BIO

BIOTECHNOLOGY
INDUSTRY
ORGANIZATION

September 13, 2002

Dockets Management Branch
Food and Drug Administration
5630 Fishers Lane, Rm. 1061
Rockville, MD 2052

Re: *Request for Comment on First Amendment Issues (Docket No. 02N-0209)*

Dear Sir or Madam:

The Biotechnology Industry Organization (BIO) submits the following analysis and comments in response to the notice published by the Food and Drug Administration (FDA) on May 16, 2002 (67 FR 3492) on the appropriate relationship between the First Amendment and the oversight of FDA-regulated products.

BIO was established in 1993 as a nonprofit trade organization. It is the largest trade organization devoted to the advancement of biotechnology in the United States and around the globe. Its members include biotechnology companies, academic health institutions, and research centers. BIO's mission includes advocating positions to elected officials and regulators, informing national and international media about the industry's progress, providing business development services, and creating a forum for members and the community to share legal, scientific, and policy information. BIO represents entities of all sizes engaged in the development of products and services in biomedicine, diagnostics, food, energy, agriculture, and environmental applications.

FDA-regulated products essentially consist of three parts: an article that is used in or on the body (*e.g.*, a food, drug, medical device, or biological product), a container that holds the article, and the labeling that describes how, when, and why to use the product. It is FDA's oversight of product labeling and related materials (including "promotional labeling" and advertising) that raises core statutory and constitutional issues. Each time FDA makes a decision about what

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can and cannot be said about a product, and who can and cannot say it, FDA's analysis must satisfy both the standards found in the Administrative Procedure Act and the First Amendment to the United States Constitution.

Within its core mandate – approving therapeutic products for specific, evidence-based uses – FDA's statutory and constitutional authority to regulate speech is firm and well established. FDA is authorized by statute to ensure that all therapeutic products are safe and effective for each use stated or suggested in the labeling that accompanies the product. *See, e.g.,* 21 USC 355(d). FDA is also authorized to ensure that all labeling that accompanies a regulated product is truthful and informative. *See, e.g.,* 21 USC 352(a) and (f).

However, when the agency seeks to extend this basic authority to activities such as continuing medical education programs, internet discussion sites, the distribution of peer-reviewed medical literature, press releases directed to the financial community, and direct-to-consumer advertising, the statutory and constitutional issues swell. The further FDA travels from its core mission of reviewing specific products for specific uses, the more difficult it is for FDA to articulate a substantial interest in regulating speech, and the more likely it is that a speech-related regulation will have the effect of suppressing important and truthful information.

We can state this with confidence for the biotechnology industry. Our products, more so than most, are the result of luminous scientific breakthroughs – ideas that can only surface through open scientific discussion; our products are used by physicians who can only diagnose patients who understand the need to visit a physician; and our products can be put to good use only if the physician knows about the product and how it may be used. In short, within the context of health, science, and medicine, it is near-impossible to restrain speech, on the one hand, and still be able to justify the social costs, on the other.

With that in mind, BIO presents the following comments.

I. FDA'S STATUTORY AUTHORITY TO REGULATE SPEECH

Foremost, FDA's regulation of speech must be based on a lawful exercise of statutory authority. The constitutional questions raised in the May 2002 notice are, in the first instance, dependent on interpretations of the Food, Drug, and

Cosmetic Act (the FDCA) that presume more authority over speech than may be warranted under current law.

Under section 502(a) of the FDCA, a drug or a biological product is misbranded if its labeling is false or misleading in any particular. 21 USC 352(a); *see* 42 USC 262(b).1/ In addition, a drug is misbranded unless its labeling contains "adequate directions for use" and adequate warnings against unsafe use, and a drug is misbranded if it is "dangerous to health" when used according to its labeling. 21 USC 352(f) and (j). Finally, prescription drugs and biological products are misbranded if they are the subject of advertising or "other descriptive printed matter issued or caused to be issued by the manufacturer" and the advertising lacks a "brief summary" of the relevant uses, side effects, and contraindications. 21 USC 352(n).

