

# Drug Company Advertising in Medical Journals About the Health-Economic Advantages of Their Products for 2000-2006 Versus 1990-1999

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## ABSTRACT

**BACKGROUND:** Section 114 of the 1997 Food and Drug Administration Modernization Act (FDAMA) effective February 19, 1998, permitted some additional flexibility for drug companies to provide "health care economic information" to "a formulary committee or other similar entity" and may have caused a decline in economic messages used in print advertisements in medical journals. We previously investigated the promotional claims made by pharmaceutical companies about the economic advantages of their prescription products in print advertisements in 6 leading medical journals from 1990-1999.

**OBJECTIVE:** To examine the hypotheses that (1) economic promotion in journals declined after the effective date of Section 114 of the FDAMA, and (2) increased calls for U.S. Food and Drug Administration (FDA) scrutiny of health-economic information was associated with an increase in the reporting of supporting information for economic advertisements in 2000-2006 compared with the 1990s.

**METHODS:** Two researchers independently reviewed all pharmaceutical print advertisements in 3 issues each year of 3 general medical and 3 specialty journals (totaling 18 issues each year) from 2000 through 2006. The type of economic claim (e.g., advertisements using the words "price," "costs less," "value") as well as the presence of supporting information for an advertisement's claims (e.g., published studies) were tabulated using a standardized data collection form. The research method was similar to that used in previous research of economic claims in advertisements in the same 6 medical journals from 1990-1999, and we compared the results from previous research for 1990-1999 with the new findings for 2000-2006. The list of health economic terms was expanded in the 2000-2006 research to include "less hospitalization"/"less treatment," "formulary"/"coverage," "co-pay"/"cost-sharing," and "in community longer."

**RESULTS:** Our results are derived from 2,144 pharmaceutical advertisements from the 10-year period 1990-1999 and 1,372 from the 7-year period 2000-2006. Economic content occurred in 11.1% (237/2,144) of advertisements in the 1990s, and 7.6% (104/1,372) in 2000-2006 ( $P < 0.001$ ). The frequency of economic advertisements rose in the 1990s to a peak in 1997 at 16.2% (31/191) (test for trend:  $P < 0.001$ ) and declined thereafter, reaching a low of 3.9% (9/234) in 2002 (test for trend:  $P < 0.001$ ) before rising again to 13.7% (25/182) in 2006 (test for trend:  $P = 0.030$ ). Economic claims centered mainly on direct costs (i.e., "less expensive") and benefit design (i.e., "one co-pay") and less on cost-effectiveness (i.e., "value"). The percentage of economic advertisements that included any supporting information was similar in the 1990s and 2000s (63.7% [151/237] vs. 61.5% [64/104],  $P = 0.70$ ). The source of information to support an advertisement's economic claims shifted away from price information (e.g., "average wholesale price" or "Red Book") towards published studies and "data on file."

**CONCLUSION:** Drug companies continue to advertise the economic advantages of their products in medical journals, though the practice declined somewhat after the 1997 FDAMA Section 114 legislation. Use of supporting references in the body of advertisements has not improved over time. The promotion of health economic information warrants more scrutiny by regulators and medical journal editors.

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## What is already known about this subject

- Previous research by the authors of the present study found economic messages in 237 (11.1%) of the 2,144 advertisements in 6 medical journals over the period from 1990 through 1999. The proportion of ads with economic content increased over time, from 8.9% in 1990 to 9.7% in 1999 ( $P = 0.003$ ). Most frequently, economic ads contained statements that drugs were "less expensive" or "cost less" than alternative treatments (50.6% of economic ads). Support for economic advertisements was clearly reported in 63.7% of cases and typically referred to published drug prices.
- A 2003 study of 287 different pharmaceutical advertisements in 6 Spanish medical journals revealed that 82.4% (84) of 102 retrievable references were randomized controlled trials (RCTs) and 44.1% (45) of the 102 were not substantiated by the cited reference. Only 0.8% (1/125) of promotional claims that were made referred to "cost."
- Research published in 2006 for 84 unique pharmaceutical advertisements published in 4 specialty journals in rheumatology found that only 29.0% (87) of 300 references were RCTs, 49.4% (43) of which were determined to be "supporting" of the claim.
- Cooper and Schriger (2005) found that 28.8% of medical claims in 438 pharmaceutical advertisements in 10 U.S. medical journals in 1999 did not have references to support the claims, and 18.7% (135/721) of the references that were used cited "data on file." Only 20.5% (18/88) of requests for "data on file" were found to be actually available.

