

## SOUNDING BOARD

## Pharmaceutical Promotion to Physicians and First Amendment Rights

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In mid-February, the Food and Drug Administration (FDA) proposed a change in its rules governing pharmaceutical promotion that would widen the ability of drug manufacturers to distribute information on unapproved uses of their products.<sup>1</sup> This proposal has rekindled the debate over the rights of drug makers to promote their medications to physicians.

Studies have highlighted the substantial effect of promotional statements on the prescribing behavior of physicians, and litigation has revealed that some manufacturers have depicted the risks and benefits of their products inaccurately.<sup>2</sup> A growing number of states are working to curb inappropriate pharmaceutical promotion by restricting electronic marketing and requiring disclosure of spending on advertising and marketing.<sup>3</sup> The federal government has taken an increasingly active interest as well, and the Department of Justice has pursued a number of high-profile cases of health care fraud involving improper marketing.

Communication by drug manufacturers to physicians has a unique status in both legal and business terms. Whereas the requirement for product claims in nearly all other industries is simply that they not be deceptive,<sup>4</sup> claims made by pharmaceutical companies about their products are held to a higher standard. For example, promotional materials currently must relate only to the uses of a drug that have been approved by the FDA; those relating to any other uses of the drug are prohibited as “off-label” promotion. In 2004, the manufacturer of the antiseizure medication gabapentin (Neurontin) paid \$430 million to the government to settle charges of off-label marketing of the drug for indications that had not been approved by the FDA (and for which evidence of efficacy was in many cases lacking).<sup>5,6</sup> Supervision of the promotional statements made by pharmaceutical manufacturers provides an incentive for manufacturers to subject their claims to rigorous scientific

evaluation. If the results do not provide appropriate scientific justification for expanded product use, FDA evaluation of a drug can protect the public from the potentially serious consequences of mischaracterizing a medication’s benefits and risks.

Drug manufacturers and activists have objected to the added scrutiny of the communications of the pharmaceutical industry, arguing that such restrictions unfairly limit the ability of drug manufacturers to disseminate truthful information about their products<sup>7</sup> and violate their right of free speech. In the case of off-label uses, the federal prosecution in the Neurontin case was criticized<sup>8</sup> because peer-reviewed, published studies demonstrated that the drug might be useful for some unapproved indications, such as migraine headaches.<sup>9</sup>

Since the 1970s, corporate advertising has been protected by the First Amendment to the Constitution, which states that “Congress shall make no law . . . abridging the freedom of speech,” and a number of Supreme Court cases have struck down government restrictions on such “commercial speech.” In this article, we consider whether public health concerns about the excesses of drug promotion should affect how the courts view regulation of commercial speech in the pharmaceutical industry.

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### THE FIRST AMENDMENT AND COMMERCIAL SPEECH

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The FDA’s authority to restrict manufacturers’ communication about their products originates from the 1938 Food, Drug, and Cosmetic Act, which prevented the movement of any new drug in interstate commerce unless it was approved by the FDA.<sup>10</sup> A set of amendments in 1962 gave the FDA additional power to regulate the advertisement of prescription drugs,<sup>11</sup> as well as to deter-

mine whether a particular drug is safe and effective for the indications set forth in its labeling.<sup>12</sup>

In contrast, pharmaceutical manufacturers view their communications about their products as commercial speech. Commercial speech was not initially considered worthy of protection under the Constitution because, as compared with personal statements regarding political or religious preferences, it was seen as having less benefit for the public and greater potential harm. However, in the 1976 case *Virginia State Board of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, the Supreme Court struck down a law that prevented pharmacies from advertising the prices of prescription drugs, thus carving out a First Amendment protection for commercial speech. The Court found value in the free flow of commercial information, which can allow consumers to make “intelligent and well informed” decisions.<sup>13</sup>

