

# Legal Overview of Likely FDA Regulation of Internet Promotion

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## I. INTRODUCTION

The traffic on the information superhighway is being directed increasingly to consumers and prescribers of pharmaceutical drugs, biologics, and medical devices. Dozens of new home pages and web sites are popping up on the Internet and World Wide Web (WWW) daily. Many of these promotional mediums are sponsored by drug and device manufacturers. This information has become so prolific that a separate Pharmaceutical Information Network (PharmInfoNet) now organizes and indexes private, government, and academic databases. These information sources span the spectrum from government disseminators (including the National Institutes of Health (NIH), the National Library of Medicine, the Agency for Health Care Policy and Research (AHCPR), the Food and Drug Administration (FDA), and many others) to medical schools, patient support groups, and pharmaceutical, biologic, and device manufacturers.

Nearly twenty-five percent of all Internet traffic is health related.<sup>1</sup> Approximately twenty-four percent of cancer patients, twenty-two percent of heart disease patients, twenty-eight percent of diabetes patients, and thirty percent of AIDS patients are on-line.<sup>2</sup> Between 16,000,000 and 22,000,000 adult Americans use the Internet,<sup>3</sup> and that number is increasing at between ten to nineteen percent per month.<sup>4</sup> Huge incentives exist to create and expand on-line information links. Physicians, patients, and managed-care providers are relying more and more on personal computers (PCs) to access information on the latest therapies. Within minutes up-to-date data can be accumulated on a disease, existing treatments, adverse drug reports, potential new therapies, ongoing investigational trials, and expanded access protocols for which a patient might be eligible.

Both the FDA and Federal Trade Commission (FTC) have noticed these developments. This article focuses on actions likely to be taken by the FDA.<sup>5</sup> The FDA's concerns have centered on the potential of drug and device manufacturers to promote prod-

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<sup>1</sup> *America's House Call Network to Go On-Line By Year End*, F-D-C REP. ("The Tan Sheet"), July 3, 1995, at 11.

<sup>2</sup> *Id.* (citing the *Yankelovitch Monitor*).

<sup>3</sup> User statistics were calculated in August 1995 by Nielson Media Research. *In a Recount, Cyber Census Still Confounds*, N.Y. TIMES, Apr. 17, 1996, at D-1, col 5. The poll provoked an academic debate that is still unresolved. Most researchers, however, agree on the 16,000,000 to 22,000,000 user range. A more recent poll conducted between September 1995 and January 1996 by Louis Harris & Associates in cooperation with the Baruch College School of Public Affairs estimated that 17,000,000 U.S. adults have used the Internet (excluding solely e-mail use). *It's Hard to Untangle the Web of Usage Claims*, PLAIN DEALER, Feb. 19, 1996, at 6D.

<sup>4</sup> *New Forms of Political Participation; Caught in the Net; What to Make of User Estimates?*, PUBLIC PERSPECTIVE, June-July 1996, at 36.

<sup>5</sup> See Memorandum of Understanding, 36 Fed. Reg. 18,538 (Sept. 9, 1971). The FDA has primary responsibility for reviewing advertising and promotion related to the marketing of prescription drug products (including biologics). The FDA also was given authority over the advertising and promotion of restricted medical devices under the 1976 Medical Device Amendments. Pub. L. No. 94-295, 90 Stat. 539.

ucts for uses not approved by it and contained within its approved labeling. An internal FDA Internet working group continues to meet to discuss regulation and surveillance. That group is composed primarily of officials from the FDA Center for Drug Evaluation and Research (CDER) Division of Drug Marketing, Advertising, and Communications (DDMAC), the FDA Commissioner's Office of Policy, and representatives of the promotions and advertising policy staff from each FDA center.

This article examines the structures used currently by drug and device manufacturers to promote products on the Internet and WWW. Those structures are analyzed under the strictures of the Federal Food, Drug, and Cosmetic Act (FDCA),<sup>6</sup> its regulations, and FDA policy guidance documents. Specific recommendations are made and conclusions reached concerning the propriety of disseminating particular information using this new information superhighway.<sup>7</sup>

## II. CURRENT FDA REGULATORY POSITION

In order to stake a position in this area, the FDA has taken the following actions:

- It has begun to monitor manufacturers' home pages using its limited resources (one PC with access to the Internet and WWW within DDMAC) and several additional PCs within its product centers.
- On October 23, 1995, Robert Temple, CDER Associate Director for Medical Policy, suggested that although the format of drug promotions on the Internet might be different, "I think the content aspects of it are more traditional than one might imagine."<sup>8</sup> In the end, he said, "there is a message and somebody has written it."<sup>9</sup>
- On May 14, 1996, the FDA requested comments on suggested changes in its direct-to-consumer promotions regulation, including letting FDA-approved patient labeling replace "brief summaries."<sup>10</sup> It also asked whether different disclosure should be required for different media such as Internet.<sup>11</sup>

Byron Tart, Director of the Center for Devices and Radiological Health (CDRH) Promotion and Advertising Policy Staff, took the lead in this area by stating publicly, as well as informally, that "we are leaning toward the fact that if you have information on your home page, we see that probably more as labeling than advertising."<sup>12</sup> He announced further that "we don't see the Internet as any different from promotional literature" sent out directly by manufacturers, so "a good test for" manufacturers "would be

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<sup>6</sup> Pub. L. No. 75-717, 52 Stat. 1040 (1938), as amended 21 U.S.C. §§ 301 et seq. (1994).

<sup>7</sup> The FDA is most likely to regulate Internet use "inside the box" of its own advertising and labeling regulations. This article analyzes that dimension of the issue. However, "technology is outpacing the law," according to Lance Hoffman of the Cyberspace Policy Center at George Washington University. *Access, Privacy and Power*, WASH. TIMES, Aug. 19, 1996, at 8. The FDA may be well advised to withhold a traditional regulatory approach that may become irrelevant or obsolete before publication in final.

<sup>8</sup> *FDA Must Address Internet Advertising, Former Agency Commissioner Hayes Suggests*, F-D-C REP. ("The Pink Sheet"), Oct. 23, 1995, at 10 (October 19, 1995, FDA public meeting on direct-to-consumer promotion).

<sup>9</sup> *Id.*

<sup>10</sup> 61 Fed. Reg. 24,314 (May 14, 1996). An advertisement of a prescription drug must include a brief summary of the package insert. 21 C.F.R. § 201.1(4)(i)(a) (1996).

<sup>11</sup> 61 Fed. Reg. 24,316.

<sup>12</sup> *Device Information on Internet Home Pages Likely Constitutes Labeling*, F-D-C REP. ("The Gray Sheet"), July 15, 1996, at I&W 5 (July 11, 1996, meeting sponsored by the Health Industry Manufacturers Association).

to say 'would I send the information I'm putting on the Internet out on hard copy?'"<sup>13</sup>

CDRH issued the first warning letter related to the Internet on March 7, 1996, to U.S. Medical Products, Inc. in Austin, Texas.<sup>14</sup> CDRH had reviewed the company's product information on its Internet and determined that the product description went beyond its intended use as cleared in its 510(k) approval. The components of its knee replacement system had been cleared for cemented use only; the information disseminated on Internet stated that the system was also available in forms suitable for "press fit."