### What this study adds

- This is the most comprehensive study of economic messages in medical journal drug advertising and compares the findings of our previous research for the 1990s with 2000-2006.
- Economic content occurred in 11.1% (237) of 2,144 ads in 10 years in the 1990s, and 7.6% (104) of 1,372 ads in the 7 years from 2000 through 2006 ( $P < 0.001$ ). Economic claims centered mainly on direct costs (i.e., “less expensive”) and benefit design (i.e., “one co-pay”) and less on cost-effectiveness (i.e., “value”).
- The present research suggests a potential influence of the FDAMA Section 114 of 1997 in a reduction of economic claims in drug advertisements with a subsequent increase beginning in 2002. The frequency of economic ads rose in the 1990s to a peak in 1997 at 16.2% (31/191) (test for trend:  $P < 0.001$ ) and declined thereafter, reaching a low of 3.9% (9/234) in 2002 (test for trend:  $P < 0.001$ ) before rising again to 13.7% (25/182) in 2006 ( $P = 0.030$ ), a proportion higher than in 8 of the 10 years of the 1990s.
- The percentage of economic advertisements that included any supporting information was similar in the 1990s and 2000s (63.7% vs. 61.5%,  $P = 0.70$ ). The source of information to support an advertisement’s economic claims shifted away from price information (i.e., “average wholesale price” [AWP] or “Red Book”) towards published studies and “data-on-file.”

Pharmaceutical advertisements in medical journals are pervasive. They represent 95% of journal display advertisements,<sup>1</sup> and their page length can exceed that of a journal’s longest article.<sup>2</sup> Many studies have examined clinical claims in journal drug advertising. In contrast, the economic content of journal drug advertisements has received limited notice.<sup>3-5</sup>

The prevalence and transparency of claims about a drug’s economic advantage merits attention. First, promotional efforts by manufacturers influence physicians’ prescribing decisions,<sup>1,6,7</sup> which have potentially important implications for patients’ health and financial burden. Second, many physicians believe that cost considerations will factor into their drug selections increasingly over the next several years,<sup>8</sup> which suggests a growing niche for economic advertising to physicians. Rising prescription drug prices and patient out-of-pocket payments in the future may further increase the influence of economic advertisements on physician decision-making.

Finally, studies have indicated that many claims in medical journals about drugs are poorly substantiated. For clinical claims, advertisements are often deficient in the use of supporting information,<sup>9-12</sup> the representativeness of the information,<sup>5,7,11,13-16</sup> the quality of the information,<sup>7,11,15-19</sup> the sponsorship of the

information,<sup>9</sup> and the availability of the information.<sup>7,9,11,16</sup> For example, Cooper and Schriger (2005) found that 28.8% of medical claims in 438 pharmaceutical advertisements in 10 U.S. medical journals in 1999 did not have references to support the claims, and 18.7% (135/721) of the references that were used cited “data on file;” only 20.5% (18/88) of requests for “data on file” was found to be actually available.<sup>9</sup> van Winkelen et al. (2006) found that only 49.4% (43) of 87 randomized controlled trials were determined to be “supporting” of the claim in 84 unique advertisements published in 4 specialty journals in rheumatology during 2002-2004.<sup>11</sup> Poor substantiation might extend to claims about economic benefits as well.