The Supreme Court, however, has not granted commercial speech the same stringent level of protection as personal speech. Limiting personal speech is permissible only if the government has a compelling interest in the matter and if the restriction is narrowly tailored to meet that interest. In practice, these are nearly insurmountable hurdles. The framework that courts use to evaluate regulation of commercial speech was established in 1980, after a legal challenge to a New York state energy-conservation policy that prevented utility companies from promoting the “use of electricity.” In *Central Hudson Gas & Electric Corp. v. Public Service Commission of New York*, the Supreme Court considered whether the government (public) had a substantial interest, whether the contested regulation directly advanced that interest, and whether the regulation was more extensive than necessary to achieve its goals (Fig. 1). The Court found the regulation unconstitutional because it also limited promotional activities that provided “information about electric devices or services that would cause no net increase in total energy use.”<sup>14</sup> A narrower restriction, the Court argued, supported conservation equally well.

Subsequent court decisions interpreting regulations regarding commercial speech have applied the *Central Hudson* test narrowly, especially with reference to the third factor, concerning the extensiveness of the restriction. For example, in a 2001 case, tobacco manufacturers and retailers objected to a proposal by the Massachusetts attor-

ney general to ban tobacco advertising within 1000 ft of a school or playground. The Court agreed that the government had a substantial interest in preventing children from smoking and that the regulation directly advanced that interest. But the Court overturned the attorney general’s plan, finding the restrictions overly extensive, since “a ban on all signs of any size seems ill suited to target the problem of highly visible billboards.”<sup>15</sup>

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JUDICIAL PERSPECTIVES ON  
REGULATION OF PHARMACEUTICAL  
PROMOTION

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Courts have consistently found pharmaceutical promotion to be commercial speech amenable to the *Central Hudson* test.<sup>16</sup> In the 2002 case of *Thompson v. Western States Medical Center*,<sup>17</sup> the Supreme Court reviewed federal legislation that precluded advertisement of “compounded” medications, individualized products that are made by a pharmacist for a particular patient.<sup>18</sup> These drugs were exempt from the usual requirements for FDA approval, and the FDA feared that larger manufacturers would start producing and marketing compounded products without undertaking the standard review process. However, the Court found the restriction unnecessarily broad. Justice Sandra Day O’Connor, for a five-member majority, wrote that even if the contested regulation rested “on the questionable assumption that doctors would prescribe unnecessary medications,” the government could not prevent the dissemination of commercial information based on a fear that physicians and patients might make bad decisions even if they were given truthful information.<sup>17</sup> Instead, she argued, the government’s interest in preventing misleading advertisements “could be satisfied by the far less restrictive alternative of requiring each compounded drug to be labeled with a warning that the drug had not undergone FDA testing.”<sup>17</sup>

