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Health Policy Analysis

FDA Actions Against Health Economic Promotions, 2002–2011

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ABSTRACT

Objective: To investigate Food and Drug Administration (FDA) regulatory actions against drug companies' health economic promotions from 2002 through 2011 to understand how frequently and in what circumstances the agency has considered such promotions false or misleading. **Methods:** We reviewed all warning letters and notices of violation ("untitled letters") issued by the FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) to pharmaceutical companies from January 2002 through December 2011. We analyzed letters containing a violation related to "health economic promotion," defined according to one of several categories (e.g., implied claims of cost savings due to work productivity or economic claims containing unsupported statements about effectiveness or safety). We also collected information on factors such as the indication and type of media involved and whether the letter referenced Section 114 of the Food and Drug Administration Modernization Act. **Results:** Of 291 DDMAC letters sent to pharmaceutical companies during the study period, 35 (12%) cited a health economic violation. The most common type of violation cited was an implied claim of cost savings due to work productivity or functioning (found in 20 letters) and economic claims containing unsubstantiated comparative claims of effectiveness, safety, or interchangeability (7 letters). The violations covered various indications, mostly commonly psychiatric disorders (6 letters) and pain (6 letters). No DDMAC letter pertained to Food and Drug Administration Modernization Act Section 114. **Conclusion:** The FDA has cited inappropriate health economic promotions in roughly 12% of the letters issued by the DDMAC. The letters highlight drug companies' interest in promoting the value of their products and the FDA's concerns in certain cases about the lack of supporting evidence.

Keywords: FDAMA Section 114, Food and Drug Administration, health economics, promotional claims.

The U.S. Food and Drug Administration (FDA) regulates pharmaceutical labeling and advertising to ensure that claims made by drug companies about their products are not false or misleading. The agency has interpreted its mandate broadly to include "virtually all information dissemination activities by or on behalf of a prescription drug manufacturer" [1]. Thus, FDA oversight includes promotional materials containing *health economic* claims, such as statements that a drug "saves money" or "lowers costs."

The FDA's Division of Drug Marketing, Advertising and Communications (DDMAC) monitors and reviews pharmaceutical promotions and takes action against advertisements found to be "false, lacking in fair balance, or otherwise misleading" [2]. (DDMAC was renamed the Office of Prescription Drug Promotions in September 2011, but we retain the name DDMAC in this article because it prevailed during all but 4 months of the study period.) All pharmaceutical promotional pieces distributed in the United States must be submitted to the DDMAC at the time of initial dissemination [3]. For promotions that the DDMAC considers in violation of regulatory standards, actions may include an "untitled" letter of notice of violation or a formal warning letter [4]. Warning letters are more serious than untitled letters, and failure to address issues raised in them may result in recalls, seizures, injunctions, administrative detention, and criminal prosecution [4].

Drug company promotion of health economic information targeted toward individual physicians or consumers must adhere to FDA's conventional "substantial evidence" provision, which typically means that statements must be supported by two adequate and well-controlled clinical trials [5,6]. U.S. law makes an exception for health economic information targeted to formulary committees or similar entities. Such communication is governed by Section 114 of the Food and Drug Modernization Act (FDAMA), which stipulates that health economic information provided under these circumstances shall not be considered false or misleading if it directly relates to an indication approved and is based on "competent and reliable scientific evidence" (rather than substantial evidence) [7].