Our goal in this study was to characterize prescription drug advertisements with economic claims in leading medical journals from 2000-2006 and to document the presence and type of supporting information for such advertisements. This paper builds upon our previous work on economic messages in pharmaceutical advertisements in medical journals from 1990-1999.<sup>4</sup>

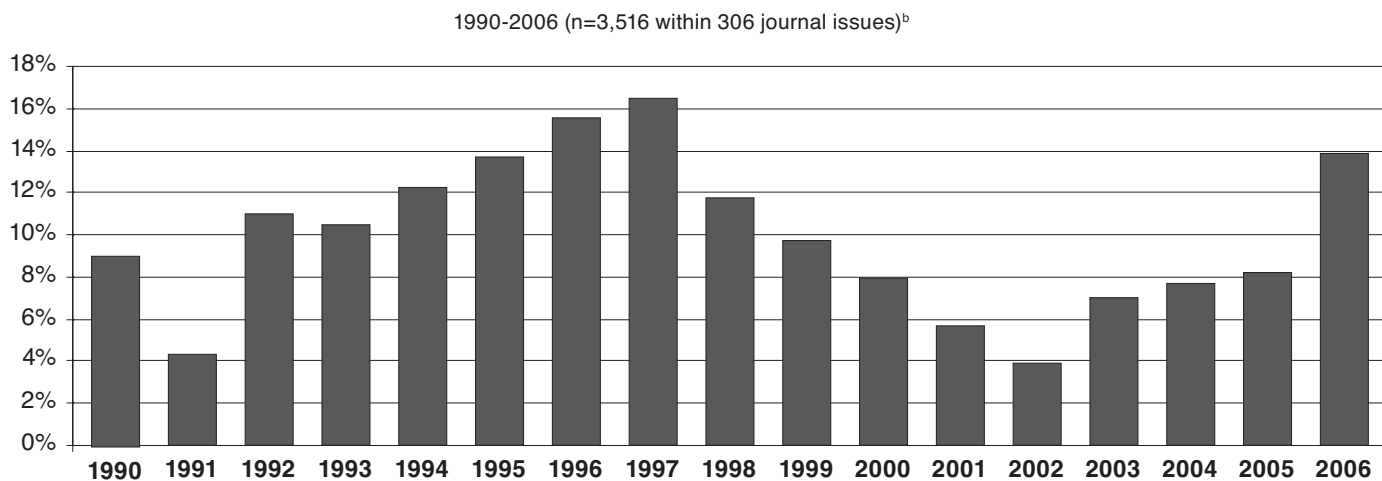
Our hypotheses stem from trends found in earlier work and reflect the policy context within which journal advertising lies. Section 114 of the Food and Drug Administration Modernization Act (FDAMA) of 1997 changed the evidentiary requirements for submissions to drug formulary committees in managed care organizations (MCOs) from “substantial evidence typically demonstrated by two adequate and well-controlled trials” to “competent and reliable scientific evidence.”<sup>20</sup> (Appendix) The new standard gives pharmaceutical manufacturers guidance and some additional flexibility in promoting economic messages to managed care audiences. Conceivably, manufacturers redirected their promotional efforts from medical journals to direct MCO communications – a medium with a potentially larger sales impact – in response to this change in evidentiary standards. Manufacturers may also have decreased use of economic claims but improved substantiation of those still used in response to concerns about economic promotion and calls for more FDA vigilance.<sup>21</sup> We therefore hypothesized that the quantity of economic claims in medical journal advertising decreased after Section 114 went into effect and that, over time, the use of information to support economic claims made in journal pharmaceutical advertisements increased.

### Materials and Methods

We examined all prescription drug print advertisements in 3 leading general medical journals (*Annals of Internal Medicine*, *Journal of the American Medical Association*, *New England Journal of Medicine*) and 3 leading specialty journals (*Circulation*, *Gastroenterology*, *Neurology*) for 3 issues per year (January, July, October, chosen arbitrarily), totaling 18 issues per year from 2000-2006. The methods are similar to those in our previous study of 1990-1999.<sup>4</sup> We considered each advertisement as a single record, even if the same one appeared multiple times

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**FIGURE 1** Economic Content as a Percentage of All Ads in 6 Leading Journals<sup>a</sup>



<sup>a</sup>Journals include: *Annals of Internal Medicine*, *JAMA*, *NEJM*, *Circulation*, *Gastroenterology*, *Neurology*  
<sup>b</sup>Cochran-Armitage Test for Trend for 1990-1997:  $P < 0.001$ ; for 1998-2002:  $P < 0.001$ ; for 2003-2006:  $P = 0.030$

in our sample, to identify the frequency with which journal readers encounter promotional messages.

