014: $n = 9$], [2015: $n = 9$], [2016: $n = 11$]). Overall, the number of letters issued in 2016 reflects nearly an 80% drop from 2010.

Types of Letters by Years

The FDA issued two types of correspondence to caution of regulatory violations (warning and untitled letters). As shown in Table 1 and Figure 1,

FIGURE 1
Types of Letters by Years



a vast majority of the letters were untitled letters ($n = 201$, 67.9%) that notified the firms about the regulatory violations. Seventy-six warning letters ($n = 95$, 32.1%) were issued to firms for significant regulatory violations. Results from a cross-tabulation with chi-square test revealed a significant relationship between type of letter and time period [$\chi^2(11) = 43.99$, $df = 11$, $p < .001$]. This indicates that while the volume of warning letters declined over the study period, the percentage of untitled letters increased sharply—particularly since 2009.

Violations

A total of 1,203 advertising and promotion violations were cited in all untitled and warning letters, averaging roughly 100 violations per year (see Table 2). The majority of the violations were related to risk information. Specifically, the most frequently cited violations were omission or lack of risk information ($n = 203$, 16.9%), with an additional 118 letters (9.8%) citing "minimization of risk information." Other major violations included misleading claims of drug efficacy ($n = 167$, 13.9%) and misleading superiority claims ($n = 131$, 10.9%). One hundred and twenty-four (10.3%) violations were associated with unsubstantiated claims that were not supported by substantial clinical evidence or substantial clinical experience.

TABLE 1
Frequency of Letters by Type and Year

Year	Warning Letter (%)	Untitled Letter (%)	Total (%)
2005	16 (55.2)	13 (44.8)	29 (100.0)
2006	14 (63.6)	8 (36.4)	22 (100.0)
2007	10 (52.6)	9 (47.4)	19 (100.0)
2008	11 (52.4)	10 (47.6)	21 (100.0)
2009	14 (34.1)	27 (65.9)	41 (100.0)
2010	14 (26.9)	38 (73.1)	52 (100.0)
2011	5 (16.1)	26 (83.9)	31 (100.0)
2012	3 (10.7)	25 (89.3)	28 (100.0)
2013	3 (12.5)	21 (87.5)	24 (100.0)
2014	0 (0.0)	9 (100.0)	9 (100.0)
2015	2 (22.2)	7 (77.8)	9 (100.0)
2016	3 (27.3)	8 (72.7)	11 (100.0)
	95 (32.1)	201 (67.9)	296 (100.0)

Note: $\chi^2(11) = 43.99$, $p < .01$.

TABLE 2
Violations

Violations	Frequency	Percent
Omission or lack of risk information	203	16.9
Misleading or false claims of drug efficacy	167	13.9
Misleading superiority claim (other than comparative advertising)	131	10.9
Unsubstantiated claims	124	10.3
Inadequate or minimization of risk information	118	9.8
Off-label use	103	8.6
Broadening of indication or patient population	69	5.7
Omission of material facts	68	5.7
Labeling issues or lack of adequate directions for use	55	4.6
Lack of fair balance	48	4.0
Failure to submit under form FDA-2253	36	3.0
Comparative advertising	31	2.6
Inadequate presentation of established name	21	1.8
Promotion of an investigational new drug	16	1.3
Other violations (e.g., inappropriate use of the word "manageable dosing," misleading multicolored image, misleading patient compliance claim, violative reminder advertisement)	13	1.1
Total	1203[a]	100

[a]Some warning letters included more than one type of violation.

One hundred and three (8.6%) letters cited off-label use in which a drug was promoted without following the FDA's approved packaging label (e.g., unapproved indication, unapproved age group, and unapproved dosage).

Sixty-nine violations were related to broadening of indication (5.7%). These promotional materials suggested that a drug was useful in a broader

range of conditions for patients than had been demonstrated by substantial evidence or substantial clinical experience. Sixty-eight letters cited omission of material facts (5.7%) and 55 mentioned labeling issues (4.6%). Forty-eight letters quoted lack of fair balance (4.0%). Less common violations included failure to submit under form FDA-2253, comparative advertising, inadequate presentation of established name, promotion of an investigational new drug, inappropriate use of the word "manageable dosing," misleading patient compliance claim, violative reminder advertisement, and so forth.