The FDA held a public meeting of its Internet working group in October 1996 to listen to additional presentations concerning Internet regulation or guidance. The agency will issue informal guidance or notice-and-comment rulemaking in the future to address what it has termed as "industry screaming for guidance in this area."<sup>15</sup> The FDA working group, however, will continue "in the learning mode" to monitor and meet periodically with Internet experts, manufacturers, consultants, and others to accumulate information.<sup>16</sup>

Three other factors have worked to temporarily reduce the possibility of the FDA challenging industry promotional practice. First, discovery continues in *Washington Legal Foundation v. Kessler*<sup>17</sup> In this case plaintiff has challenged the FDA's authority to prohibit certain information dissemination practices as commercial speech protected by the First Amendment of the U.S. Constitution.

Second, with regard to FDA reform legislation, Congress continues to examine agency policy on restricting information dissemination by manufacturers, and is seeking to negotiate a legislative solution with the FDA. Proposals in the 104th Congress centered around permitting, in some form, manufacturer dissemination of peer-reviewed scientific journal articles and medical texts that discuss unapproved uses of drugs, biologics, and medical devices. Linked closely to this is an FDA proposal to streamline the process of reviewing efficacy supplements. Congress is seeking a system designed to meet the FDA's stated goal: to encourage submission of supplements by manufacturers and reduce the number of additional uses of approved products for which applications are not submitted to the FDA.

Third, on May 13, 1996, the U.S. Supreme Court decided a landmark case defining modern "commercial free speech." *44 Liquormart v. Rhode Island*<sup>18</sup> may have direct implications on the FDA's restrictions on disseminating scientific information. By unanimous decision,<sup>19</sup> the Court overturned a state law banning the advertisement of retail

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<sup>13</sup> *Id.*

<sup>14</sup> Warning letter issued by FDA to U.S. Medical Products (Mar. 7, 1996). On July 11, 1996, Mr. Tart reported a second warning letter concerning a "distributor of a particular device which was very aggressive on the Internet in promoting the effectiveness of the device, which was way beyond the effectiveness which had been cleared by the Agency." *Device Information on Internet, supra* note 12, at I&W 5.

<sup>15</sup> *FDA-Approved Patient Labeling Could Replace Brief Summary for Direct-to-Consumer Ads*, F-D-C REP. ("The Pink Sheet"), May 20, 1996, at 9-10 (statement of Ilisa Bernstein, Senior Policy Advisor, Office of Policy, FDA).

<sup>16</sup> *Id.*

<sup>17</sup> 880 F. Supp. 26 (D.D.C. 1995).

<sup>18</sup> 116 S. Ct. 1495, 64 U.S.L.W. 4313 (U.S. May 13, 1996) (No. 94-1140).

<sup>19</sup> All the Justices voted to overturn the 1st Circuit Court of Appeals which found "inherent merit" in the states' justification for the advertising ban; however, three concurring opinions were written. Justices Stevens, Kennedy, Souter, and Ginsburg also concluded that although the First Amendment protects the dissemination of truthful and nonmisleading commercial messages about lawful products and services to ensure that consumers receive accurate information, states are authorized to regulate potentially deceptive or overreaching advertising more freely than other forms of protected speech, and require less than strict review of such regulations. 64 U.S. L.W. at 8-13.

liquor prices, ruling that the First Amendment protects truthful and nonmisleading commercial speech about lawful products.<sup>20</sup> Strict scrutiny of the government's reasons for abridging these rights will be applied. The government bears the burden of justifying an advertising ban. The Court rejected Rhode Island's contentions that this ban made its citizen's drink less, and that the ban was not more extensive than necessary to serve this stated intent.

Likewise, the FDA might be unsuccessful if it tries to defend restrictions on the free dissemination of product information by a manufacturer on the Internet, as the least restrictive way to prevent consumer use of prescription drugs or devices for unapproved indications.

### III. COMMON ELEMENTS OF MANUFACTURER WEB SITES

The scope and sophistication of Internet home pages or WWW sites sponsored by drug and device companies varies greatly. This technology and its substantive application, however, remains in its infancy. Many sites are still under construction with large data components remaining inaccessible. Companies are comparing databases and formats with their on-line competitors, and may become more innovative if other competitors move in that direction.

According to recent listings included on network indexes such as PharmInfoNet, approximately eighteen pharmaceutical manufacturers sponsor listed WWW sites. Many of those sites are place holders with off-the-shelf information on company operations taken from their most recent annual reports. Several more sophisticated sites are limited to diagnostic and treatment information on disease states for which the company markets products (although those products generally are not mentioned). Only true "trail-blazers" include descriptions of drug product lines and products in the development pipeline.

Generally, information included in manufacturer home pages and WWW sites can be divided into the following categories accessible by clicking a mouse on words on the screen or locator bars:

#### A. *General Corporate Information*

This information generally includes: company backgrounders and mission statements, organization charts and pictures of personnel or pictures of company production facilities and laboratories, letters from the Chief Executive Officer, and chronologies or timelines of milestones in company development. Some more highly developed databases also include discussion of collaborations with government or universities, employee profiles, research and development objectives, and patient opportunities to receive experimental treatments or participate in clinical trial protocols.

#### B. *Investor Relations Information*

The core of the investor relations section is usually the prior year's annual report. Readers can scroll between narrative on performance, forecasts, investment advisor projections, or financial statements and balance sheets. Market trends may be discussed. Graphs or pie charts may be included that compare current performance to prior years, the company to its competitors, or products by class or market share. Formats generally

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<sup>20</sup> *Id.* at 9.

have mirrored the annual report, including profiles of individual patients who have benefited from manufacturer therapies.

### *C. Career Opportunities or Other Employment Information*

Information is included to entice potential applicants to consider employment with the sponsor company. Favorable descriptions of corporate campus-like culture, research opportunities, service to the poor, and child care take top billing. Job listings are posted on bulletin boards. Resumes according to prescribed formats and applications can be completed and transmitted by e-mail. Announcements of job fairs and scientific seminars in which companies plan to participate also are included in these sections.

### *D. News and Information Directed to the Media*

Company press releases are posted in this section of their WWW sites contemporaneously with their release to create a centralized and reliable distribution source. Archives and indexes of other releases, press kits, and background materials also are indexed and accessible. Data links are provided to other trade periodicals or databases covering specific diseases, drugs, biologics, or devices. News rooms or news groups are provided for the media to talk with one another or with company officials.

### *E. General Scientific and Disease Information*

Basic information and “primers” are provided and addressed to laymen concerning the processes and science used by the companies. Innovations invented by particular companies are identified and discussed. Processes are explained including common research and development techniques, cell culture (for biologics), recovery science, analytical chemistry, and the patent process. Topics are archived and indexed, and may change frequently to encourage return visits to the site. Secondary sources are referenced, included in bibliographies, and may be accessed directly from the company database.

Other databases include extensive medical encyclopedias or discussions of disease states for which companies manufacturer effective therapies. These disease discussions can be rotated in advance of, or immediately following, approval of a new therapy by the FDA. For example, Merck highlighted “what everyone should know” about chickenpox following approval of its new chickenpox vaccine, Varivax.<sup>21</sup> Following direct-to-consumer advertising rules, Merck included a section entitled “can chickenpox be avoided?” thus informing consumers they should ask their doctor about new “preventative measures against chickenpox in children, teens and adults.” Another section of the same file contained a consumer questionnaire to evaluate “Hepatitis B — Are You at Risk?” Merck manufactures a new vaccine to treat that disease. No mention of the vaccine was made.