Little is known about how the FDA has regulated health economic promotions, including how vigilantly it has overseen the area, and the types of economic promotions it has found lacking. Previously, we analyzed FDA regulatory actions on health economic promotions from 1997 through 2001 [8]. We found that roughly 5% of the letters issued during that period cited a false or misleading health economic claim—most commonly an economic promotion containing an "unsupported comparative claim of effectiveness, safety, or interchangeability." Since 2001, the health care landscape has changed with ever more intense focus on the

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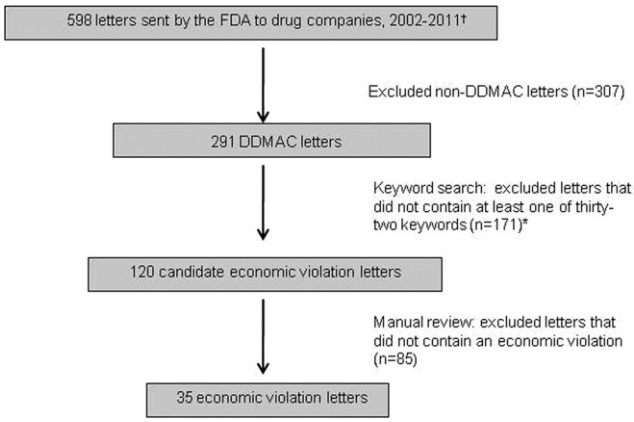

Fig. 1 – Search methodology. *Includes letters sent by FDA's Division of Drug Marketing, Advertising and Communication (DDMAC), Division of Compliance Risk Management and Surveillance, Division of Manufacturing and Product Quality, Division of New Drugs and Labeling Compliance, or the Division of Scientific Investigations between January 22 and December 2011. DDMAC was renamed the Office of Prescription Drug Promotions in September 2011, but we retain the name DDMAC in this article because it prevailed during the study period. †Keywords included cost, savings, expenditure, expensive, expense, spending, price, pricing, economic, affordable, value, cost-effectiveness, cost effectiveness, cost-benefit, cost benefit, pharmacoeconomic, hospitalization, utilization, doctor visit, physician visit, office visit, registry, observable data, copay, co-pay, budget, productivity, Section 114, fired, job, and work (defined as place of employment [n.] or to be employed [v.]).

economic value of therapies. In this article, we expand on our previous analysis and update it through 2011. Our objectives were to understand the frequency and nature of FDA regulatory actions against inappropriate health economic promotions since 2001. We also investigated whether the FDA has ever issued a regulatory action pertaining to a violation of FDAMA Section 114.

Methods

FDA notice of violation and warning letters

The FDA's Web site provides the full text of all warning letters and notices of violation ("untitled letters") issued to pharmaceutical companies for various kinds of infractions [9,10]. Between January 2002 and December 2011, the FDA issued 598 such letters. We restricted our review to the subset of letters issued by FDA's DDMAC during this time period (n = 291). Thus, we excluded letters pertaining to manufacturer site inspections or good laboratory practices, investigator- or sponsor-related conduct, approval and labeling requirements and drug security, and other uncategorized compliance issues (Fig. 1).

Data abstraction and analysis

We searched the DDMAC letters for health economic violations in several stages. First, we entered all 291 DDMAC letters into a single pdf file and searched it electronically by using 32 key words, such as "cost," "savings," "expenditure," "spending," "price," "economic," "affordable," "pharmacoeconomics," and "productivity" (see Notes to Fig. 1 for the full list).

The key words were selected on the basis of our earlier work and expanded upon to include economic terms found in health economic print advertisements [8,11]. Note that we included "productivity" claims, because work productivity is an important component of health economic analysis, though we had neglected to include it in our previous work. This search yielded 120 candidate letters. We randomly selected a sample of 30 of the 291 DDMAC letters for manual reading to examine whether any contained health economic claims not captured in the electronic search. We identified no such letters.

One of us (SKB) then read the entire text of each of the 120 candidate letters to determine whether it contained a genuine health economic violation. We considered a letter to contain a health economic violation if it included an infraction cited by the FDA pertaining to drug price or co-payment, cost per dosage, failure to consider or advertise certain costs, misleading or inappropriate claims about work productivity, or avoided hospitalization or surgery, or any mention of other economic or financial issues. Finally, we reviewed each of the resulting economic violation letters with the aid of a data abstraction form. On the basis of public remarks by a DDMAC official about the type of action that may constitute a health economic violation [12] and an expansion of our earlier work [8], we categorized each letter into one of several possible categories:

- Implied claims of cost savings due to work productivity/functioning;
- Unsupported claim of effectiveness, safety, or interchangeability;
- Implied claims of cost savings to broader audience than applicable;
- Claims of cost savings when there are obvious additional costs that may affect cost savings;
- Cost comparisons of dosages that are not comparable;
- Claims that encouraged switching on the basis of a lower price when there may be risks associated with the switch; and
- Other misleading price comparisons.