Violations by Years

In line with number of letters issued, the greatest number of violations occurred in 2010. However, there was a substantial decline in overall violations from 2010 ($n = 289$) to 2016 ($n = 19$). Other important findings indicate that off-label use was most frequent in 2009 ($n = 27$) and 2010 ($n = 24$), and omission of material facts was a particularly common violation in 2013. Results also show that the greatest number of labeling issues was highest in 2009, while the most comparative advertisements were cited in 2007 and 2010. Interestingly, promotion of an investigational new drug was the highest in 2011 and 2012.

Importantly, despite the substantial drop in overall violations occurring from 2014 to 2016, when violations do occur, they are most frequently due to omission/lack of risk information or misleading/false claims about drug efficacy. Specifically, in every year except 2016, one of these two categories of violations was the most common violation.

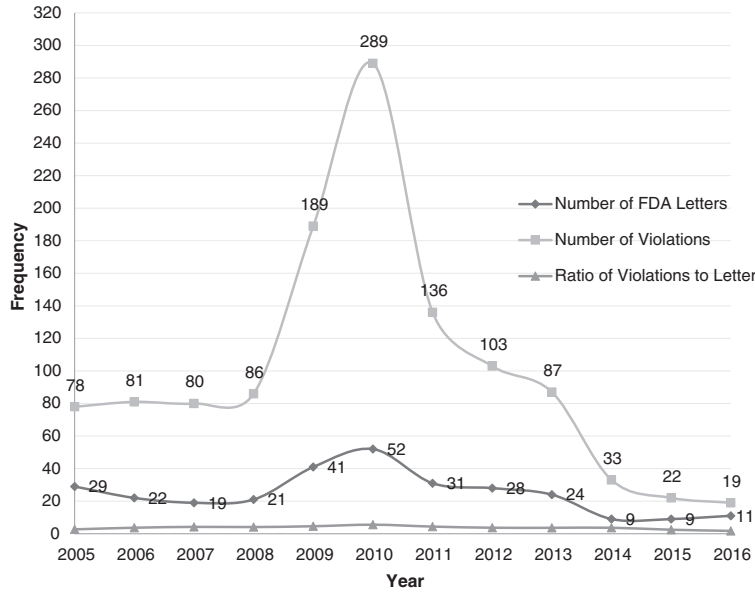
Number of Letters and Violations by Years

Despite a substantial decline in number of both letters and violations in recent years, the ratio of violations to letters remains steady over the 12-year period, suggesting that the average frequency of violation per letter did not decrease (see Figure 2).

Average Number of Violations per Letter by Types of Letters

A one-way ANOVA examined if the average number of violations per letter (counted by the number of headings in each letter) differed between two types of regulatory letter. Results showed that warning letters ($M = 4.63$) comprised a significantly higher number of violations than untitled letters ($M = 3.72$), $F(1, 294) = 12.57$, $p < .001$.

FIGURE 2
Number of Letters and Violations by Years



Average Number of Violations per Letter by Time-Period

One-way ANOVA was performed to determine if the average number of violations differs significantly between the first (2005–2010) and last (2011–2016) six-year periods. Results indicated that the average number of violations during the first six-year period ($M = 4.31$) was significantly higher than the last six-year period ($M = 3.53$), $F(1, 294) = 9.95$, $p < .01$).

Violations by Media Platforms

As shown in Table 3, the most frequently cited media platforms were brochures ($n = 59$, 17.5%), sales aids ($n = 50$, 14.8%), corporate websites ($n = 51$, 15.1%), and print ad ($n = 44$, 13.1%). Regulatory letters relating to company-sponsored websites or links increased substantially in 2009. Print material was the most frequently cited medium (52.3%). Eighty-six letters were related to Internet-based materials.