### *F. Product Information*

Approximately one-third of manufacturer-sponsored home pages surveyed included product information. Some listed only approved products manufactured and marketed by the company and their approved indications, in separate files marked “medicines,”

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<sup>21</sup> See <http://www.merck.com> (Internet home page of Merck & Co., Inc., Vaccine Division).

“drugs,” or “products.” Others included drug or device summaries resembling patient package inserts or MedGuides,<sup>22</sup> together with brief summaries or full disclosure labeling accessible by clicking on highlighted words at the bottom of the page entitled “product insert information.” Other subfiles, accessible from the main drug file, provide information concerning patient assistance programs for those who need drugs but cannot afford them, or patient registries. A reference section contains a bibliography of journals, medical texts, and other published studies of the drug or disease condition.

### *G. Product Pipeline Information*

Detailed descriptions of drugs under development and not yet approved by the FDA are included in only a few home pages under “product pipeline” categories. Some summarize the FDA investigational new drug (IND) and drug development processes in detail. Others describe on-going research by disease classification. Products are categorized within Phase I, Phase II, or Phase III development with a disclaimer that none of the drugs have been approved by the FDA as safe or effective. Possible uses are related generally, such as “may be useful to treat cancer patients so they can tolerate higher doses of anti-cancer treatment.” Details may be included of trial locations, entry criteria, and investigator contacts.

### *H. Special Programs and Collaborations*

The special program category generally has highlighted or linked users to other on-line services produced by the sponsor. For example, Genentech operates a database entitled “Access Excellence” that links high school biology teachers to state-of-the-art scientific instruction, news, and chatrooms so that lesson plans and teaching innovations can be shared. All Internet users can access the full range of the scientific programming. For example, Merck links users to the Medco database, its mail order pharmaceutical benefit manager, and to managed care testimonials concerning its pharmacy management expertise.

## IV. OVERVIEW OF RELATED GOVERNMENT, ACADEMIC, MEDICAL, AND PATIENT GROUP DATABASES

For several years, following the legislative mandates of Congress, the NIH and other components of the Public Health Service have compiled vast cancer and AIDS-related databases that have been integrated into the on-line information superhighway. These WWW sites frequently include links to the National Library of Medicine’s on-line databases (e.g., MEDLINE). Specifically, NIH and the FDA operate the AIDS Clinical Trials Information Service (ACTIS).<sup>23</sup> The National Cancer Institute operates

<sup>22</sup> 60 Fed. Reg. 44,182 (Aug. 24, 1995).

<sup>23</sup> Created by the Omnibus Programs Extension Act of 1988, Pub. L. No. 100-607, 102 Stat. 3048 (codified at 42 U.S.C. §300cc-17(d) (1994)), following recommendations of the Presidential Commission on the HIV Epidemic. The program includes a toll free 800 phone number (1-800-TRIALS-A) and a data bank of clinical trial information compiled for and accessible to all on-line users through MEDLINE. The legislative intent for the program was to inform physicians, researchers, support groups, and AIDS patients and their families of the availability and status of investigational new medicines. The data includes a registry of all clinical trials conducted by public and private sponsors under INDs, as well as a description of treatment INDs, protocol design, site locations, investigators, inclusion-exclusion criteria, enrollment information, phone numbers, trial phases, and preliminary results. It is updated weekly. ACTIS also produces a database of biomedical information on AIDS-related drugs. Any information provided about a drug used in

the Physician Data Query System (PDQ), which contains peer-reviewed statements on anti-cancer drugs and records of over 9600 clinical trials.<sup>24</sup> Both on-line services contain information on drugs not yet approved, or approved for one use while listed for other uses not approved by the FDA. This information is based on requests for voluntary information from the drug industry.

Hundreds of other databases that describe drugs and devices have been added to the Internet and WWW. Many of these are indexed through PharmInfoNet and similar indexing programs. Some function as interactive physician and consumer drug references sponsored by consumer groups and trade publications that are browsable by generic and trade names. Others function as drug information services and updates of medical literature sponsored by universities and medical schools.<sup>25</sup>

A final category of related databases involve specific diseases and are sponsored on home pages by patient support groups such as the American Heart Association, the American Cancer Society, and many other groups.

Mr. Tart has stated that, while the FDA is evaluating the links from a manufacturer home page to other sites on which off-label uses are discussed, it probably will not see a problem unless a manufacturer "link[s] to a specific site where all they do is talk about the off-label use of a product, then we would think that you would be responsible for that."<sup>26</sup>

## V. STATEMENT OF ISSUES

Some components of manufacturer WWW sites may be types of information compiled in traditional printed materials used to market drugs, biologics, and devices. This information can include annual reports, brochures, detailing pieces, and professional labels.

Dr. Temple properly has stated that "the format of drug promotions on the Internet might be different."<sup>27</sup> The audience is much broader and often beyond the control of the information disseminator. Using the Internet, the language of a product brochure does not remain in a doctor's office to be reviewed by the practitioner and his patients. It travels to an audience across the country and around the world, and may be by any person with a PC or lap-top computer. For example, a Hopi Indian medicine man may access information on active ingredients or indicated uses to administer a pharmaceutical's herbal base to a suffering child. A pharmacy student could use scientific information to supplement course curricula or study for exams. A university inves-

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clinical trials is made available voluntarily by government and manufacturing sponsors including: adverse effects, pharmacology, and dosage forms. The system is operated by Aspen Systems, a private information consulting firm in Rockville, Maryland.

<sup>24</sup> Established pursuant to the National Cancer Act of 1971, Pub. L. No. 92-218, § 407, 85 Stat. 881, 882 (codified at 42 U.S.C. § 285a-2), the PDQ system is an on-line database accessible to physicians through the National Library of Medicine (with limited access to certain topics by patients) on the Internet (<http://www.wicic.nci.nih>). The database contains peer-reviewed statements on anti-cancer drugs that are updated monthly by five editorial boards of oncology specialists.

<sup>25</sup> See University of Maryland Drug Information Service (UMDI) (established to aid health-care professionals and consumers with unanswered medical and pharmaceutical questions); Sci. Med. Pharmacy Newsgroup (to provide pharmacists with a forum for discussion of the teaching and practice of the profession); University of Wisconsin Drug Formulary; Medical College of the University of Wisconsin Antibiotics Utilization Guidelines; Iowa Drug Information Service; and other institutional sponsored services including University of Kentucky College of Pharmacy, USC School of Medicine, Mass General Hospital, and the University of Texas.

<sup>26</sup> *Device Information on the Internet*, *supra* note 12, at I&W 6.

<sup>27</sup> *FDA Must Address Internet Advertising*, *supra* note 8, at 10.

tigator could use published trial data as a historical control in testing an alternative therapy. A foreign competitor could adopt label language, or expand indicated uses, in a new application or product insert. A foreign patient could use a product for an indication approved in the United States, but not yet approved in his or her home country. The opportunities are endless.

This dynamic medium moves static text into three dimensions. In order to cultivate a broad audience, graphics likely will accompany the text, thus making the text interactive. For example, a graphic of the fictional "Marcus Welby" could provide indicated uses or dosing information, and the mechanism of action of a monoclonal antibody may be illustrated with a moving model. Text can be accessed selectively so that risk factors or disclaimers, for example, can be by-passed. A chat room allows patients and their families to exchange advice and information, or to ask questions of an expert panel. Complementary guidelines or endorsements of professional medical groups can be accessed from other databases sponsored by those organizations (occasionally compiled using grants from the manufacturer).

