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Analysis of US Food and Drug Administration Warning Letters: False Promotional Claims Relating to Prescription and Over-the-Counter Medications

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Abstract

Background—Recent studies have suggested that there has been an increase in the number of ‘warning letters’ issued by the US Food and Drug Administration (FDA) despite the publication of the FDA advertising guidelines. However, limited information is available on the description of warning letters. The objective of this study was to analyse the frequency and content of FDA warning letters in relation to promotional claims and discuss the influence of regulatory and industry constraints on promotion.

Methods—All warning letters published by the FDA between 5 May 1995 and 11 June 2007 were reviewed. Warning letters related to promotional issues were included and analysed. Information related to the identification number, date of the warning letter, FDA division that issued the letter, drug name, manufacturer, specific warning problem, type of promotional material and requested action was extracted. Two independent investigators reviewed and classified each PDF file, any differences were discussed until a consensus was reached.

Results—Between May 1995 and June 2007 a total of 8692 warning letters were issued, of which 25% were related to drugs. Of these, 206 warning letters focused on drug promotion and were included in this study: 23% were issued in 2005, 15% in 2004 and 14% in 1998. In total, 47% of the warning letters were issued because of false or misleading unapproved doses and uses, 27% failed to disclose risks, 15% cited misleading promotion, 8% related to misleading labelling and 3% promoted false effectiveness claims.

Discussion—There is an important variation in the number of warning letters issued in the last decade, probably because of the increasing number of drugs approved by the FDA, drug withdrawal scandals, and the publication of the FDA and the Pharmaceutical Research and Manufacturers of America (PhRMA) guidelines.

Conclusion—We found that benefit-related claims, such as unapproved uses or doses of drugs, and failure to disclose risks, are the main causes of FDA issued warning letters for promotional claims related to medications.

Background

Since 1962, the US Food and Drug Administration (FDA) has been charged with the responsibility of regulating prescription drug advertising and labelling.^[1] The regulations

include reviewing written, printed or graphic material accompanying a regulated product ('promotional labelling'), materials published in journals and newspapers, and information distributed via broadcast and telephone communications systems.^[2,3] However, the FDA does not have the authority to require sponsors to submit promotional materials for approval prior to use.^[4,5] Therefore, the FDA frequently sees promotional materials only after they have been released or broadcast.^[6]

Once an advertisement is disseminated that is deemed to contain a prohibited message, the FDA can require corrective actions by means of untitled letters, warning letters, injunctions and consent decrees, referrals for criminal investigation, or prosecution and seizures.^[6] 'Warning letters' are notices issued by the FDA when there are serious violations (such as repetitive misconduct) or a potential for serious health risks to the public; 'untitled letters' are issued for less serious violations.

These notices usually require the sponsor to discontinue use of the false or misleading advertising materials. Warning letters contain a statement that failure to respond may result in further regulatory action and the FDA can initiate court proceedings for seizure, injunction, or criminal prosecution.^[4] Therefore, when manufacturers receive a warning letter, they are supposed to correct the problem immediately and disseminate the correct message using mailings and journals. However, a previous study^[7] showed that the FDA enforcement actions against false and misleading drug advertisements declined in 2002 and that there were also delays in enforcement actions.^[7-12]

Limited information is available on the content of FDA warning letters. Therefore, the objective of this study was to describe the number, type and content of warning letters for medications in relation to promotional claims, and to discuss the influence of regulatory and industry constraints on promotion.

Methods

Source of Data

The FDA warning letter databases, which can be accessed via the FDA's Electronic Freedom of Information Reading Room, were reviewed. These files are made available to the public under the 1996 amendments to the Freedom of Information Act that mandates publicly accessible 'electronic reading rooms' with electronic search and indexing features.

For this project, two databases were reviewed, the 'archive' database and 'current' database. The archive database contained letters issued between 5 May 1995 and 25 May 2006 (http://www.accessdata.fda.gov/scripts/wlcfm/export_report_excel_archive.cfm). The current database included letters issued between 26 May 2006 and 11 June 2007 (http://www.accessdata.fda.gov/scripts/wlcfm/export_report_excel.cfm).