Our data collection form was based on our previous work and updated for clarity and completeness. Both forms (previous and current) included items on the type of economic claims contained anywhere in the body of the advertisement. We defined economic content as mentioning terms such as “price,” “less expensive,” “costs less,” “value,” “cost-effectiveness,” and “productivity.” In the updated form, we specified some new terms, such as “less hospitalization/ less treatment,” “co-pay/cost-sharing,” “in community longer,” (as stated within the context of claiming delayed nursing home placement) and “formulary/coverage.” These terms were added because they represent potentially important, more specific economic claims with regards to insurance benefit design and “indirect” economic impact.

We documented use of supporting information for economic advertisements and types of supporting information used (i.e., “price information,” “data on file,” or “published studies”). “Price information” refers to several different resources on drug prices. One of these, the AWP or “average wholesale price,” is the “list price” reported to commercial publishers by drug companies that is used to inform levels of drug reimbursement. These publishers, also used in advertisements’ references, include the “Red Book: Pharmacy’s Fundamental Reference,” “First Databank, Inc.,” and “Scott Levin Formulary Drug Audit.” Other references that fall into this “price information” category include citations of “wholesale acquisition cost” (the amount a company charges a wholesaler for a pharmaceutical) and “weighted average cost” (the summed total of an average price per package of a drug during a

certain time period multiplied by the number sold, and divided by the number sold).

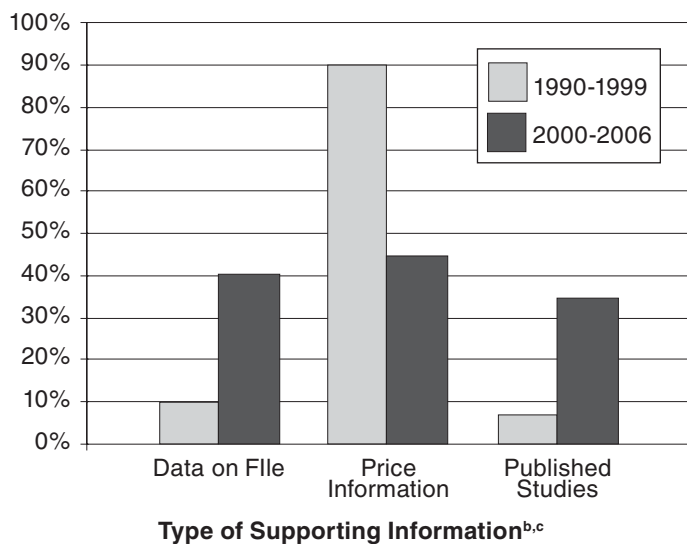
Further, types of supporting information were classified as “data on file” if those words were used verbatim, or if other unpublished company documentation was cited, i.e. “formulary status report” or “formulary access status.” “Published studies” as a source consisted of published peer-reviewed studies, mostly, as well as a presentation at a professional membership conference, a published abstract, and an on-line patient registry.

We considered published sources to reflect more transparent and potentially better substantiating information than price information, in that price alone does not capture the full economic consequences of using a drug, whereas published studies may. We considered data on file to be the least transparent source of evidence. We recognize that published sources may not always reflect rigorous or appropriate evidence, but use this categorization for convenience and discuss this further in our limitations section.

Two trained readers extracted data from each advertisement. After completing the form individually, these 2 reviewers convened to decide upon the final consensus answers which were used for analysis. The Cochran-Armitage test for trend was used to assess the statistical significance of changes over time in the proportion of advertisements containing economic content by year. The Pearson chi-square test was used to assess the statistical significance of differences by time period in type of information used to support economic claims. The SAS 9.1 statistical software package was used to run all of our descriptive and inferential statistics.

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**FIGURE 2** Percentage of Economic-Content Ads by Type of Supporting Information<sup>a</sup>



<sup>a</sup>Chi-square test:  $P < 0.001$

<sup>b</sup>Not mutually exclusive

<sup>c</sup>Data on file=unpublished manufacturer documentation; price information=price lists (i.e., "Red Book" or "average wholesale price;" published studies=journal, conference, or on-line published data

**Results**

We reviewed 1,372 drug advertisements for the 7-year period from 2000 through 2006 (compared with 2,144 advertisements from 10 years in the 1990s), representing 220 different drugs. The 1,372 total for 2000-2006 included 567 (41.3%) advertisements from general medical journals and 805 (58.7%) from specialty journals. Of this total, 788 (57.4%) were unique (each advertisement appeared an average of 1.8 times in our sample; SD = 1.2; range = 1-8).