If the FDA chooses to venture beyond review of labeling text into the dynamics of an interactive user, it could move beyond its usual regulatory expertise and possibly discourage innovation. Few studies are available on which to base judgments regarding user behavior. Interactive elements, in turn, could increase utilization of product labeling and the sophistication of the patient community.

The FDA and the regulated community has raised the following specific issues:

- Is the information most commonly included in a manufacturer home page or WWW site advertising, promotional labeling, or something else? Does a manufacturer need to provide a paper copy of Internet information to the FDA using Form FDA 2253 when that information is accessible to the FDA on-line? Must the FDA be notified each time text is updated or the format is rearranged?
- Can simplified product-specific patient information be used in lieu of the standard "brief summary" or full disclosure product insert? In what form? Can the labeling be included in a separate site? Because the Internet and the WWW are accessible to all users, including consumers, must a sponsor comply with the direct-to-consumer rules for all information segments even if the information is intended for investors, physicians, insurers, or other audiences? Are fair balance requirements evaluated by the file as a whole or on each computer screen of text?
- Is the selection of information on a home page considered solicited or unsolicited for purposes of adhering to labeling requirements, and under what circumstances?
- Under what circumstances can a manufacturer include product information, pipeline information, financial information, or press releases.
- Under what circumstances can interactive graphic representations of a product's chemistry, physiology, or mechanisms of action be used?
- To what extent is information exchanged in chat rooms included in a manufacturer-sponsored site attributed to the manufacturer? Under what circumstances can scientific employees of a manufacturer answer questions or otherwise participate?
- What references can be made to scientific literature, or databases sponsored independently by government, medical, or patient groups that contain information on unapproved uses of a product? Can links to related sites be provided?
- Under what circumstances can information on international approvals or uses not yet approved in the United States be accessible to U.S. audiences?

## VI. ANALYSIS OF ISSUES

A. *Is This Advertising or Promotional Labeling?*

The FDA has authority to determine the content of drug "labeling" and deem a product misbranded.<sup>28</sup> The definition of "labeling"<sup>29</sup> in the FDCA has been expanded by the FDA to include most written, printed, or graphic matter that supplements or explains a drug product, regardless of whether it physically accompanies the product.<sup>30</sup>

The FDA was given authority over prescription drug advertisements in the Drug Amendments of 1962,<sup>31</sup> although no definition of "advertisement" was provided. The FDA subsequently has issued regulations interpreting advertisements to include advertisements published in journals, periodicals, and newspapers, as well as broadcasts through media such as radio, television, and telephone communications.<sup>32</sup> A separate regulation applies to promotion of an IND.<sup>33</sup> A sponsor or investigator, or their agent, is not permitted to represent that such a drug is safe or effective for its investigated use, or otherwise promote the drug.<sup>34</sup> An exception exists for the "full exchange of scientific information."<sup>35</sup>

If the FDA intends to regulate Internet transmissions, it must first determine whether these communications, or any portion of them, are "advertising" or "labeling." If they are labeling, part 201 of title 21 of the *Code of Federal Regulations* applies;<sup>36</sup> if they are advertising, part 202 of the regulations applies.<sup>37</sup> This distinction has been lost in the informal guidance provided by DDMAC that requires all promotional materials be fairly balanced in both content and format regardless of whether it is advertising or labeling.<sup>38</sup> At a minimum, Internet sites may be required to contain "full disclosure" (the full approved package insert) required for labeling, as opposed to the "brief summary" of side effects, contraindications, and effectiveness required of advertisements.<sup>39</sup>

While no decision has been made by the agency, the most recent statement by CDRH Promotions and Advertising Policy Director Byron Tart indicates that the FDA views "[home page information] probably more as labeling than advertising."<sup>40</sup> This interpretation is consistent with the intent of the written on-line information that is product specific to "supplement or explain the drug product." Implicit in the FDA's statement is that the space available for text on the Internet is much more expansive than the finite and expensive advertising space in written publications or on broadcast media.

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<sup>28</sup> 21 U.S.C. § 352(n).

<sup>29</sup> "Labeling" is defined under section 201(m) of the FDCA as "written, printed, or graphic matter (1) upon or (2) accompanying [the product]. *Id.* § 321(m). A "label" is defined under section 201(k) as "written, printed or graphic matter upon the immediate container" of a drug. *Id.* § 321(k).

<sup>30</sup> See *Kodel v. U.S.*, 335 U.S. 345 (1948). Dietary supplement literature was shipped separately from the container or packaging. The U.S. Supreme Court held that no physical attachment was necessary. Booklets and drugs are part of an integrated distribution program. *Id.* at 350.

<sup>31</sup> The advertising provision of the Amendments, commonly known as the Kefauver-Harris Amendments, were codified at section 501(n) of the Act. 21 U.S.C. § 351(n).

<sup>32</sup> 21 C.F.R. § 202.1(l)(1) (1996).

<sup>33</sup> *Id.* § 312.7(a). An IND is defined as "a new drug . . . that is used in a clinical investigation." *Id.* § 312.3(b).

<sup>34</sup> *Id.* § 312.7(a).

<sup>35</sup> *Id.*

<sup>36</sup> *Id.* § 201.1 et seq.

<sup>37</sup> *Id.*

<sup>38</sup> DDMAC, *FDA CURRENT ISSUES AND PROCEDURES* (1994). See also 21 C.F.R. § 202.1(e)(6), (7).

<sup>39</sup> See 21 C.F.R. § 202.1(e).

<sup>40</sup> *FDA Must Address Internet Advertising*, *supra* note 8, at 10.

Even though biologics and drugs are regulated under slightly different statutes, the FDA's Center for Biologics Evaluation and Research (CBER) and CDRH apply principles substantially identical to CDER-DDMAC.<sup>41</sup>

### *B. Requirement to Submit Information to the FDA*

For already approved new drugs, FDA regulations state, and CDER has taken the position that, advertising and promotional labeling materials must be submitted routinely at the time of first use.<sup>42</sup> This does not require preclearance or FDA approval before the information is used. Copies of advertising and labeling are required to be submitted routinely via FDA Form 2253 and a copy of approved labeling.<sup>43</sup> Preclearance is required only in "extraordinary circumstances" as defined by CDER, or if a company wants an opinion in advance of use.<sup>44</sup> Occasionally, such preclearance is mandated in a consent decree if a company has violated the agency's promotional rules and the FDA has gone to court to enforce its requirements.

In the case of a pending approval of a new drug, CDER has expanded its regulatory authority by requesting review of all advertising and promotional material intended to launch a product. This material generally is requested to be submitted voluntarily by a company. Because a company wants favorable exercise of the FDA's discretion to approve a new drug application as quickly as possible, most companies comply with the agency's request.

Finally, in the case of a drug application considered under the FDA's accelerated approval regulations, sponsors are required to submit launch materials and all promotional labeling and advertisements for review by the FDA at least thirty days before the intended time of initial dissemination of labeling or the initial publication of the advertisement, unless informed that that submission is not necessary.<sup>45</sup> Approval can be withdrawn if a manufacturer fails to adhere to this requirement or if the promotional materials are false or misleading.<sup>46</sup>

In private discussions the FDA has taken the hypothetical position that because drug consumers have on-line access to Internet information, the direct-to-consumer advertising rules might apply to all information on-line.<sup>47</sup> For direct-to-consumer advertising the FDA has viewed advertising broadly as including any materials intended

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<sup>41</sup> See 58 Fed. Reg. 42,340 (Aug. 9, 1993). Notice of formation of CBER Advertising and Promotional Labeling Staff (APLS) where CBER notes that its information review policies are "more consistent with practices currently followed by CDER." CDER rules and regulations also have provided the basis for regulation of device promotion because those rules are more specific and fully developed. Devices are viewed as different, however, by the APLS particularly regarding the need to educate and train physicians. Despite the FDA's authority to regulate only advertising and promotion of "restricted" devices (with the FTC given the jurisdiction to regulate other device advertising), no definition has been issued by regulation. 21 U.S.C. § 352(q), (r). CDRH also uses its additional labeling authority to regulate device promotion.