Excel spreadsheets of both databases were downloaded and reviewed independently by two investigators (Salas and McCall). Only the content of warning letters related to medications was analysed; warning letters with an unclear subject or nonspecific warning information were also downloaded and analysed.

Inclusion/Exclusion Criteria

In the first review, the subject of each warning letter was analysed and letters not related to drugs in humans (e.g. food, animal products, etc.) were excluded. Then, PDF files of the remaining letters were downloaded and reviewed. Letters related to drug manufacturing, clinical investigators, natural products (e.g. herbs) or nondrug-related issues were subsequently excluded. Only PDF files of warning letters related to prescription or over-the-

counter (OTC) medications that were focused on promotional claims were included in the study, irrespective of the issue date or the issuing office (figure 1).

Data Extraction and Analysis

Information extracted from the warning letters included identification number, date of the warning letter, FDA division that issued the letter, drug name, manufacturer, specific warning problem, type of promotional material and requested action. Two investigators independently reviewed each PDF file and any differences were discussed to reach a consensus (Salas and McCall). The type of warning was classified using the original wording of the letters and they include:

- unapproved doses and uses
- failure to disclose risks
- misleading promotion
- false effectiveness/superiority claims
- misleading labelling.

'Misleading promotion' included false information in drug advertisements such as misleading graphs or tables. 'Misleading labelling' included all labelling-related letters without specification of the type of false labelling. The original letters did not define the terms 'label', 'promotion' or 'advertising', but they reported to be based on the Food, Drug and Cosmetic Act (FD&C Act) of 1938. According to Section 502(n) of the FD&C Act, 'advertising' is considered to be messages published in journals, magazines, other periodicals and newspapers, or broadcast through media such as radio, television and telephone communications systems, as well as computer programs, fax machines or electronic bulletin boards. 'Labelling' means all labels and other written, printed or graphic matter accompanying a drug article.^[10]

Some warning letters had more than one warning and, if that occurred, each warning was coded separately. For example, if the warnings were "the promotional material makes unsubstantiated superiority claims and fails to reveal important risk information", the warning letter was coded as false effectiveness claims and also as failure to disclose risks.

Descriptive statistics such as percentages and frequencies were used to analyse warning letters information. We analysed the absolute number of warning letters, the number of unique medications involved, the issuing office and the total number and type of violatory issues.

To analyse the type of warnings issued in letters per year, we stratified the dataset by annual periods starting on 1 May and ending on 30 April of each year. For example, in the year 1996, the starting date was 1 May 1995 and the end date was 30 April 1996. We then estimated the percentage of type of warning letters per year, classified by violatory issue.

Results

There were a total of 8692 warning letters issued between May 1995 and June 2007. Of these, 8255 letters were issued between 5 May 1995 and 25 May 2006 ('archive' database), and 437 were generated between 26 May 2006 and 11 June 2007 ('current' database); 25% of letters were related to drugs.

A total of 8486 warning letters were excluded from this study: 8082 from the first database and 404 from the second database (table I). In total, 38% (3225) of the excluded warning

letters were related to devices, 35% (2970) were focused on food, 21% (1782) were related to manufacturing issues and 6% (509) related to animal products and other nonprescribing drug-related issues (figure 2). Most of the warning letters were excluded in the first review but 24% required a second review because the reason for the warning was unclear.

A total of 206 warning letters were included in the study, with the highest number of letters issued for medications in 2005 (23% of all letters), followed by 2004 (15%) and 1998 (14%) [figure 3].

In some years, many warning letters were issued for only one medication because the drug was manufactured by various drug companies. For example, in 2002, 72 warning letters were issued for guaifenesin while in 2007, 21 warning letters were issued for ergotamine.

As expected, most of the warning letters were issued by the main offices at the FDA (85%), the Division of Drug Marketing, Advertising and Communications (DDMAC) and the Center for Drug Evaluation and Research (CDER). FDA local district offices issued the remainder of the warning letters.