Economic content appeared in 7.6% (104/1,372) of advertisements from 2000-2006, compared with 11.1% (237/2,144) from 1990-1999 ( $P < 0.001$ ). While the economic advertisements appeared with similar frequency in the specialty journals across time periods (1990s: 8.6% [81/942] vs. 2000-2006: 8.5% [68/805];  $P = 0.91$ ), they declined in frequency in the general medical journals (1990s: 13.0% [156/1,202] vs. 2000-2006: 6.4% [n = 36/567];  $P < 0.001$ ). The frequency of economic advertisements rose in the 1990s to a peak in 1997 of 16.2% (31/191) (test for trend:  $P < 0.001$ ) and declined thereafter, reaching a low of 3.9% (9/234) in 2002 (test for trend:  $P < 0.001$ ) before rising again, to 13.7% (25/182) in 2006 ( $P = 0.030$ ). (Figure 1)

In the 2000s, drug advertisements with economic promotion referred mostly to direct costs and/or benefit design (i.e.,

"co-pay," formulary availability). (Table 1) This included mention of "less hospitalization/less treatment" (26.0% of economic advertisements), "formulary/coverage" (23.1%), "co-pay/cost-sharing" (19.2%), "price" (16.3%), and "cost less/less expensive" (14.4%). While 1990s advertisements cited terms that indicated the concept of cost-effectiveness (i.e., "economical," "value," "savings," "cost-effective"), the 2000-2006 advertisements did at a significantly lower rate or not at all. (Table 1)

The frequency of supporting information for advertisements with economic claims has not changed over time (1990s: 63.7% [151/237] and 2000-2006: 61.5% [64/104]), although the type of citation used to support advertisements has varied ( $P < 0.001$ ). In the 2000s, supporting information pertained less to price information (1990s: 90.1% [136/151] vs. 2000-2006: 43.7% [28/64]) and more to data on file (1990s: 9.3% [14/151] vs. 2000-2006: 40.6% [26/64]) and published studies (1990s: 6.6% [10/151] vs. 2000-2006: 35.9% [23/64]). (Figure 2)

**Discussion**

Our study sheds light on the evolving practice of economic promotion in medical journal advertisements. First, economic promotion in pharmaceutical advertising continues, increasing in recent years after a decline during 1998-2002. Second, the economic advertisements from 2000-2006 refer more to direct cost (i.e., "costs less," "price," "affordable/affordability") than to indirect costs ("back-to-work") and cost-effectiveness ("value"). Perhaps pharmaceutical companies favor such claims as more concrete and easier to substantiate.

Third, the overall use of substantiating information has not increased with time. Even when references are provided, questions about their transparency persist. On the positive side, more published studies have been referenced in recent years. On the other hand, references to "data on file," a company's in-house form of evidence which has not been published or peer-reviewed, also increased over time.

Our findings suggest the possible influence of external policies on promotional activities for drugs. In particular, the FDAMA Section 114 legislation in 1997 may have contributed to the decrease in economic advertisements in general medical journals post-1997. Section 114 may have precipitated a shift in drug company's targeted audience from individual physicians making prescribing decisions at the patient level to formulary committees making coverage decisions at the health plan level.<sup>4</sup> It is also possible that the increased scrutiny of economic promotion accompanying the legislation created a spillover chilling effect on its use in print advertising.<sup>22</sup> The more recent increase in economic advertisements (post-2002) may reflect a renewed interest among drug companies in this type of promotion perhaps due to tougher competition in the generic market, heightened interest in cost by payers, typified by the release of versions of the Academy of Managed Care Pharmacy (AMCP) Format for Formulary Decisions (in 2000, 2002, 2005),<sup>23</sup> which call for a

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**TABLE 1** Health Economic Terms<sup>a</sup> Used In Medical Journal Advertisements: 1990s versus 2000-2006