<sup>42</sup> 21 C.F.R. § 314.81(b)(3)(i) ("The applicant shall submit specimens of mailing pieces and any other labeling or advertising devised for promotion of the drug product at the time of initial dissemination of the labeling and at the time of the initial publication of the advertisement for a prescription drug product.").

<sup>43</sup> *Id.* Form FDA-2253, "Transmittal for Advertisements and Promotional Labeling for Drugs for Human Use," currently contains no category for on-line information. The FDA either will amend the form or will argue that a print out of Internet information should be submitted, and that information breaks down into one of the other established categories such as: brochures, promotional letters, literature reprints, or similar documents.

<sup>44</sup> FDCA § 502(n), 21 U.S.C. § 352(n).

<sup>45</sup> 57 Fed. Reg. 58,942, 58,943 (Dec. 11, 1992).

<sup>46</sup> *Id.*

<sup>47</sup> Meeting with officials at DDMAC (Feb. 29, 1995).

for consumers including not only traditional print and electronic advertisements, but also videotapes, cassettes, pamphlets, brochures, and any other printed material intended to be seen or used by a consumer, and that mention directly or indirectly a specific product made by the company sponsoring the advertisement.<sup>48</sup> In 1991, DDMAC reportedly requested informally that all direct-to-consumer materials be submitted for preclearance.<sup>49</sup> In light of *Washington Legal Foundation*, which challenges this authority, voluntary compliance has been requested by the agency. FDA spokespersons have stated that it has asked manufacturers to submit informally direct-to-consumer material for comment on a "voluntary basis."<sup>50</sup>

None of these formal and informal document review requirements contemplated the Internet. The reason behind submitting promotional materials to the FDA is that the agency would not otherwise have access to documents used in the field. This does not apply to the Internet. Through careful monitoring, the FDA can access all information disseminated through this medium. Because of this difference, the FDA may be open to receiving written notice that a home page has been established and a copy of a manufacturer's Internet address.

Yet, if the FDA is to be taken at its word that Internet materials are to be treated the same as any other promotion, a hard copy of all Internet materials related to drugs should be submitted "voluntarily" to the agency with FDA Form 2253 under the requirements stated in section 314.81(b)(3)(i) of title 21 of the *Code of Federal Regulations* at the time the information becomes accessible to on-line users. In the meantime, even if consumers can access this information, DDMAC has no expectation that preclearance or comment are required. The FDA, however, is willing to comment on any materials provided.

### C. Use of Simplified Specific Product Information

If product information included on an Internet home page is treated as labeling and not advertising, the brief summary requirements in the drug advertising regulations do not apply.<sup>51</sup> Manufacturers may be required under the labeling regulations, however, to include the full professional label for each product discussed. This can be accomplished easily in home page design by including one file that contains the full product insert information. An icon or highlighted phrase might be included within a product summary that would allow a reader to access the complete information.

The FDA probably would prefer that a manufacturer provide a summary of specific products directed at consumers. Since 1968, the FDA has attempted to require manufacturer preparation of nontechnical labeling directed to consumers to be dispensed

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<sup>48</sup> FDA ADVERTISING AND PROMOTION MANUAL § 430 (1996).

<sup>49</sup> *Id.* The FDA acknowledged this policy by stating that the "FDA had informally requested manufacturers to submit, on a voluntary basis, proposed DTC promotional labeling and advertising for review and comment prior to use." 61 Fed. Reg. at 24,314. DDMAC Guidance issued to the industry in July 1993, however, omitted the word "voluntary" in stating that "DDMAC requests that application holders continue to submit for pre-clearance all promotional labeling and advertising that are intended to be used in direct-to-consumer promotion." DDMAC, FDA CURRENT ISSUES AND PROCEDURES (1993).

<sup>50</sup> *FDA Must Address Internet Advertising*, *supra* note 8, at 10. The FDA further stated that "it appears that the agency's request that manufacturers obtain advice on proposed DTC materials has been misinterpreted as a requirement. . . . FDA reiterates that it does not now require, nor has it ever required, manufacturers to submit DTC promotional labeling and advertising for preclearance." *Id.*

<sup>51</sup> 21 C.F.R. § 202.1(e) requires that all advertisements be accompanied by a "true statement of information in a brief summary related to side effects, contraindications and effectiveness."

by pharmacists with a drug.<sup>52</sup> Recent proposed regulations sought mandatory (and voluntary) preparation of medication guides (MedGuides) to promote proper consumer use of prescription drugs.<sup>53</sup> Those regulations have been withdrawn, but industry now must work with consumer groups and the medical community to improve consumer information on prescription drugs.<sup>54</sup>

These on-line product summaries must be "fairly balanced" in both content and format.<sup>55</sup> Fair balance must be achieved "between information relating to side effects and contraindications and information relating to effectiveness of the drug."<sup>56</sup> The FDA will consider both the representations made and the extent to which the labeling fails to reveal "material facts about potential consequences from product use."<sup>57</sup> A question remains whether each page of text must be balanced. Given the uniqueness of the Internet where computer screens are various sizes, the FDA should adopt a reasonableness standard where balance is determined based on each article or section of text. In the past, the FDA has assumed that a person will read completely a topical article. Given the interactive nature of home pages where a reader can shift quickly between text sections, the FDA may reconsider this informal "rule of thumb." Companies, therefore, should consider carefully how they format product summaries and how they break them into topics. Negative information or warnings could be interlaced throughout a summary to balance text pages, rather than being grouped separately or at the end of textual material. Another technique could include a red "warning" stop sign or related graphic on each text page that could transfer a user to a contraindication section.

Traditionally, companies have opposed requirements that they provide labeling information directly to consumers in order to preserve the "learned intermediary doctrine."<sup>58</sup> This doctrine places a higher burden of proof on plaintiffs asserting product liability claims, and requires juries to consider what information a reasonable prescriber (physician) with the knowledge and training common to such prescribers, would need in determining the adequacy of a product's labeling. Thus a lower "reasonable man" standard is avoided. The learned intermediary, in turn, exercises professional judgment

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<sup>52</sup> Generally, the FDA required distribution of such patient information to alert patients of adverse reactions associated with a drug or to provide information about the product's use, contraindications, precautions, and effectiveness. *See, e.g.*, 33 Fed. Reg. 8812 (June 18, 1968) (isoproterenol inhalation drug products); 35 Fed. Reg. 9001 (June 11, 1970) (oral contraceptives); 43 Fed. Reg. 4212 (Jan. 31, 1978) (estrogen drugs). In 1980, final regulations were published, then later withdrawn by the incoming Reagan Administration, that would have required manufacturers to prepare patient package inserts for their drug products. *See* 45 Fed. Reg. 60,754 (Sept. 12, 1980), *revoked* 47 Fed. Reg. 39,147 (Sept. 7, 1982).