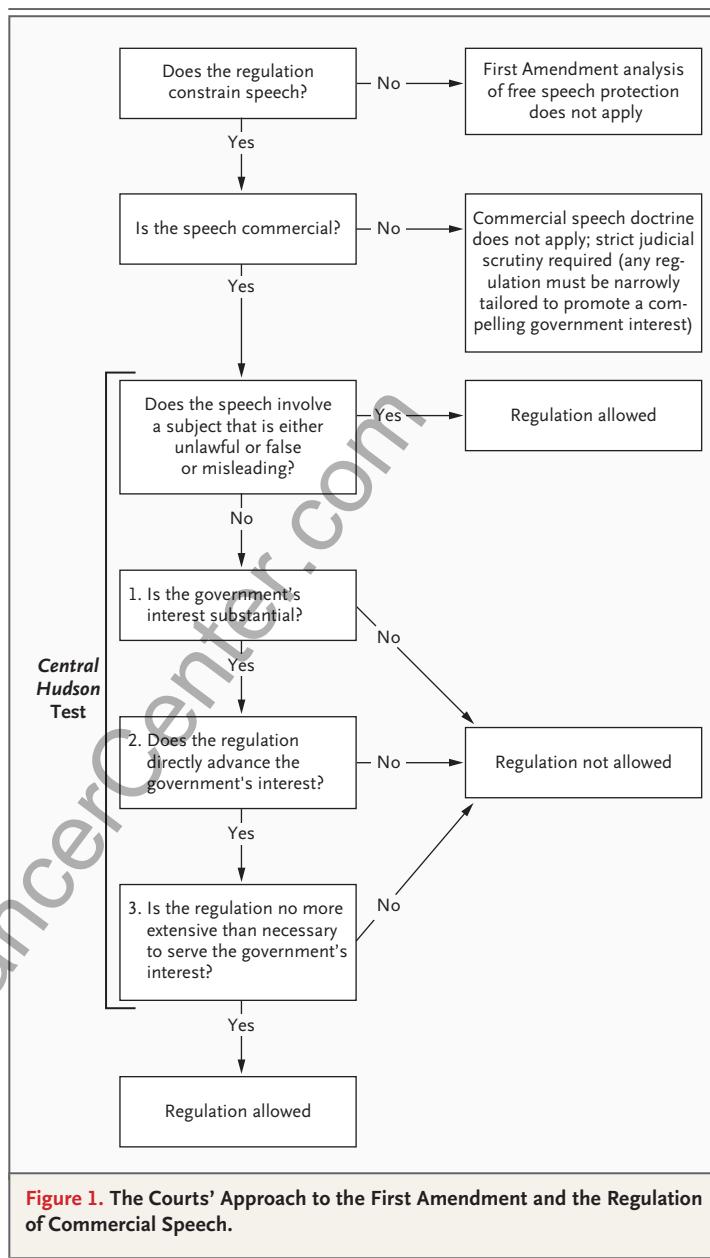
Other federal courts have applied similar reasoning in evaluating restrictions on pharmaceutical promotion. In the late 1990s, the **Washington Legal Foundation**, a conservative law policy center, challenged FDA guidelines that prevented manufacturers from promoting off-label uses of their drugs through distribution of articles and textbooks or sponsorship of continuing-medical-education seminars. The federal court acknowledged that disseminating such information was

intended to encourage the purchase of the featured product and, as in *Thompson*, found a substantial government interest in encouraging rigorous scientific evaluation and FDA review.<sup>19</sup> However, the court determined that the regulations were “more extensive than necessary” because a “full, complete and unambiguous disclosure by the manufacturer” that the use was off-label would be sufficient to alert physicians that the FDA had not reviewed the claims and would allow physicians to “evaluate the communicated message accordingly.” After many appeals, the case was resolved — in the words of one court, “without clear guidance”<sup>20</sup> — when the FDA agreed not to use violations of these guidelines to prosecute manufacturers for promotion of off-label uses of medications.<sup>21</sup>

At least one federal court has upheld the FDA’s efforts to block off-label promotion. In that case, the government charged the manufacturer of a surgical-instrument sterilizer with conspiracy to engage in off-label promotion of its device, although some of the promotional statements it cited were neither false nor misleading. An Illinois federal court upheld the charges and ruled that FDA limitations on promoting off-label uses were constitutional because there was no “less burdensome alternative that would advance the government’s substantial interest.”<sup>22</sup> In a brief, the **Washington Legal Foundation** called for an end to the FDA’s prohibition of off-label promotion, arguing that a disclaimer indicating that the proposed use was not reviewed by the FDA would be both effective and less restrictive of the manufacturer’s commercial speech.<sup>23</sup> On February 27, 2008, the Seventh Circuit Court of Appeals ruled against the company but declined to rule on the First Amendment aspects of the case.