Words Used	All Ads			Economic Ads		
	1990-1999	2000-2006	P Value	1990-1999	2000-2006	P Value
	% (n) N=2,144	% (n) N=1,372		% (n) N=237	% (n) N=104	
"Less Expensive" / "Costs Less"	5.6% (120)	1.1% (15)	<0.001	50.6% (120)	14.4% (15)	<0.001
"Price"	1.4% (30)	1.2% (17)	0.710	12.7% (30)	16.3% (17)	0.363
"Productivity/Back to Work"	0.6% (13)	1.0% (13)	0.249	5.5% (13)	12.5% (13)	0.025
"Economical"	1.8% (39)	0% (0)	<0.001	16.5% (39)	0% (0)	<0.001
"Value"	1.5% (33)	0.2% (3)	<0.001	13.9% (33)	2.9% (3)	0.002
"Savings"	3.3% (71)	0.1% (2)	<0.001	30.1% (71)	1.9% (2)	<0.001
"Cost-effective"	0.7% (16)	0% (0)	0.001	6.8% (16)	0% (0)	0.004
"Affordability" / "Affordable"	0.5% (10)	0.3% (4)	0.422	4.2% (10)	3.9% (4)	1.00
"Less Hospitalization" / "Less Treatment"	N/A <sup>b</sup>	2.0% (27)		N/A <sup>b</sup>	26.0% (27)	
"Formulary"/"Coverage"	N/A	1.7% (24)		N/A	23.1% (24)	
"Co-pay" / "Cost-sharing"	N/A	1.5% (20)		N/A	19.2% (20)	
"In Community Longer" <sup>c</sup>	N/A	0.9% (12)		N/A	11.5% (12)	

<sup>a</sup>Not mutually exclusive; each advertisement may have more than 1 economic term.

<sup>b</sup>N/A = Not applicable; data on these terms were not extracted for the 1990-1999 data collection process.

<sup>c</sup>"In community longer" is an economic claim given its context in the advertisements of delaying nursing home placement – a direct treatment cost.

health plans to request economic data and models from drug companies, or increased comfort with the FDA's relative lack of scrutiny over economic messages in ads.

Given the recent resurgence of economic advertisements after a decline in the late 1990s, the question of whether this trend is desirable or not warrants discussion. Economic claims in drug advertising offer potential benefits. Physicians believe that cost to the patient is an important consideration in their prescribing practice,<sup>8,24,25</sup> though very few of them know the relative or absolute prices of the drugs they prescribe.<sup>24-26</sup> With an advertisement possibly serving as an important introduction to a technology,<sup>27</sup> physicians may be able to make better decisions on the value of drugs and guide their patients in doing the same. This could result in better clinical decisions and even significant cost savings for both the patient and the health care system. Providers could avoid more costly but equally effective products with accurate information<sup>7</sup> or select products that cost more but offer good value.

The uncertain nature of much of the substantiating information that comes with less transparent practices, however, tempers these advantages. Indeed, as discussed before, the field is scattered with examples of biased, unsubstantiated, unavailable, and misleading clinical claims.<sup>5,7,11,13-19</sup> For example, expert reviewers considered 34% of medical journal advertisements with clinical claims in need of major revisions, 28% not acceptable for publication, and, most importantly, 44% capable of causing inappropriate prescribing if journal advertisements served as the sole source of information.<sup>7</sup>

Similarly with regard to economic claims, physicians could prescribe drugs on erroneous economic pretense if relying on

misinformation. A prescription based on an unsubstantiated advertisement could result in foregone clinical, economic, and quality-of-life benefits. As with clinical claims,<sup>7</sup> inaccurate or misleading economic claims could result in inadequate care from physicians.<sup>21</sup> This effect may be unduly heightened given the credibility attributed to referenced claims that appear in medical journal advertising.<sup>27</sup>

Accordingly, economic content in prescription drug advertisements may warrant more attention from journal editors and perhaps regulators. The FDA could help matters by establishing clear guidelines about what economic claims and what level of transparency are acceptable in promotions targeting providers<sup>21</sup> and implementing an effective surveillance system to monitor compliance.<sup>7</sup> This is particularly vital, as physician-targeted advertising generates the most FDA citations of any type.<sup>28</sup>