Interestingly, we found a perfect negative correlation between the frequency of violations on traditional media and the frequency of violations on online media over the 12-year period ($r = -1.000$, $p < .001$). While traditional media directed solely at health care providers were cited more

TABLE 3
Violations across Different Media Platforms

Media Outlets		Frequency	Percent
Traditional Media		216	64.1
1. Brochures	59		
2. Sales aid	50		
3. Print ad	44		
4. Direct mailer	15		
5. TV advertisement	13		
6. Oral statement by sales representative	10		
7. Exhibit banner	7		
8. Introduction/pitch letter announcing approval	7		
9. Electronic display TV and visual aids	6		
10. Billboard	3		
11. Pharmacology aid (e.g., tablet)	1		
12. Radio ad	1		
Internet media		86	25.5
1. Corporate website	51		
2. Company-sponsored website or link	15		
3. Social media (Facebook, YouTube, Twitter)	8		
4. Email (e.g., e-Pharm/alert)	6		
5. Independent third-party website	4		
6. Online advertisement	2		
Video segment		18	5.3
Other promotional materials		17	5.1
Total		337[a]	100.0

[a]Some letters cited more than one media.

frequently ($n = 216$, 64.1%), the proportion of violations on Internet media that are directed at both patients and health care providers increased in recent years (see Figure 3). This trend is consistent with the ratio of eDTCA to DTCA that rose to 54.5% in 2016 (Figure 4).

FDA's Recommendation to Firms

FDA offered three types of recommendations to firms (see Table 4). One hundred and seventy-one (55.8%) letters stated that firms had to immediately cease the dissemination of violative promotional materials and submit a written response to the letter to DDMAC stating whether the firm intended to comply with the request (Recommendation 1). In addition to ceasing the dissemination of violative promotional materials and submitting a written response to DDMAC, 112 letters (37.8%) recommended submitting a plan of action to discontinue use of such materials because the violations described in the letters were serious in nature (Recommendation 2). In addition to these three recommendations discussed above, 13