We also collected information from each correspondence on the type of letter (warning or untitled), the company, product, indication, type of media involved (e.g., print, video), target audience (consumers, professionals), and whether the letter made any mention of FDAMA Section 114. FDA requires pharmaceutical companies to submit all pieces of promotional labeling or advertising for a drug product at the time of its initial release, and each must be accompanied by Form 2253, "Transmittal of Advertisements and Promotional Labeling for Drugs and Biologics for Human Use" [3]. We based our media category on the scheme used on Form 2253.

We pilot-tested the form on a sample of 25 letters and revised it for clarity and completeness. Most warning or untitled letters on the FDA's Web site are accompanied by the actual promotional materials containing economic violations, either as separate documents or at the end of letters themselves. In the majority of the cases (32 out of the 35 letters with health economic violations), we were able to download the promotional materials containing the economic violation. For the three cases in which we could not download the promotional materials, one was an oral statement made at a conference, one was a DVD that was not posted, and one provided a link to a file that was not working.

Results

Of the 291 DDMAC letters issued to pharmaceutical companies (196 untitled letters and 95 warning letters), 35 (12%) cited an economic violation (including 14 warning letters and 21 untitled letters). The number of economic violation letters has remained

Table 1 – DDMAC warning letters and notices of violation for economic claims 2002–2011.

Year	DDMAC Letters	Number of letters with economic violations	Percentage of letters with economic violations
2002	28	1	3.6
2003	25	4	16.0
2004	23	3	13.0
2005	29	2	6.9
2006	22	2	9.1
2007	19	3	15.8
2008	21	5	23.8
2009	41	3	7.3
2010	52	11	21.2
2011	31	1	3.2
Total letters	291	35	12.0

DDMAC, Division of Drug Marketing, Advertising and Communication.

steady over time, with roughly 2 to 3 per year, with the exception of 2010, during which 11 were issued (Table 1).

The most common type of economic violation (found in 20 letters) was an implied claim of cost savings due to work productivity or functioning (Table 2). The next most frequent type pertained to an economic promotion containing an unsupported comparative claims of effectiveness, safety, or interchangeability (7 letters), followed by implied claims of cost savings to a broader audience than applicable (3 letters), and cost comparisons of dosages that are not comparable (3 letters). Appendix 1 in Supplemental Materials found at http://dx.doi.org/10.1016/j.jval.2012.05.002 contains examples of the relevant text from selected FDA letters citing economic violations.

The type of media cited in the economic violation letters has varied (Table 3). Twelve letters (30%) cited economic promotion violations in professional sales aids, which included detailers, brochures, and leave behinds. Six (15%) contained economic claims in Internet promotions, while other letters cited video (four letters), consumer print advertisements (three letters), consumer television advertisements (two letters), and direct mail (two letters). Over one third of the media cited was directed to consumers, while 23% targeted professionals. Economic violation letters have covered various indications, mostly common psychiatric disorders (six letters), pain (six letters), and cancer (four letters) (Table 4). All the economic violations relating to psychiatric disorders and five of the six letters relating to pain pertained to inappropriate productivity claims (data not shown).

Discussion

How actively the FDA has regulated economic promotions has been little studied. Moreover, the FDA has never released formal guidance about what constitutes an inappropriate economic claim, leaving some question about what constitutes an infraction. However, by analyzing FDA warning letters and notices of violation, one can quantify the agency's regulatory activities and begin to infer its thinking about the topic. The economic violation letters in our sample thus comprise a body of "case law" on the types of economic claims the FDA considers false or misleading.