Under section 505(a), and section 351 of the Public Health Service Act (the PHS Act), all "new drugs" and biological products must be the subject of premarket approval or licensing for their labeled uses. 21 USC 355(d); 42 USC 262. Under section 301 of the FDCA, the introduction or delivery for introduction of a misbranded or unapproved drug or biological product is prohibited and is subject to civil and criminal liability. 21 USC 331-334.

Based on these provisions, FDA has specific statutory authority to regulate speech or, more particularly, to regulate the labeling that accompanies a product and the advertising used to promote the product. "Labeling," according to the FDCA, is any written, printed, or graphic matter that is either on the article or its container or that "accompanies" the article. 21 USC 321(m). Based on a series of court cases originating with *Kordel v. United States*, 335 U.S. 345 (1948) and *United States v. Urbuteit*, 335 U.S. 355 (1948), FDA considers all "textually related" product information disseminated by the manufacturer to be "labeling" within the meaning of the FDCA, even if the product is not distributed with the information. *See, e.g.,* 21 CFR 202.1(l)(2) (listing examples of information FDA considers to be labeling).

1/ All products that meet the definition of a "biological product" under section 351 of the Public Health Service Act also meet the definition of a "drug" or the definition of a "device" under sections 201(g)(1) and 201(h) of the FDCA, respectively. As a result, all biological products are subject to either the drug or device provisions of the FDCA, except that licensed biological products do not require pre-approval under section 505 of the FDCA. *See* 42 USC 262(j).

Thus, any material that FDA may categorize as "labeling" is subject to the misbranding provisions in section 502 and can trigger the premarket approval or licensing provisions of the FDCA and the PHS Act. For example, a manufacturer's press release that makes a representation regarding the use of a specific drug product is considered by FDA to be "labeling." *See* Letter to Industry from the Director (Carl C. Peck), Center for Drug Evaluation and Research dated July 24, 1991. And, handouts developed for a continuing medical education conference may, according to FDA, be treated as labeling if a drug sponsor contributed to the content of the materials. *See Guidance for Industry: Industry Supported Scientific and Educational Activities*, 62 FR 64093, 64097 (Dec. 3, 1997).

Finally, all such materials – as well as advertising and promotional materials distributed by a manufacturer – bear on the "intended use" of the product. There is no statutory requirement under section 505 of the FDCA, or section 351 of the PHS Act, that a drug or biological product must be approved for each intended use. Rather, a product is approved for each use "prescribed, recommended, or suggested in the proposed labeling thereof." 21 USC 355(d). Nevertheless, all drugs must bear "adequate directions for use" under section 502(f)(1) and, by regulation, FDA has defined the term to mean directions for each purpose for which the drug is "intended." *See* 21 CFR 201.5 (incorporating by reference 21 CFR 201.128, defining the term "intended use").

Based on this construct, the agency asserts the statutory authority to regulate virtually all product-specific speech by drug and biological product sponsors (*i.e.,* those persons who introduce the products into commerce). In light of recent First Amendment jurisprudence, culminating in the *Western States* decision, BIO urges the agency to focus not only on core First Amendment principles, but on the manner in which the agency has extended the FDCA into commercial and scientific activities several steps removed from the introduction of drugs and biological products into commerce.

That is, many of the speech-related issues presented in the May 2002 notice raise, in the first instance, questions of statutory construction. These questions include the scope of FDA's premarket approval authority (should it extend to the sponsor's proposed uses rather than to all "intended uses"?); the scope of FDA's authority to regulate incidental communications about drugs and biologics (is it limited to statements made in a medical or scientific context, or does it also include statements made in a commercial or financial context?); and, the scope of FDA's "labeling" authority (should it be read broadly to extend to all manner of

speech or, in an "information age," should it be confined to certain very specific forms of communication?).

II. THE *WESTERN STATES* DECISION

In a series of cases over the last two decades, the Supreme Court and lower federal courts have grown to doubt claims by the government that certain information must be kept from the public for the public's own good. 2/ Even more, the courts have become sensitive to all manner of regulation that seeks to control or constrain speech for the sake of achieving a non-speech policy or regulatory goal.