#### THE ROLE OF PROMOTION IN PRESCRIPTION DRUG SAFETY

Although there are several ways in which physicians learn about pharmaceutical agents, commercial sources play a particularly large role in disseminating information to physicians and in influencing their therapeutic decisions.<sup>24</sup> The most effective marketing strategy is personal visits from manufacturers’ sales representatives (or “detailers”). Meetings with detailers have been shown to influence physicians’ prescribing practices, as well as spark requests by physicians to add a drug



to their hospitals’ formularies.<sup>25</sup> Such contact predicts early adoption by physicians of pharmaceutical products whether or not they are the most clinically appropriate or cost-effective choices.<sup>26</sup> For example, marketing campaigns involving detailers that were initiated in the 1990s to promote calcium-channel blockers for the treatment of hypertension made these drugs the most common treatment choice, even though clinical guidelines do not recommend them as first-line therapy for most patients.<sup>27</sup> The use of such products in

the elderly alone may have added more than \$1 billion to national expenditures for drugs.<sup>28</sup>

Detailing often involves new, patented products that might be riskier than agents that are more well established, because a full understanding of a drug's side-effect profile may not be complete when the drug is first approved.<sup>29</sup> For example, aggressive promotional strategies for rofecoxib (Vioxx) that de-emphasized its cardiovascular risks contributed to the rapid, widespread adoption of a product later found to be too unsafe to remain on the market.<sup>2</sup> One jury concluded that Merck "recklessly [sold] Vioxx with knowledge of the risks associated with taking the drug" and held the company liable in a patient's death because of inadequate disclosure of the drug's risks.<sup>30</sup> Similarly, intravenous nesiritide (Natrecor) had been approved for the management of severe exacerbations of congestive heart failure in hospitalized patients, but its manufacturer helped persuade some cardiologists to prescribe it for a much broader population of patients, including outpatients, who were given costly infusions in an ambulatory setting.<sup>31</sup> The use of this drug was later curtailed sharply when attention was drawn to preexisting data documenting its adverse effects on renal function and an increased risk of death associated with its use.<sup>32</sup>

Off-label promotion may impede rigorous scientific study of uses other than those that have been approved by the FDA by reducing the motivation of manufacturers to conduct such trials. In certain patient groups, such as children and patients with rare diseases, off-label use may reflect the standard of care.<sup>33</sup> Nevertheless, recent research indicates that nearly half of all prescriptions in some drug classes may be off-label, and more than 70% of off-label uses may have insufficient scientific support<sup>34</sup>; such off-label uses may result in inadequate efficacy or an unjustified risk of harm to the patient. For example, there is a disproportionate use of off-label antipsychotic medications in elderly patients for conditions such as dementia and affective disorders,<sup>35</sup> which accounts for billions of dollars in annual spending by public health insurers.<sup>36</sup> However, the risk of death among the elderly who take atypical antipsychotic drugs,<sup>37</sup> as well as conventional drugs in this class,<sup>38</sup> is nearly double that among those who do not take these medications. Thus, although off-label use of drugs may sometimes represent a reasonable therapeutic choice, the sub-

stantial influence that promotion can have on the prescribing practices of physicians, combined with the potential risks to patients and the often greater costs associated with off-label use, in our view justifies the higher level of scrutiny applied to statements made by pharmaceutical manufacturers.

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#### THE FUTURE OF PHARMACEUTICAL PROMOTION AS COMMERCIAL SPEECH

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With increasing calls for First Amendment protection of promotional statements made by drug manufacturers, the courts will have to determine whether to follow the trend of applying the *Central Hudson* test narrowly in cases involving commercial speech and overturn state or federal restrictions on promotional statements by pharmaceutical manufacturers to physicians. We believe there is ample evidence to support regulating pharmaceutical promotion differently from other forms of commercial speech. Former Chief Justice William Rehnquist recognized such a distinction in the original *Virginia State* case when he wrote in his dissenting opinion that "there are sufficient dangers attending [the] widespread use [of pharmaceuticals] that they simply may not be promoted in the same manner as hair creams, deodorants, and toothpaste."<sup>13</sup>