While the letters themselves do not provide information about the frequency with which drug companies make health economic claims, they do indicate that companies are, at least to some extent, actively promoting the economic value of their products. In other work, we have reported that roughly 10% of print drug advertisements in major clinical journals contain an economic message, most frequently a statement that a drug is "less expensive" or "costs less" than its competitors [11,13]. In addition, elsewhere we have surveyed drug company officials who report some degree of health economic promotion directly to formulary committees by using the provisions of FDAMA Section 114 [6].

The current study confirms that the FDA continues to monitor the field, at least to some extent, and to express concern about certain inappropriate economic promotions. The agency has issued several letters per year pertaining to economic violations. In 2010, 11 such letters were issued— the spike in that year coincided with a greater number of total DDMAC letters sent to pharmaceutical companies, apparently reflecting President Obama's appointment of Margaret A. Hamburg, MD, as FDA Commissioner and her pledge to step up enforcement of misleading industry practices [14,15].

The FDA has expressed concern mostly about work function and "backdoor" clinical claims (i.e., about effectiveness or safety) embedded in economic promotions. The 20 FDA letters mentioning work productivity provide a window into how drug companies are promoting the workplace-enhancing potential of their products, as well as FDA unease about the practice. These letters cover various diseases, particularly attention deficit/hyperactivity disorder (five letters) and pain (five letters).

The five letters on attention deficit/hyperactivity disorder, for example, highlight FDA's distress over promotions linking attention deficit/hyperactivity disorder to poor work performance, and implying—without substantial evidence or substantial clinical experience—that the medications themselves reduce unemployment, improve job success, or enhance economic status [16–20]. In other such letters, the agency has cited promotions implying, without substantiating evidence, that drugs providing pain relief will cause fewer work disruptions [21] or allow patients to resume normal daily activities such as going to work [22,23]. A promotion for Pamine (methscopolamine) was cited for suggesting that freedom from diarrhea led to improved work performance [24].

In similar fashion, the FDA has called out a promotion for Luvox CR (fluvoxamine) for social anxiety/obsessive-compulsive disorder [25] for implying that the product would help return patients to normal work functioning. A letter on Provigil (modafinil) stated that while the drug may improve wakefulness, it does not necessarily follow—as implied in the promotion—that Provigil is bene-

Table 2 – Economic violations cited by DDMAC 2002–2011 (N = 35).

Violation	Number	%
Implied claims of cost savings due to work productivity or functioning	20	55.6
Unsupported comparative claim of effectiveness, safety, or interchangeability	7	19.4
Implied claims of cost savings to broader audience than applicable	3	8.3
Cost comparisons of dosages that are not comparable	3	8.3
Other misleading price comparisons or financial claims	2	5.6
Claims of cost savings when there are obvious additional costs that may affect cost savings	1	2.8
Total number of economic violations	36*	100

DDMAC, Division of Drug Marketing, Advertising and Communications.

* One letter contained two economic violations. Thus, the total number of economic violations cited (36) exceeds the total number of letters with economic violations (35).

Table 3 – Communication media cited in economic violation letters*.

Medium	Number	%	Professionals	Consumers	Unspecified*
Professional sales aid (detailer)	12	30.0	6	4	2
Internet promotion	6	15.0	0	1	5
Video or video tape	4	10.0	0	3	1
Consumer print advertisements	3	7.5	0	3	0
Consumer radio	1	2.5	0	1	0
Professional file card	1	2.5	1	0	0
Professional slides	1	2.5	1	0	0
Consumer television	2	5.0	0	2	0
Direct mail	2	5.0	1	0	1
Other†	8	20.0	0	1	7
Total number of communication media‡	40	100.0	9	15	16

* Excluded media cited in economic letters unrelated to the economic violation.

† Other includes all terms used in letters that did not match categories presented on Form 2253, including cost chart, pocket dosing card, promotional statements (either oral or in printed quotation), patient profile piece/card, and other unspecified promotional pieces.