FIGURE 3
Ratio of Violations on Online Media to Traditional Media by Years

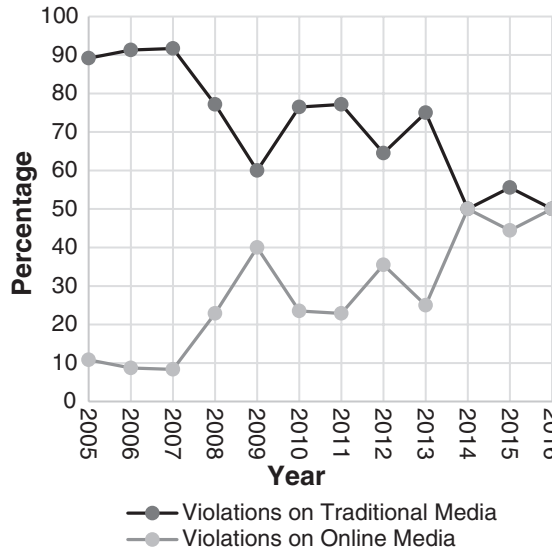


FIGURE 4
Ratio of eDTCA to DTCA by Years

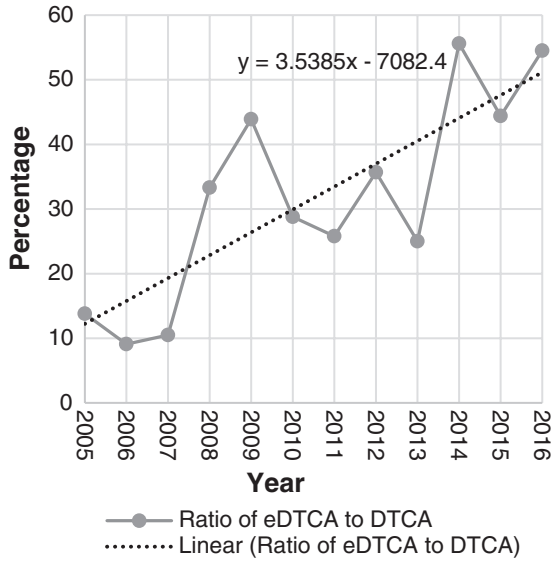


TABLE 4
FDA's Recommendation to Firms

Recommendations	Frequency	Percent
1. "immediately cease the dissemination of violative promotional materials" and "submit a written response to this letter to DDMAC stating whether you intend to comply with this request"	171	55.8
2. "immediately cease the dissemination of violative promotional materials," "submit a written response to this letter to DDMAC stating whether you intend to comply with this request," and "submit a plan of action to discontinue use of such materials"	112	37.8
3. "immediately cease the dissemination of violative promotional materials," "submit a written response to this letter to DDMAC stating whether you intend to comply with this request," "submit a plan of action to discontinue use of such materials," and "review your promotional materials for the other prescription drug products that your company promotes in the United States"	13	4.4
Total	296	100.0

letters (4.4%) encouraged firms to review their promotional materials for the other prescription drug products that their companies promoted in the United States (Recommendation 3).

FDA Recommendations by Letter Type and Time Period

The result from the cross tabulation analysis suggests that FDA recommendations are significantly related to types of letter [$\chi^2(2) = 202.84$, $p < .001$]. About 96% of warning letters recommended ceasing the dissemination of violative materials, submitting a written response to DDMAC stating whether the firm intended to comply with the request, and submitting a plan of action to discontinue use of such materials (Recommendation 2). The majority of untitled letters (83.6%) recommended ceasing the dissemination of violative materials immediately and submit a written response to DDMAC (Recommendation 1).

Another cross tabulation analysis suggests that FDA recommendations are significantly associated with time-period [$\chi^2(2) = 38.58$, $p < .001$]. Most letters (80.2%) cited Recommendation 2 during the first six-year period. Interesting, all 13 letters that cited Recommendation 3 occurred during the first six-year period.

Other Findings

Warning Letters by Types of Company

The number of regulatory letters received by a firm ranged from 1 to 11 during the study period. Twenty-one firms were sent three or more letters.

The letters were issued mostly to big, well-known, and domestic companies. Most of them were private firms ($n = 178$, 60.1%) and full-service firms that were involved in all core business functions such as research and development, manufacturing and operations, and marketing and sales ($n = 244$, 82.4%). This was followed by companies engaged in research and development only, and marketing, sales, and distribution activities only. About 46% of all companies were foreign-owned subsidiary companies. Only 26% of all pharmaceutical companies were biotechnology.

DISCUSSION

In an effort to highlight and address US pharmaceutical advertising regulatory violations, this investigation explored the content of FDA warning letters focusing on time-frame, types of letters, and media outlets. Unlike prior investigations, this study provided a more comprehensive investigation of longitudinal changes in the nature and presence of violations across multiple media platforms. Results showed a significant and steady decline in the overall number of regulatory letters issued since 2010; however, the frequency of violations per letter did not decrease. In recent years, the FDA issued untitled letters more frequently than warning letters and recommended ceasing the dissemination of violation materials and submitting a written response to DDMAC. Results also showed that the proportion of regulatory violations through online media increased in recent years. The major violations include failure to provide sufficient risk information or misleading claims about product benefits, misleading superiority claims, unsubstantiated claims, and off-label use. While most violations were cited on traditional media such as brochures, sales aids, and print advertisement, surprisingly, corporate websites emerged as the third frequently cited medium. Below we address the broader significance of the findings to consumer advocacy and public policy efforts.