In terms of content, most of the warning letters included general statements about violations, such as lacking fair balance between benefits and risks. From our analysis of the violations, it was evident that benefit-related claims (unapproved dose, use and false effectiveness or superiority claims) comprised half of the problem, while a third of the letters were related to safety issues. The specific problems included: false or misleading unapproved doses and uses (47%), failure to disclose risks (27%), misleading promotion (15%), false labelling (8%) and false effectiveness claims (3%). In the last decade, the promotion of unapproved doses or uses of drugs has been one of the main reasons to issue warning letters, which reached a peak in 2002. In 2006, the highest percentage of warning letters were issued because of failure to disclose risks (figure 4).

There was a wide variation in the drugs involved in the issued letters: 35% to guaifenesin, 10% to ergotamine, 2% progesterone, and more than 50% to other drugs. The most frequent approved classes of drugs mentioned in the warning letters were expectorants (37%), analgesics (10%), hair loss agents (2%), anaesthetics (1%), hormones (1%), smoking cessation therapies (1%) and antidiabetic drugs (1%) [figure 5].

In 63% of the warning letters there were no details about the promotional material. Of the rest (38%), the misleading information was published in websites, medical journals, television advertisements, brochures, sales aids and 2% involved drug representatives directly (figure 6).

Discussion

Our study found that half the warning letters were issued because of benefit-related claims, particularly the promotion of drugs for unapproved (nonFDA approved) 'off-label' indications or unapproved doses. Health professionals can legally use drugs for off-label indications but it is prohibited for manufacturers to promote drugs for these indications. So, a question that can be raised is why do manufacturers promote off-label indications? Presumably, they do so to enlarge the size of the market for a given drug, and to increase their sales and profit.^[11–13] The recent case of gabapentin (marketed as Neurontin®¹) and the publication of its internal marketing and promotional plans^[14,15] has opened many

¹The use of trade names is for product identification purposes only and does not imply endorsement.

questions related to the off-label use of medications, particularly the marketing strategies used by manufacturers. Another such example is oxycodone.^[16]

We found two peaks of warning letters issued during the period 1996–2007. The first peak occurred in 1998, when the number of warning letters relating to broadcast advertisements increased considerably, probably as a consequence of the publication of the 1997 FDA draft guidance, which clarified and offered examples of advertising regulations, mainly direct-to-consumer advertising.^[17] Between 2002 and 2005 there was a progressive increase in the number of warning issued, which may have been the result of new draft guidance published by the FDA in 2001 (*Using FDA-Approved Patient Labeling in Consumer-Directed Print Advertisements*) that clarified the promotion regulations.^[18] In these guidelines the FDA did not object to the use of the approved patient labelling for promotion, as long as the labelling was reprinted in full, communicated in lay language and included drug-associated risks.^[6] The increase in the number warning letters issued after 2002 might also be a consequence of the number of drugs approved by the FDA. In 2001 the FDA CDER approved 66 new drug applications, in 2002 that number was 78 and in 2003 it was 72.^[19]

Interestingly, since 2005 fewer warning letters have been issued, which may reflect the lessons learnt from the rofecoxib scandal in 2004,^[20] increasingly stringent FDA requirements,^[21] reduction in the number of new chemical entities approved by the FDA^[22] and as a consequence of the Pharmaceutical Research and Manufacturers of America (PhRMA) guidelines. The PhRMA guidelines were issued in November 2005 to guide manufacturers on the principles of prescription drug advertising. Over the next few years, it is possible that fewer FDA warning letters may be issued because of the expiration of patent protection for 52 major drugs in the period 2007–11 and the recent issuance of the FDA draft guidelines regarding the distribution of journal articles mentioning unapproved uses of drugs^[19,23]

We found that 2% of warning letters involved drug representatives directly, and 17% contained promotional material for health professionals such as journals, brochures and sales aids. However, the warning letters did not describe how those materials were distributed to health professionals; it is possible that drug representatives were involved in that process. In recent years, the role of drug representatives has become more controversial because some professionals argue that drug representatives provide unbalanced information about the efficacy and safety of drugs,^[24,25] while others feel that they improve the quality of prescriptions by presenting up-to-date information on new products.^[26–28] Universities such as Stanford University School of Medicine in California and the University of Pennsylvania School of Medicine have banned drug representatives from their facilities.^[29,30] This position is questioned by some since banning drug representatives might prevent students and residents from learning how to differentiate unbiased from biased information. The alternative to banning drug representatives from universities might be to better educate students about promotional activities and strategies so that they are better able to respond to pharmaceutical marketing campaigns.