‡ Does not equal total number of letters because more than one media type may be cited per letter.

ficial with respect to . . . occupational function associated with shift-work sleep disorder [26]. Yet another letter pertaining to Vivitrol (naltrexone) for alcohol dependence cited a brochure linking dependence to serious problems at work. The FDA stated that the brochure inappropriately implied that the drug had demonstrated productivity benefits [27]. Two letters on HIV treatments cited promotions that suggested that HIV management enhanced work productivity while maintaining undetectable HIV ("It enables me to also be a businessman once I manage my HIV" and "I still work and have a long day in the office and I think that the medicine has really been good for me") [28,29]. Finally, in one case, FDA cited promotions for Eligard (leuprolide), a palliative for advanced prostate cancer, that implied, without evidence, that a less demanding injection schedule would make it easier both for patients to keep appointments between business trips and for physicians to improve the efficiency of their daily office practice [30].

Regarding nonproductivity economic violations, FDA has expressed concern mostly about comparative clinical content embedded in economic claims. As an example, one letter noted that an advertisement misleadingly suggested that because Flonase (fluticasone) was "comparable or superior to other allergy medicines, the consumer need consider only the possible insurance co-payment cost in considering switching to Flonase" [31].

FDA concerns also pertain to economic promotions containing implied claims to broader dosages and audiences than are applicable. One letter stated, for example, that "a cost chart suggests that Norvir (ritonavir), at a dosage of 100 milligrams/day, has the lowest daily cost of all the antiretroviral drugs listed. However, FDA has found Norvir to be safe and effective only at the dosages set forth in the PI (300-600 mg twice daily)" [32]. Another cited Nasonex (memotasone), indicated for allergic rhinitis, for claiming that congestion affects over half of all people at work, and implying inappropriately that the product is indicated for congestion in addition to allergic rhinitis [33].

Table 4 – Indications cited in economic violation letters.

General indication	Number of economic letters citing the indication*	%†
Psychiatric disorder	6	17.1
Pain	6	17.1
Cancer or cancer-related	4	11.8
HIV	3	8.8
Nasal/respiratory illness	3	8.8
Irritable bowel syndrome	2	5.9
Other*	11	32.4
Total	35	100

* Indications mentioned in one letter include alcoholism, bacterial infection, imaging, infertility, myelodysplastic syndrome, psoriasis, hepatic injury, skin/frown lines, sleep disorder, testosterone replacement, and unknown.

† Percentages add up to more than 100% because one drug is indicated for two disease areas.

Importantly, our study highlights that the FDA has never issued a warning letter or notice of violation pertaining to an infringement of FDAMA Section 114. In some ways, this is surprising, given the prominence of the provision—it is the only statutory language devoted specifically to evidentiary standards for health economic promotions.

The absence of any DDMAC letters on Section 114 may reflect one or more of several factors. On the one hand, it may signal relatively little use of the provision by drug companies. In particular, the emergence of the Academy of Managed Care Pharmacy format and its use by US health plans as a vehicle for receiving information on the clinical and economic value of drugs has provided a separate nonpromotional channel for the exchange of health care economic information between drug companies and health plans. Dossiers submitted under the Academy of Managed Care Pharmacy format can contain economic models and off-label data, but the information can be provided by drug companies only in response to a health plan's "unsolicited request'" and thus is nonpromotional [6]. To some extent, this channel for communicating health economic information may have co-opted Section 114 [34]. The advantage of Section 114, however, is that it permits the active promotion of health economic information. It permits drug companies to initiate a conversation about health economics. Indeed, our previous research on the topic suggests that outcomes directors in drug companies view this type of promotion as important—and as more important than Academy of Managed Care Pharmacy dossier economic information [6].

The absence of FDA letters about Section 114 may simply reflect the challenges FDA faces in regulating the kinds of business-to-business promotions covered by the law (e.g., companies may promote economic claims under Section 114 via in-person presentations, which are difficult to police). It also suggests that FDA has assigned a low priority to regulating Section 114 promotional claims compared with other areas.