Consumer Implications

In defense of DTCA, drug companies argue that ads help educate consumers about pharmaceuticals, disease conditions, and treatment options and help promote early recognition of symptoms. Ultimately, this should motivate patients to contact their physicians to develop greater dialogue about health concerns. Opponents of DTCA have argued that ads are problematic for numerous reasons, including promoting unrealistic treatment expectations (Paul et al. 2002; Pinto et al. 1998), leading physicians to

feel pressure to acquiesce to patient demands, and increasing drug costs (Perri et al. 1999). Our results suggest that some drug marketers continue to communicate incomplete, biased, and misleading information that may have a negative impact on overall consumer health and well-being. Overall, however, the findings from this study indicate that, from a regulatory perspective, pharmaceutical companies appear to be engaging in less overt deceptive marketing tactics. These results may hold particular significance given that consumers' trust and perception of the credibility of DTCA has declined markedly since 1997 (Kaiser Family Foundation 2008). Given the substantial drop in *overall* violations—from a peak of 289 in 2010 to 19 in 2016—the most frequent, and arguably, most problematic violations are becoming increasingly rare. Specifically, in 2010 there were 184 infractions related to inadequate risk information or misleading claims. In contrast, there were only eight such violations in 2016. These results provide encouragement to regulators and public health advocates concerned over the negative influence of DTCA advertising on personal health outcomes. Specifically, as pharmaceutical marketers present more accurate risk and claim information, this may conceivably diminish the impact deceptive marketing has on consumers' likelihood to minimize health risks and/or develop false perceptions of product efficacy. However, it is important to note that a decline in violations does not necessarily mean pharmaceutical firms improved their marketing and promotional approaches. Rather, this may indicate that the FDA guidelines are not comprehensive. For example, under current regulation, direct-to-consumer television ads should include only major risks associated with a product, rather than all risks.

In addition, these findings only indicate the *absence* of FDA violation via a decline in warning letters. The results do not provide insight as to whether pharmaceutical companies are engaged in measures to properly educate consumers. Prior research has shown that DTCA marketing tactics involve slightly more than the bare minimum required to prevent complaints (Macias et al. 2007). This includes multiple features that increase the visibility of risk information, but not fully embracing a true "fair-balance" approach whereby risk information is given a prominent position time-wise and creatively.

The tremendous use of pharmaceutical drugs among US consumers, as well as the high risk of misuse and addiction, indicates that the public must be made aware of potential risks related to these medications. Consequently, greater attention needs to be focused on industry efforts to properly educate and inform consumers. A key step in this process is for pharmaceutical companies to fully comply with FDA regulations and make

conscientious efforts to minimize omission errors, misleading/false claims of drug efficacy, and issues associated with labeling.

The results also show that pharmaceutical marketers are increasingly utilizing a wide range of electronic media to promote their products to consumers. They frequently omit or convey inadequate risk information associated with prescriptions drugs and promote products without following the FDA's approved packaging label. Furthermore, firms often present unsubstantiated and misleading information about drug benefits. Importantly, the absence of final regulations and lack of clarity in draft guidelines has created uncertainties for both marketers and regulators, which might pose a serious threat to consumers, as the information communicated through eDTCA are easily accessible and used by consumers globally. Therefore, consumer advocacy groups can play an important role through both educating consumers about potential risks associated with eDTCA information, and in advocating for comprehensive regulations.

Public Policy Implications

The results have significant implications for health care policy and public health initiatives. The number of regulatory letters peaked in 2010. This increase in FDA letters may be attributed partly to the enforcement procedures implemented by the FDA during the first year (August, 2009) of the Obama administration. These procedures were designed to facilitate FDA issuance of warning letters in a timely manner by the OPDP and district offices, prioritize enforcement follow-up on warning letters to assess companies' reported compliance, and ensure that all violations have been appropriately rectified (Hamburg 2009).

However, while new FDA procedures may have factored into the initial rise in violations, this strategy may have ultimately contributed to the long-term declines in warning letters. Specifically, the volume of enforcement letters decreased significantly from 2014 to 2016, especially with regard to traditional media. Furthermore, as noted, the volume of violations during the most recent six-year period was significantly lower than the previous six-year examination. However, this trend could conceivably be reversed if the Trump administration eliminates some of the current FDA regulations—something indicated in a recent administration meeting with Pharma CEOs.