Future research could help shed more light on this topic. Only 2 prior studies have assessed economic claims in drug advertising in medical journals.<sup>3,5</sup> The first is outdated (published 1993), and, while finding prices advertised in nations with a public insurance model (out of 18 nations total), does not examine practices in the United States. The second, which targets Spanish medical journals, found "cost" claims only in 0.8% (1/125) promotional claims backed by supporting information. New studies should address this gap in the knowledge base about economic promotion of drugs in U.S. medical journals. Studies should also assess how and to what extent journal advertisements with economic messages influence physicians' drug choices and whether or not that is a beneficial end-result. Other possible explanations of

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the dip and subsequent rise in economic advertisements in the past decade, besides FDAMA Section 114's influence, should be examined, such as an initial lack of familiarity followed by an increasing comfort level with FDA rules among pharmaceutical manufacturers.

To improve the transparency of journal drug advertisements, researchers could build upon this work by examining the representativeness, sponsorship, and availability of supporting information for economic promotion. Manufacturers, too, can help by supporting economic claims with rigorous and transparent scientific support that is readily available. Finally, journal editors might subject economic advertisements to more stringent peer and editorial review processes.<sup>7,29</sup>

### Limitations

Our study has several limitations. One is the somewhat simplistic classification that we used to describe the sources of supporting information. We did not examine the quality or level of evidence in sources such as "data on file" or published studies. Instead, we defined published studies as more transparent than price information (i.e., "average wholesale price" or "Red Book") and, in turn, price information as more transparent than data on file, a relatively crude metric. Second, the number of economic claims in the 2000s may be inflated due to the inclusion of new economic terms in the data collection instrument for 2000-2006. This effect may have contributed to the increase in economic advertisements in the mid-2000s. Third, we did not determine inter-rater reliability but instead used a consensus measure. This method does not permit examination of the role of bias in our results.

Fourth, our reviewers in this study were different individuals than those who reviewed the 1990-1999 data and may have categorized the information differently. Fifth, the advertisement content in the leading medical journals in our sample may not be representative of the advertisement content in all medical journals. Finally, our study does not include other important areas of pharmaceutical promotion such as direct-to-consumer advertising, physician detailing and sampling, which are fertile ground for investigation of economic promotional practices.

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### DISCLOSURES

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Peter Neumann was responsible for study concept and design. Jennifer Palmer and Alison Timm collected the data. Timm conducted the data analyses, and all 3 authors shared in data interpretation. Palmer performed the majority of the writing of the manuscript with assistance from Neumann. Palmer, Timm, and Neumann revised the manuscript after peer review.

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### APPENDIX A

#### SEC. 114. Health Care Economic Information<sup>a</sup>

(a) In General.--Section 502(a) (21 U.S.C. 352(a)) is amended by adding at the end the following: "Health care economic information provided to a formulary committee, or other similar entity, in the course of the committee or the entity carrying out its responsibilities for the selection of drugs for managed care or other similar organizations, shall not be considered to be false or misleading under this paragraph if the health care economic information directly relates to an indication approved under section 505 or under section 351(a) of the Public Health Service Act for such drug and is based on competent and reliable scientific evidence. The requirements set forth in section 505(a) or in section 351(a) of the Public Health Service Act shall not apply to health care economic information provided to such a committee or entity in accordance with this paragraph. Information that is relevant to the substantiation of the health care economic information presented pursuant to this paragraph shall be made available to the Secretary upon request. In this paragraph, the term 'health care economic information' means any analysis that identifies, measures, or compares the economic consequences, including the costs of the represented health outcomes, of the use of a drug to the use of another drug, to another health care intervention, or to no intervention."

<<NOTE: 21 USC 352 note.>> (b) Study and Report.--The Comptroller General of the United States shall conduct a study of the implementation of the provisions added by the amendment made by subsection (a). Not later than 4 years and 6 months after the date of enactment of this Act, the Comptroller General of the United States shall prepare and submit to Congress a report containing the findings of the study.

<sup>a</sup> Abstracted from Public Law 105-115, the Food and Drug Administration Modernization Act of 1997. Available at: [www.fda.gov/CDER/guidance/105-115.htm](http://www.fda.gov/CDER/guidance/105-115.htm). Accessed September 20, 2008.