The *Western States* decision makes this and several other points regarding the regulation of commercial speech abundantly clear. 3/ In *Western States*, the government sought to defend a prohibition on the rights of pharmacists to advertise and solicit their product-specific compounding services. The government, however, failed to persuade the Court that the restriction was necessary and that the government's interests could not be achieved through non-speech measures. Moreover, when the Court weighed the alleged need for the restriction against the amount of otherwise truthful and beneficial speech being blocked, the restriction collapsed of its own weight.

The *Western States* case is significant in at least four respects relevant to the biotechnology industry. First, it is significant with respect to the government's burden of proof. As the majority opinion makes clear, the government must show that a restriction on speech is directed at a concrete harm and is not being imposed in place of a less intrusive option. The government must clearly articulate the risk that it is seeking to address and must show why a speech restriction is necessary to manage that risk. This is a far more exacting standard than the "rational basis" standard on which most agency decisions rest.

2/ *See Virginia State Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748 (1976) (recognizing consumer "interest in free flow of commercial information"); *44 Liquormart, Inc. v. Rhode Island*, 517 U.S. 484 (1996) (characterizing the assumption that the public will respond irrationally to truthful commercial speech as "offensive"); *WLF v. Friedman*, 13 F.Supp.2d 51 (D.D.C. 1998) (describing FDA's argument about the need to restrict dissemination of scientific research to the public "even more unsupportable than usual").

3/ *Thompson v. Western States Med. Ctr.*, 122 S.Ct. 1497 (2002).

Thus, for example, when the agency seeks to prohibit a sponsor from using a certain proprietary or "brand" name to market a product, the agency bears a heavy burden. It must identify the specific harm raised by the name, the evidentiary basis that demonstrates the risk and, importantly, the agency must show that the harm cannot be managed through means other than prohibiting the use of the name. The agency must affirmatively show why other techniques it has allowed in the past – *e.g.,* distinctive packaging or lettering, "dear health professional" letters, or informative launch materials – cannot be used to manage the risk.

Second, *Western States* is significant because of the doubt cast on the argument that FDA can – without running afoul of the First Amendment – regulate speech as a "fair proxy" for determining whether a person is acting in violation of the FDCA. 122 S.Ct. at 1505. As the government argued in *Western States*, large scale manufacturing by pharmacists clearly triggers the premarket approval provisions of the FDCA. If, however, a pharmacist confines his activities to the "practice of medicine/practice of pharmacy," premarket approval is not necessary. Thus, by regulating speech (in the form of advertising), the government was simply ensuring that pharmacists stayed within the lawful confines of the practice of pharmacy. This approach did not resonate on a positive note with the Court. *Id.* at 1506, 1509.

The same logic has routinely been relied upon by FDA to limit the off-label use of drugs and biologics to "the practice of medicine." Much as in *Western States*, FDA allows a manufacturer to distribute its products to physicians for unapproved uses, so long as the manufacturer does not actively promote its product for the unapproved use. Once the manufacturer begins to promote its product for this use – through CME or the distribution of peer-reviewed journal articles – the manufacturer is considered by FDA to have crossed a regulatory line. If *Western States* is an indicator, the use of speech in this manner – to ensure regulatory compliance – is unlikely to withstand constitutional challenge.

Third, *Western States* is significant with regard to the Court's concern about suppressing speech in the context of health and medicine. The majority of the Court clearly recognized the importance of informing patients and physicians about available therapeutic options. Moreover, the Court reacted sharply to the concept of prohibiting useful speech about medical options to protect a purely regulatory interest. *Id.* at 1509. Again, for the biotechnology industry, *Western States* is an

important precedent; it demonstrates the exceptional burden FDA must carry when seeking to suppress speech to physicians and patients about our products.

Finally, *Western States* is significant in its recognition of the role of the physician. As the Court aptly noted, the government's substantial interest in protecting patients from unapproved drugs can, in the case of prescription drug products, be adequately managed by the physician. *Id.* at 1507, 1508.

The reasoning of *Western States* can and must be applied to FDA's oversight of the biotechnology industry. As the Court recognized, the flow of information to patients and physicians about FDA-regulated products is highly beneficial. Government policies that suppress such information, to achieve regulatory goals such as adding new indications to the labeling of approved products, face a steep evidentiary burden.