<sup>53</sup> 60 Fed. Reg. 44,182 (Aug. 24, 1995).

<sup>54</sup> Senators Edward M. Kennedy (D-MA) and Dan Coats (R-IN) brokered a compromise between industry and consumer groups that included language in H.R. 3606, the fiscal 1997 agriculture appropriations bill. Pub. L. No. 104-180, 110 Stat. 1569 (1996). Section 601 requires industry to work with health care and consumer groups to provide oral and written prescription drug information to consumers. The FDA has no authority to regulate in this area if a voluntary plan is provided within six months of enactment.

<sup>55</sup> 21 C.F.R. § 201.1(e)(5)(ii).

<sup>56</sup> *Id.*

<sup>57</sup> 21 U.S.C. § 201(n); DDMAC, *supra* note 38. Although the fair balance requirements are contained in the advertising regulations (21 C.F.R. § 202.1(e)(6)), the FDA has stated that the requirement applies to all types of promotional materials disseminated about specific products, including advertisements, detailing pieces, and public relations materials.

<sup>58</sup> Courts have held that a manufacturer has no duty to assist physicians as learned intermediaries in warning patients of risks inherent in use of their products. *See* *Spychala v. G.D. Searle & Co.*, 705 F. Supp. 1024 (D.N.J. 1988). To the extent that FDA regulations require manufacturers to provide information to patients, it abrogates the learned intermediary rule and should be narrowly construed. *Tarallo v. Searle Pharmaceutical Inc.*, 704 F. Supp. 653 (D.S.C. 1988). *See also* *Brecher v. Cutler*, 578 A.2d 481 (Pa. Super. Ct. 1988); *Durkin v. Syntex Laboratories, Inc.*, 443 F. Supp. 121 (D. Tenn. 1977).

in selecting the drug and communicating necessary information to the patient.

An important issue for a company always has been how it effectively communicates labeling information to consumers without providing all the complexity and cautionary information of a professional label to protect itself from liability. The Internet provides an answer. A company can provide an understandable brief summary while still providing the full patient label under a separate accessible file. Consumers then cannot contend that they were not apprised adequately of a product's risks when the FDA approved professional label is available for their use. The uniqueness of this format also should protect companies that elect to produce consumer labeling for the Internet from future FDA actions to mandate distribution of manufacturer MedGuides where prescriptions are dispensed.

#### *D. Unsolicited Requests for Information*

Users of an on-line interactive medium can communicate easily with a manufacturer directly. Physicians, investors, or consumers might request additional information that might include, for example, copies of cited studies for investigational or off-label uses. WWW sites frequently include icons that can be selected for additional information. Once selected, a user might be presented with an address file and a check-off list requesting categories of additional available information to complete. Is such a progression solicited or unsolicited by the site sponsor?

The FDA has taken the informal position that "individual nonpromotional responses by pharmaceutical companies to specific, unsolicited requests for information will not be considered as promotional labeling."<sup>59</sup> The sponsor is required to maintain documentation concerning the nature of the request.<sup>60</sup> The FDA also has required that there be no pattern of routine dissemination of materials, or no evidence that such requests were solicited by the sponsor (e.g., preparation of material for routine dissemination).<sup>61</sup> Activities that invite or otherwise prompt requests for information, including responses to 1-800 telephone numbers disclosed in promotional labeling or advertising, are considered forms of solicitation.<sup>62</sup>

This informal FDA position could preclude a sponsor from using an Internet prompt mechanism to disseminate materials on investigational or unapproved uses. While an argument can be made that the on-line user freely sought out the home page and the "additional information prompt," the FDA likely would respond that requests for this information were prompted, and were analogous to a 1-800 number or a reply card included in a promotional pamphlet. This mechanism could be used, however, to disseminate information that is screened carefully to be within the parameters of approved product labeling.

A bibliography could be presented at the end of a product file that includes a listing of all journal articles of drug trials for approved and unapproved uses. If a user accesses a list and contacts a company independently for a reprint, a stronger argument could be made that the company can provide that information even if it describes off-label uses.

#### *E. Use of Investor Information*

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An interesting question arises concerning investor information, which generally is

<sup>59</sup> DDMAC, *supra* note 38, at 4.

<sup>60</sup> *Id.*

<sup>61</sup> *Id.*

<sup>62</sup> *Id.*

directed to an audience other than physicians and consumers of company products. On the Internet, while financial information may be contained in a separate file, this information is available to all audiences. Investor information generally includes annual reports, prospectuses, and letters to stockholders.

The FDCA generally does not differentiate between information directed at investors as opposed to the medical community. In practice, however, the FDA has not taken enforcement action against a company for materials issued exclusively to the investment community.<sup>63</sup> DDMAC generally considers investor materials as not intended to promote use of a particular product.<sup>64</sup> There is also a recognition that these materials must not be false or misleading within a relevancy standard set by the securities laws and the rules of the Securities and Exchange Commission.<sup>65</sup> DDMAC occasionally has objected to display of annual reports and other investment information in booths at scientific meetings.<sup>66</sup>

In a 1986 warning letter and related correspondence issued to the Upjohn Company concerning a financial press release for minoxidil, the FDA applied the labeling standard to a financial audience.<sup>67</sup> It stated that

[i]nvestor disclosure requirements do not mandate the kind of highly detailed reporting of study results as was done in this case. . . . Intended audience is not and never has been part of the determination of what constitutes labeling. Further, because this release was reported widely in the lay press, many potential buyers of the product received information which may have unrealistically raised their expectations about a drug still under investigation.<sup>68</sup>

While DDMAC has backed away some from this approach, Internet sponsors can expect the FDA to review even investor information with the same labeling and "fair balance" criteria, especially for off-label representations and where, as on the Internet, investment information is disseminated and accessible to medical and consumer audiences.

If a manufacturer includes in its WWW site discussions of products in the pipeline or off-label uses of approved products, disclaimers should be considered. It is unlikely that placement of investment information in an investor file alone will be sufficient to merit FDA attention. Several companies already on-line have attempted to create "fair balance" by explaining the Phase I to III system of FDA drug review. Pipeline drugs are summarized based on their investigational status. Indications are revealed using cautionary language such as "efficacy is not proven until final FDA approval" and "while preliminary results are promising, the safety and efficacy of many drugs are disproved through these clinical trials."

#### F. Under What Circumstances Can Interactive Graphics Be Used?

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<sup>63</sup> FDA ADVERTISING AND PROMOTION MANUAL, *supra* note 48, § 443.

<sup>64</sup> *Id.*

<sup>65</sup> *Id.*

<sup>66</sup> The FDA's position applies primarily to sponsor dissemination of information concerning unapproved investigational new drugs using the "full exchange of scientific information" exception in the IND regulations. 21 C.F.R. § 312.7(a). Information about these drugs can be displayed at scientific and educational exhibits separated from commercial exhibit areas and devoid of commercial materials for distribution. DDMAC, FDA PRE-APPROVAL PROMOTION GUIDANCE 2 (1994).

<sup>67</sup> Warning letter from FDA to The Upjohn Company (May 15, 1986).

<sup>68</sup> *Id.*

Companies, especially in the biotechnology industry, are using advanced manipulatable color graphic representations to illustrate their products' mechanisms of action. PCs offer high-resolution interactive moving illustrations not available in print advertisements, brochures, or other product labeling. The function of DNA, messenger RNA, and protein synthesis, for example, in creating a new therapy or use of monoclonal antibodies to reorder proteins and correct a deficient cell function, can be portrayed vividly and manipulated by an on-line user.