Our previous research on FDA regulatory letters regarding economic claims, the only empirical analysis on the subject of which we are aware, also revealed some level of vigilance by the agency.

From 1997 to 2001, roughly 5% of the DDMAC letters to drug companies cited inappropriate economic promotion [8]. Our current study includes work productivity violations, which were not accounted for in our previous analysis, and which comprise over half of the violations from 2002 to 2011. In terms of nonproductivity economic violations, FDA issued economic violation letters in roughly the same percentage of total letters from 2002 to 2011 (6%) compared with the earlier period (5%), though the total number of FDA letters issued per year has declined over time from 114 per year between 1997 and 2001 to 29 per year between 2002 and 2011. The trend may suggest less rigor in the degree to which the DDMAC has regulated promotional activity overall, though little change in its oversight of economic claims relative to clinical claims.

There are several limitations to this analysis. As noted, our study does not shed light on the extent to which drug companies are actually promoting economic information, only the degree to which the FDA is regulating such activity. There are no data on the total number of submissions of promotional materials to the DDMAC, or the number of these submissions that are actually reviewed by the FDA. Thus, we do not know whether the FDA is being particularly vigilant about health economic promotions relative to their frequency in practice. In addition, there are no data on regular correspondence between the DDMAC and pharmaceutical companies over economic claims that did not result in either a notice of violation or a warning letter. Another limitation is that we did not include adherence, compliance, or convenience claims or any patient-reported outcomes (PROs), and the field would benefit from future work in those areas.

In general, data should be interpreted with caution. One might infer that given the relatively low frequency of economic violation letters, the FDA ignores most health economic claims or that the pharmaceutical industry generally avoids making such claims. Moreover, when claims about health economics are made, the FDA tends to examine the "clinical aspects" underlying these claims and objects to those aspects. This is consistent with the finding of the two major categories where violations were cited: productivity and "unsupported claim of effectiveness, safety, or interchangeability." Furthermore, the flurry of "productivity" letters may reflect industry promotional efforts more than FDA enforcement trends, though it could also reflect the FDA's focus on an area of promotion that it believes is out of hand.

In terms of recommendations for the field, possibly formal FDA guidance on economic claims would help. On the one hand, such guidance may be unnecessary, given that linking a claim to the required level of evidence is a fundamental expectation for pharmaceutical companies and that FDA has generally made requirements for superiority claims clear. Moreover, it is not clear how much confusion actually exists within pharmaceutical companies about what types of economic claims are permissible. To some extent, the regulatory letters may reveal a "cat-and-mouse" game, with some companies trying to push the boundaries in making economic claims, despite lacking supporting evidence. Rather than a call for guidance, our findings could be interpreted as simply underscoring the need for companies to be more careful about making promotional claims and more disciplined about using existing FDA guidance when creating and approving economic claims.

On the other hand, guidance could help clarify certain gray areas surrounding health economic claims. One example pertains to FDAMA Section 114, where studies have suggested that confusion persists within pharmaceutical companies about when to use the section [13]. Our prior survey of outcomes directors within drug companies found that 75% of the respondents favored FDA guidance on Section 114, particularly surrounding the definition of "competent and reliable scientific evidence'" [6].

FDA guidance might also address other areas, such as productivity claims. Arguably, such claims are covered by the FDA's existing guidance for industry on PRO measures [35]. The PRO guidance states, for example, that "PRO-based evidence of improved symptoms alone will only support claims specific to improvement of the symptoms and would not support a general claim related to improvement in a patient's ability to function or the patient's psychological state." Such language might be interpreted as prohibiting the kinds of productivity claims cited in this article—for example, those extrapolating from symptom relief to work function. Nonetheless, further clarification of when it is permissible to make work productivity claims and what substantiating evidence is needed might be helpful.

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Supplemental Materials

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