There may exist a number of explanations for the decline in drug promotion-related regulatory letters and violations. One possible reason is that DTCA of prescription drugs became a controversial advertising practice in the early 2000s with various stakeholders, including

lawmakers and consumer advocates pressuring the FDA to more vigilantly regulate drug promotions. As a result, pharmaceutical firms likely became more concerned with receiving warning letters and, hence, are now more prudent about complying with FDA regulations. Consequently, FDA guidance tied to traditional DTCA may be adequately effective to address e-marketing efforts. Second, the voluntary guidelines for drug promotions issued by the Pharmaceutical Research and Manufacturers of America for its members could have played some role in reducing the number of violations. Consequently, the regulators should continue encouraging pharma companies to self-govern in more socially responsible ways.

One unique finding of this study is that the frequency and proportion of violations in traditional platforms differs from online media. While most violations were cited on traditional media (e.g., brochures, sales aids, and print advertisement), the proportion of violations through online media—especially corporate website and social media—increased in recent years. These findings may be the result of a lack in FDA regulations tied specifically to eDTCA. While the FDA issued three draft guidances addressing social media and digital marketing in 2014 and requested comments and suggestions from the industry, the Pharmaceutical Research and Manufacturers of America continue to criticize the draft guidances for being impractical and ambiguous, as well as not addressing a number of eDTCA issues. Critics argue that these draft guidances do not provide a clear direction regarding whether a firm has an obligation to correct misleading user-generated content. The guidelines are also silent on how to address the fair-balance requirement (i.e., presenting an accurate and fair assessment of a drug's risks and benefits) on social media with character-space limits, such as Twitter. Given that eDTCA continues to grow, it is critical that the FDA issues final guidelines for Internet and digital promotion of prescription drugs (Huhmann and Limbu 2016).

Finally, the results indicate that the ratio of some violations such as omission or lack of risk information, misleading or false claims of drug efficacy, unsubstantiated claims, and omission of material facts, did not change over the study period. Thus, the policymakers and regulators should focus on these violations when issuing, reviewing, and revising guidance for pharmaceutical promotions. In conclusion, despite the drop in warning and untitled letters in last three years, it is critical that the FDA continues to increase its regulatory presence and the resources dedicated to monitoring/enforcement functions for both identifying and addressing violations as well as monitoring firms' subsequent actions.

Areas for Future Research

Since digital marketing continues to evolve as a popular tool for pharmaceutical marketers, further research is needed to shed more light on content of enforcement letters related to social media and Internet marketing. In particular, future investigations should focus on how digital platforms differ from traditional media outlets in terms of type, nature, and extent of violations, and so forth. Prior research indicates that over time shifts in warning letters may be associated with current presidential administration policy direction (Ventola 2011). Interestingly, during the Obama administration, warning letters initially increased (2009–2010), but then fell substantially by 2015–2016. Consequently, it will be critical to examine whether Trump administration policy has any direct and/or indirect influence on the frequency and nature of FDA warning letters issued. Future longitudinal studies are needed to compare and contrast the impacts of federal policies and regulations of last four administrations (i.e., Clinton, 1993–2001, Bush, 2001–2009, Obama, 2009–2016 and Trump 2017-). In addition, the current study did not include FDA regulatory letters issued to dietary supplement companies. Additional investigations are needed to explore FDA's regulatory letters sent to other industries, including dietary supplement marketers.

CONCLUSION

This study content-analyzed warning and untitled letters issued by the FDA to firms over a 12-year period. Results showed that frequency of warning letters and violations peaked in 2010 but declined to its lowest levels in 2015 and 2016. The most frequently cited violations involved omission or lack of risk information, minimization of risk information, misleading or unsubstantiated claims, and off-label use. Results also showed that violations occurred most frequently on brochures, sales aids, corporate websites, and print ads. Furthermore, while violations on traditional media continue to decrease, the proportion of violations on Internet media continues to rise. Overall, while the findings provide encouragement for public policy and public health initiatives, researchers must continue to monitor online advertising tactics to ensure companies are not engaging in misleading and/or unethical practices.

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