Interestingly, there was a high number of warning letters concerning OTC drugs, which might reflect the large number of OTC drugs available in the US market (>100 000),^[31] the increase in the number of new OTC medications approved for marketing between 1995 and 2002 (95 in total^[32] or the closer FDA supervision of promotional materials for OTC medications, especially their doses and indications for uses.^[33,34]

As we expected, most of the warning letters were issued by the central FDA office, but it is important to note the role that FDA local district offices play in the production of warning letters related to promotional activities of manufacturers. The activities of the local

authorities has been more relevant in recent years when a series of scandals have been published for drugs approved and promoted through direct-to-consumer advertising.^[35–37]

From a consumer and prescriber perspective, one might wonder how the reporting system for unlawful promotional activities could be improved. According to the FDA, the public can participate in reporting the unlawful promotion of medications. For example, anyone can contact the State Board of Pharmacy to notify them of problems related to the dispensing and sales practices of pharmacies, a website that illegally sells human drugs², or e-mails that illegally promote medical products.^[38] However, it is unclear what options are available to the public for reporting potentially illegal promotional materials in newspapers or other non-electronic media.

We commend the initiative from the FDA to release their warning letters database. However, for research purposes, we feel that the FDA could improve the system, as we found the content of the current system to be too general, difficult to analyse, lacking in definitions and we were unable to distinguish advertising from labelling issues. The FDA database could also take advantage of current technology and use better interfaces to present more specific information about the drugs involved (e.g. dosages) and types of media (e.g. radio, website, magazines, etc.) through which the drugs were promoted.

Since it is the responsibility of the FDA as a regulator and supervisor of manufacturers' promotional activities to protect the public, high quality information for consumers and prescribes is important, particularly in this era where patients are more actively participating in their care and want to discuss their treatment options with their healthcare provider.^[18,39–42] We think that the FDA should have more active participation in the process to initiate enforcement actions on promotional materials that are false or misleading; to compare the product labelling and promotional materials of various closely related products to ensure that the regulatory requirements are consistently and equitably applied; to travel to major medical meetings and pharmaceutical conventions to monitor promotional exhibits and activities; and to better coordinate activities between DDMAC and other FDA divisions on promotional issues.

Our study has limitations. We included and analysed information posted on the FDA website but do not know to what degree that information is complete. However, we have no reason to suspect that information focused on promotional warnings was more or less incomplete than for other type of warnings.

Conclusions

In conclusion, benefit-related claims such as unapproved uses or doses of drugs, and failure to disclose risks are the main causes of FDA warning letters. The number of warning letters can fluctuate quite dramatically from year to year and may reflect the introduction of new advertising guidelines and regulations or other market forces. Further research would be needed to clarify the influence of these and other factors on promotional misconduct.

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²These can be reported via e-mail to webcomplaints@ora.fda.gov.

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Fig. 1.
Process used to select warning letters for inclusion in the study.

Fig. 2.
Number of FDA warning letters excluded from the study, by topic.

Fig. 3. Number of FDA warning letters issued for drugs between 1996 and 2007. Years were defined as periods ending on 30 April and including all letters issued since 1 May of the previous year.

Fig. 4. Number of FDA warning letters by type of warning. Years were defined as periods ending on 30 April and including all letters issued since 1 May of the previous year.

Fig. 5.
Number of FDA warning letters by drug class.

Fig. 6.
Number of FDA warning letters by type of promotional material.

Table I

Number of included and excluded warning letters from the US FDA databases

Warning letters	<u>Archive database 1995–2006</u>		<u>Current database 2006–7</u>	
	excluded	included	excluded	included
First review	6094	173	362	33
Second review	1988	0	42	0
Total	8082	173	404	33