In the pharmaceutical market, determining whether a drug is safe and effective for an intended use can involve dozens of FDA scientists poring over extensive databases of studies in animals, toxicologic evaluations, and clinical trials. In essence, the agency acts as a learned intermediary on behalf of prescribing physicians, who then synthesize the available data and make judgments about risks and benefits for their patients. If this buffering were not required, manufacturers could potentially bury physicians and patients in an avalanche of "information" to promote drugs, including reports of individual cases, uncontrolled or biased clinical studies, and poorly conducted observational analyses. Each might be technically nonfraudulent, but the body of material could be chosen selectively to create an appearance of safety or efficacy that would not meet FDA standards. It is unrealistic to expect each physician to have the time and expertise to subject such claims to the same kind of scrutiny that the FDA exercises when it reviews a drug application or a request for a new indication. The complexity of the assess-

ment that is required, along with the high stakes of getting the assessment wrong, provided the rationale for having a formal drug-approval process in the first place, even if inadequate financial resources or external pressures can occasionally impose institutional constraints on the FDA's decision-making ability.<sup>39,40</sup>

Ensuring that information is presented to physicians in as neutral a way as possible will continue to require legal restrictions on pharmaceutical promotion. The clinical and public health consequences of communications relating to drugs warrant a distinction in the interpretation of the commercial-speech doctrine between statements made about medications and those made about other products.

In some circumstances, including promotion of off-label uses of medications, drug-industry advocates have argued that a disclaimer neutralizes these potential harms. Disclaimers are currently included on the labeling for many widely used but ineffective herbal remedies and other "dietary supplements."<sup>41</sup> However, there is substantial evidence that consumers either do not interpret such disclaimers properly or ignore them altogether.<sup>42</sup> Even if information about off-label uses carried a small disclaimer, wider promotion in this area would result in increased prescription of products with dangerous side effects that are out of proportion to their benefits. Allowing companies to skip the FDA's evaluative step and promote unapproved indications directly to physicians would rapidly undermine the regulatory safeguards that have taken so long to develop.<sup>43</sup>

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## CONCLUSIONS

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State and federal regulation of promotional statements made by pharmaceutical manufacturers can improve prescribing decisions and protect the public's health. Such oversight can enable physicians to evaluate drugs on the basis of a balanced presentation of their risks and benefits and can counter marketing presentations that are aimed more at increasing sales than at depicting the best possible evidence. Courts should consider the complex nature of the evaluation of medications when applying the *Central Hudson* test in the pharmaceutical context and should permit appropriate and necessary constraints on commercial speech in the pharmaceutical industry.

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## Tectonic Shifts in the Health Information Economy

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In a recent shift in the health information landscape, large corporations are seeking an integral and transformative role in the management of health care information. The mechanism by which this transformation is likely to take place is through the creation of computer platforms that will enable patients to manage health data in personally controlled health records (PCHRs). Two types of large corporations are involved. Technology companies such as Google and Microsoft see business opportunities,<sup>1</sup> whereas Fortune 100 companies in their role as employers<sup>2,3</sup> see efficiencies and cost savings when patients can securely store, access, augment, and share their own copy of electronic health information. Though this shift in the locus of control of health information is driven largely by a need to provide assistance with clinical care processes, it will also profoundly affect the biomedical research enterprise. We illustrate this shift with a two-part scenario in which a patient fills her PCHR with data from multiple sites of care and then participates in research.

The first part of this scenario involves information integration. The patient, who has inflammatory bowel disease, is treated at a gastroenterology practice and has had an inpatient admission

at one hospital, a visit to an emergency department at another hospital, and test results at a laboratory. She logs into her hosted PCHR at a secure Web site. Since she has established subscriptions to automatic updates from each of these clinical entities, her PCHR is current with copies of those data.

The PCHR enables the patient to authorize access to information (views or even copies of the record) to others, including clinical providers, family members, health care proxies, and researchers, and to intelligent software agents such as a disease-management tool.

The second part of this scenario involves participation in research. Through her PCHR interface, the patient signs up for notification of open research studies on inflammatory bowel disease. Her eligibility is determined by a combination of her demographic characteristics, responses to a brief survey, and the clinical contents of her PCHR (e.g., diagnoses and medications). Five study matches are returned, and she chooses to participate in two. The first match is a randomized clinical trial of a medication with local enrollment at the hospital where she visited the emergency department. She makes an appointment and enrolls