IV. SPECIFIC COMMENTS

BIO fully supports FDA's authority to ensure that marketed biotechnology products are shown to be safe and effective, based on adequate and well controlled clinical studies, for the uses for which they are labeled. With that, BIO has the following comments regarding the application of FDA's premarket approval authority in the several speech-related contexts.

A. Press Releases and Promotional Labeling

The agency has specific authority to require pre-approval submission and review of promotional materials for fast track and accelerated approval products. Nevertheless, it has become agency practice for medical reviewers to request that biotechnology sponsors voluntarily submit their promotional materials for review. This is often done informally (by telephone call), for the stated purpose of ensuring that the sponsor's materials are consistent with the proposed labeling for the product. In fact, the promotional materials can be a factor in labeling negotiations with the agency. Similarly, press releases that announce the results of clinical trials are often analyzed in advance by medical reviewers.

BIO appreciates the agency's interest in these materials and, in particular, BIO understands the agency's concern that sponsors should refrain from pre-judging the safety or efficacy of an experimental product. With that said, most

of these materials pose little risk to core FDA concerns. To our knowledge, FDA has never established a relationship between promotional labeling or press releases, on the one hand, and prescribing habits on the other. Most clinical trial press releases pre-date the eventual approval of the product by several or more years. The idea that the suppression of such announcements – because they constitute "labeling for unapproved uses" – is a leap that may no longer be persuasive under current Supreme Court precedent.

B. Direct-to-Consumer Advertising

BIO members support direct-to-consumer (DTC) advertising in a truthful and balanced format. DTC advertising is a useful mechanism for raising public awareness about FDA-approved biotechnology products. Consumers cannot access these products without first consulting with a physician, and BIO believes that information that tends to promote doctor-patient communications regarding available therapies can only enhance medical care.

DTC advertising is commercial speech that is fully protected by the First Amendment. Before FDA may impose limitations or conditions on any manner of DTC advertising, or on the content of such advertising, it must proceed through the *Central Hudson/Western States* analysis.

With that in mind, BIO is concerned about the possibility that FDA will weaken the principles behind *Western States* through overuse of the "false and misleading" standard. That is, rather than reach the second, third, and fourth prongs of *Central Hudson*, the agency may begin to lower the standard for deeming speech to be misleading. Such an approach would represent a significant step backward.

Such an approach also misapprehends the Court's commercial speech doctrine. The fundamental principle behind the doctrine is the idea that:

> the commercial marketplace, like other spheres of our social and cultural life, provides a forum where ideas and information flourish. Some of the ideas and information are vital, some of slight worth. But the general rule is that *the speaker and the audience, not the government, assess the value of the information presented.*

Id. at 1503 (emphasis added) (citing *Edenfield v. Fane*, 507 U.S. 761 (1993)).

Even when assessing a DTC advertisement or other promotional piece for "misleading" information, FDA must ensure that it is not simply making a value judgment. And, the agency must consider whether there is a way to achieve its interest in ensuring truthful and accurate information through means other than total suppression. As the *Western States* Court explained:

> Even if the Government did argue that it had an interest in preventing misleading advertisements, this interest 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 and that its risks were unknown.

Id. at 1508. Thus, the "misleading" standard does not end the First Amendment analysis; to the contrary, it invites essentially the same questions. Again, in the words of the Court, "[i]f the First Amendment means anything, it means that regulating speech must be a last—not first—resort." *Id.* at 1507.

C. Investigational Products

FDA prohibits drug sponsors, investigators, and persons acting on their behalf from promoting or otherwise commercializing an investigational drug or biological product. 21 CFR 312.7(a). At the same time, FDA has made clear that its policy "is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media." *Id.*

At the center of the agency's policy is the concept that statements about investigational products must not be made "in a promotional context." *Id.* Even if the statement is truthful and non-misleading, FDA will insist on suppression if the context in which it is made is "promotional." This standard, along with the basis upon which FDA assesses whether a statement about an investigational product is truthful and informative, must be revisited by the agency. Among other things, the agency must consider whether – with adequate disclaimers and disclosures – more information can be made available about investigational products without fear of FDA reprisal.