It is likely that while most textual material contained on a WWW site may be viewed as labeling, graphic material could be viewed as advertising. The FDA's regulations relating to advertising content provide that an advertisement for a prescription drug is false, lacking in fair balance, or otherwise misleading if it uses pictorial or other graphic matter in a way that is misleading.<sup>69</sup> Information can be misleading, for example, if in the interest of simplicity it glosses over or does not list side effects<sup>70</sup> or mechanisms that might block a drug's therapeutic benefit. Similarly, if a drug appears visually useful in a broader range of conditions or patients, it may be viewed as misleading.<sup>71</sup>

Preparation of graphic materials on the Internet may be much more expensive and time-consuming than textual material that changes frequently. Therefore, sponsors could consider submitting such information to the FDA for comment prior to going on-line, based on the possibility that such information might be challenged.

### *G. Use of Chat Rooms in Manufacturer Sponsored Sites*

There are several formats Internet sponsors are experimenting with to encourage additional interaction with users. One offers a "feedback" or "question and answer" prompt where a user can transmit a message directly to a manufacturer via Internet e-mail, and receive a company prepared response or further written information. The other format includes a "chat room" where site users can converse contemporaneously with each other. A manufacturer and its scientists can monitor e-mail flow, but need not participate in the discussion.

The issue of concern is whether by using either of these formats, the substance of all the discussions can be attributed to the manufacturer merely because it has provided a forum to exchange information. Participants not affiliated with a manufacturer, for example, might ascribe uses of drugs or devices beyond approved FDA labeling. If the statements are attributed to the site sponsor, chat rooms might not survive regulatory scrutiny.

CDER generally regards all materials used by drug company representatives and their verbal statements as subject to the advertising regulations.<sup>72</sup> CDRH generally regards these materials and statements as labeling that must meet all labeling requirements.<sup>73</sup> Both maintain that their regulatory authority extends to all communications between sales representatives and physicians, although verbal communications have been difficult to monitor. Reportedly there has not been an enforcement action against a drug company based solely on what an individual sales representative told a physician or managed care provider. A written record seems essential to support a warning letter

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<sup>69</sup> 21 C.F.R. § 202.1(e)(6)(xviii).

<sup>70</sup> *Id.* § 202.1(6)(i).

<sup>71</sup> *Id.*

<sup>72</sup> 21 C.F.R. § 202.1 et seq.

<sup>73</sup> *Id.* § 801.1 et seq.

or other FDA enforcement action.

An approach that the FDA might adopt would be a requirement that only a manufacturer and its employees and agents are required to restrict comments or answers to questions to the terms of approved labeling. Therefore, if a user suggested, for example, that a stomach acid inhibitor helped eliminate a duodenal ulcer painlessly when used with an antibiotic to kill H-pylori bacteria, but it is only approved for use for peptic ulcers, a manufacturer would have to be silent or state that such use is being studied but that FDA approval for that use has not been granted.

Use of chat rooms to increase professional and consumer education should be encouraged. The First Amendment protects commercial free speech about a lawful product that is truthful and nonmisleading. The FDA also should favor an approach in which discussions might be monitored periodically (unlike claims made by detailees in the field). The agency has announced its interim intention to treat Internet communications the same as standard manufacturer promotion.<sup>74</sup> Chat room discussions can be viewed as analogous to communications made by detailees in the field.

#### H. *References to Other Databases*

Perhaps the most difficult legal and policy issue is the question of whether a manufacturer's home page can reference or connect a user to an independently sponsored WWW site that may discuss off-label product uses. Government sponsors, patient groups, and medical specialty societies are some of the most prolific sponsors of home pages and WWW sites. Manufacturers could provide valuable information to on-line users by referring them to related information sources. For example, in a discussion of breast cancer or its newest therapy, reference, or linkage to the on-line databases of the National Cancer Institute or the National Cancer Society could expand the educational dimensions of a company's home page. The National Cancer Institute's PDQ System and the National Cancer Society's home pages, however, often reference uses of manufacturer products not sanctioned by the FDA.

In a sense, an analysis of this issue is similar to the policy turmoil created by the current legislative debate about manufacturer dissemination of medical journal articles or texts that list off-label uses. This information is already in the public domain. The issue is to what extent should manufacturer resources expand utilization of these ancillary databases. In addition would manufacturer dissemination of this information actually discourage submission of scientific data to the FDA in efficacy supplements?

The FDA has received inquiries about home page links to sites such as the National Library of Medicine or the *Journal of the American Medical Association*, in which there may be discussion of unapproved uses.<sup>75</sup> Mr. Tart has stated that "probably for those general areas, we wouldn't have any problem. However, if you link to a specific site where all they do is talk about the off label use of a product, then we would think that you would be responsible for that."<sup>76</sup> He added that company sponsored sites that primarily address off-label device use also would be a "problem" for the agency.<sup>77</sup>

On December 6, 1995, the FDA modified its general prohibition against a manufacturer distributing information about unapproved uses of its products. Under the nar-

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<sup>74</sup> 61 Fed. Reg. 48,707 (Sept. 16, 1996); *Device Information on Internet*, supra note 12, at I&W 5.

<sup>75</sup> *Device Information on Internet*, supra note 12, at I&W 6.

<sup>76</sup> *Id.*

<sup>77</sup> *Id.*

row exception for "the full exchange of scientific information" in its IND regulations,<sup>78</sup> the FDA provided in an informal guidance that peer reviewed scientific journal articles or medical tests discussing unapproved product uses could be distributed by a manufacturer if: (1) the information served as the basis of approval of the product, (2) the principal subject is use approved by the FDA, (3) a sticker provides that the information is unapproved or contradictory to approved labeling, and (4) all material facts are disclosed and the reprint is not false or misleading.<sup>79</sup>

The FDA may not be as concerned about home page linkages as direct dissemination to drug or device customers of such information by manufacturer sales forces. Industry could argue that by accessing a company home page and then accessing additional information by linking to, for example, the National Cancer Institute's PDQ system, the additional information was sought by the user unsolicited by the company.<sup>80</sup> Such information is accessible more quickly and efficiently than by returning to an Internet search device to seek the related database separately. Also it would be difficult for the FDA to deny utilization of data prepared and reviewed by other sectors of the Public Health Service, although it has done so on occasion.<sup>81</sup>

The First Amendment arguments are strong and will be tested by the courts again in the pending Washington Legal Foundation lawsuit, and litigation certain to flow from final tobacco advertising regulations.<sup>82</sup> A public health benefit also flows from more Americans becoming increasingly sophisticated about the course of their therapies. The greater the number of physician and patient users of the public sponsored National Cancer Institute's PDQ system or the NIH's ACTIS, the more qualified patients enroll in clinical trials and expanded access protocols.

Additional complexity arises when a linked database recommending an off-label use is sponsored by an organization (e.g., the National Osteopathic Foundation or groups supporting patients with epilepsy, stroke, diabetes, or other diseases) that receives a large portion of its funding from a drug manufacturer, even if the grant is unrestricted. While no regulations have been provided to help address drug company sponsorship of patient groups, independent organizations like the Institute of Medicine, for example, accept only forty-nine percent sponsorship by private companies to underwrite workshops or seminars. Independent management and membership of patient groups, unrestricted grants, and peer-review of recommended therapies should help allay many of the FDA's possible concerns in this area.

The FDA also might allow reference (and not actual linkage) to a database that contains a greater degree of off-label discussion, less peer-review, or more company sponsorship. Disclaimers could be included on a manufacturer linkage, for example, the American Cancer Society description of breast cancer therapies contains information on X company's product that is beyond the labeling approved by the FDA. Such a disclaimer, however, could highlight an off-label use that the FDA might seek to avoid.

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<sup>78</sup> 21 C.F.R. § 312.7(a).

<sup>79</sup> 60 Fed. Reg. 62,471, 62,472 (Dec. 6, 1995).

<sup>80</sup> DDMAC, *supra* note 38. Utilization data available to home page sponsors could indicate the number of users accessing a linked database, but not their identities. The criteria established by DDMAC in its April 1994 guidance likely could not be met sufficiently in this electronic forum. Specifically, DDMAC deemed a request for additional information unsolicited if: (1) the sponsor maintained documentation concerning the nature of the request, and (2) there was no pattern of repeated dissemination. This linkage by icon resembles responses to 1-800 telephone numbers disclosed in promotional labeling which DDMAC considers a form of solicitation in its guidance. *Id.*

<sup>81</sup> Therapies recommended by the Public Health Service's Preventive Services Task Force or AHCPR may not be approved for such uses on product labeling or in over-the-counter drug monographs.

<sup>82</sup> 61 Fed. Reg. 44,396 (Aug. 28, 1996) (to be codified at 21 C.F.R. pt. 801 et seq.).

Attempts by the FDA to regulate the content of home pages sponsored by medical or patient communities because of a linkage to a manufacturer home page could be resisted. Before taking any action the FDA should consider the likely harm such linkages could elicit (e.g., diminished incentive to file efficacy supplements) against the benefits of increased utilization of these databases by physicians and consumers, and the other protection inherent to the system (e.g., peer review and sophisticated users).

### *I. Information on International Approvals*

Not only is information contained in a sponsor home page generally accessible to physicians, patients, investors, academics, competitors, and other U.S. audiences, but it also is available to audiences in other countries. Similarly, WWW sites sponsored by foreign manufacturers are accessible to Americans. The information superhighway has brought the international community closer together than ever before.

The FDA, by its statutory authority, is limited to evaluating the domestic, or in-bound, component of this information transfer to users within the United States and for products marketed in American interstate commerce.<sup>83</sup> FDA staff has warned that a troublesome aspect of the promotion of unapproved uses is discussion on a home page of indications approved outside the United States. Mr. Tart has stated, "We have not looked too favorably on the use of country flags" or disclaimers.<sup>84</sup>

U.S. companies seeking to reach audiences within the United States as well as abroad have two alternatives: provide information on the same home page for audiences in every country or create one home page directed at U.S. audiences and another home page directed at international audiences. The latter approach allows a U.S. company to argue that, although U.S. audiences could access the foreign home page, it was directed abroad, was not likely to be used by Americans due to the availability of a separate U.S. home page, and was not intended to promote products in interstate commerce.

The FDA also might allow a general listing of approved indications within each designated country to be included on both the international and domestic home pages. A strong argument exists that such material is only informational and not promotional. By an international home page, a user might obtain the approved labeling in a native language. Disclaimers could be included that approval in another country does not imply that the drug has been evaluated by the FDA, and is safe and effective in the agency's view.

Expanded use of the Internet worldwide should lead to a session of the International Conference on Harmonization devoted to advertising and labeling use on this medium. The laws of all countries differ dramatically in this area. Protection of First Amendment commercial speech exists in few other countries. At the same time, few drug and device regulators seek to protect consumers with a regulatory scheme as comprehensive as the United States and several other western countries. Until international agreements can be reached, the FDA should not seek to police the world through a restrictive regulatory scheme, but instead learn by the evolution of laws on the export of

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<sup>83</sup> "The term interstate commerce means (1) commerce between any State [of the United States] or Territory [or possession of the United States] and any place outside thereof, and (2) commerce within the District of Columbia or within any other Territory [or possession of the United States] not organized with a legislative body." FDCA §201(b), 21 U.S.C. §321(b).

<sup>84</sup> *Device Information on Internet*, supra note 12, at I&W 5.

unapproved products, and recognize that other countries have different needs and regulatory structures.

## VII. CONCLUSION

An initial "rule of thumb" exists for all companies and their counsel in evaluating Internet design. Written and interactive Internet components should be dissected and analogized individually with traditional promotional materials with which companies and the FDA have experience. The FDA has acknowledged, however, that the format of information, as opposed to its content, is different. That format difference will impact significantly the manner of its regulation.

The FDA is inclined to view the bulk of information contained on the Internet as labeling, not advertising. This will require use of a full approved package insert in any program design. The insert can be separated from more "user friendly" content in a separate, but linked file.

While the FDA informally seeks a copy of all Internet information used by a sponsor at the time it becomes accessible to on-line users, the agency may be open to receiving only a notice letter that includes the Internet address. Through careful monitoring, the FDA can access all information disseminated on the Internet in an organized methodical mode of transmission.

Manufacturers may elect to create on-line product summaries to promote products to a broader audience that includes sophisticated physicians and investigators as well as less sophisticated patients, investors, and other consumers. Such summaries might help market drugs and satisfy new voluntary consumer labeling proposals, while still preserving the learned intermediary protection against product liability claims.

A sponsor probably will be precluded from using an Internet "prompt mechanism" where users may request materials on off-label uses by asserting that this information was unsolicited. This mechanism, however, could be used to disseminate other promotional information within the parameters of approved product labeling.

Investor information including annual reports, prospectuses, and stockholder letters may be available to all audiences (including physicians and consumers). The FDA can be expected to review this information, even if separated in an "investor" file, with the same labeling and "fair balance" criteria applied to product information. Sponsors may be caught between the competing requirements of Securities and Exchange Commission disclosure, FDA promotional review, and the company's marketplace objectives.

It is likely that while the bulk of textual material contained on a WWW site may be viewed as labeling, graphic material could be viewed as advertising. Pictorial or graphic material may be viewed as misleading if, for example, in the interest of simplicity it glosses over or does not list side effects or mechanisms that might block a drug's therapeutic benefit, or appears useful in a broader range of conditions or patients. Because preparation of graphic material is more expensive and time consuming than text, sponsors may wish to submit such material as work-in-progress prior to going on-line in case such representations are challenged.

Use of chat rooms to encourage professional and consumer education should be encouraged. These discussions, if they include the sponsor, are analogous to communications made by detailees in the field. Only the manufacturer and its employees and agents should be required to restrict comments to the terms of approved labeling.

Any attempt to regulate the content of home pages sponsored by the medical or

patient communities because of a linkage to a manufacturer home page undoubtedly will be resisted. Before taking action that could prevent these network linkages, the FDA should weigh the harm such linkages could elicit (e.g., diminished incentive to file efficacy supplements) against the benefits of increased utilization of these databases and the other protections inherent in the system (e.g., peer review and sophisticated users).

Finally, until international agreements are reached to harmonize regulation of promotional activities on the Internet, the FDA should not restrict the exchange of information on foreign approved uses. If used responsibly, the Internet provides a powerful interactive educational tool. The marketplace, in collaboration with government, the medical community, insurers, patients, and consumer groups, can accomplish the FDA's primary goal: a community better informed and more sophisticated to the benefits and risks of chemical and biologic drug products and medical devices.