D. Dissemination of Information on Unapproved Uses

Sections 551 through 557 of the FDCA (as amended by the FDA Modernization Act of 1997) describe the conditions under which a manufacturer may disseminate scientific information regarding unapproved uses. These conditions essentially allow for the dissemination of peer-reviewed journal articles, provided the article includes a prominent disclaimer that the use discussed in the article has not been approved by FDA, and provided the sponsor commits to submitting a supplemental application for the use discussed in the article.4/ An array of other conditions are also imposed, all of which – taken together – have rendered the provision ineffectual.

BIO supports the principle that off-label uses should be supported by sound science. There are, however, practical reasons why off-label uses may not be presented for FDA review, including the time and expense of the process and the inability to obtain exclusive marketing rights. 5/ Moreover, many sponsors simply cannot justify devoting the resources to gaining approval of an already accepted off-label use of an approved product. The "price" for this decision, according to FDA, is that the sponsor cannot openly advertise or promote this use.

This "sell but don't tell" policy may be unsustainable under current law. Even under a "commercial speech" analysis, 6/ it is difficult to envision the *Western States* Court being persuaded that peer-reviewed scientific information

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4/ *See* 21 USC 360aaa(b)(1)-(6).

5/ There are also non-speech incentives for seeking approval of an off-label use, including favorable third-party reimbursement, product liability protection, and access to federal research grants.

6/ The Supreme Court has distinguished between commercial and noncommercial speech for purposes of First Amendment analysis. The Court has defined commercial speech as speech that "propose[s] a commercial transaction." *Board of Trustees of State Univ. of New York v. Fox*, 109 S.Ct. 3028, 3031 (1989); *Central Hudson Gas & Electric Corp. V. Public Service Comm'n of New York*, 447 U.S. 557, 562 (1980); *Virginia Bd. of Pharmacy v. Virginia Citizens Consumer Council, Inc.*, 425 U.S. 748, 762 (1976). All other speech is classified as noncommercial speech. Speech about science and medicine, in particular, "reside[s] at the core of the First Amendment" and deserves the utmost protection. *WLF v. Friedman*, 13 F.Supp. at 62 (citing *Keyishian v. Board of Regents*, 385 U.S. 589, 603 (1967) and *Board of Trustees of Leland Stanford Junior University v. Sullivan*, 773 F.Supp. 472, 474 (D.D.C. 1991)).

must be kept from patients and physicians in order "to protect the integrity of the drug approval process."

Nor are courts likely to agree, following *Western States*, that the government can prohibit speech about conduct that it otherwise allows. FDA follows a policy, correctly, of permitting health professionals to exercise their informed judgment in prescribing approved products as they see fit, to best meet the needs of their patients. FDA also allows manufacturers to sell their products for these uses. 7/ As a result, and where there is no apparent safety concern, there is a serious question as to whether FDA can maintain policies that discourage manufacturers from supplying accurate information to physicians about possible uses of approved products.

BIO recognizes that unapproved uses must be distinguished in some meaningful way from FDA-approved uses. However, in light of *Western States*, BIO also urges the agency to consider ways to maintain a distinction without effectively suppressing all company-sponsored communications about unapproved uses.

V. CONCLUSION

BIO fully supports FDA's role as a leader in assessing the quantity and quality of evidence needed to support the leading medicines of our time. BIO also supports the important role FDA plays in ensuring that patients and physicians receive the very best information available. At the same time, FDA must not limit the free expression of ideas and information only to that with which it agrees.

7/ This practice is common in the area of generic drugs, where the generic may be prohibited from bearing labeling for certain uses protected by patent or "exclusivity" but, nevertheless, is substituted and sold "off-label" for the protected use.

On behalf of BIO's members, we thank the agency for initiating this proceeding and we look forward to working closely with the agency to ensure continued innovation in the field of biotechnology.

Sincerely,

Stephan E. Lawton
Vice President and General Counsel

cc: Hogan & Hartson L.L.P.