



February 26, 2010

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

Re: Promotion of Food and Drug Administration-Regulated Medical Products Using
the Internet and Social Media Tools (Docket No. FDA-2009-N-0441)

Dear Sir or Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) is pleased to submit these comments in response to the Food and Drug Administration's (FDA) notice on promotion of FDA-regulated medical products using the Internet and social media.¹ PhRMA is a voluntary, non-profit association that represents the country's leading pharmaceutical research and biotechnology companies, which are dedicated to developing medicines that allow patients to live longer, healthier, and more productive lives. In 2008 alone, PhRMA members invested over \$50 billion in the research and development of new medicines.

PhRMA is committed to helping assure that promotion of medicines is truthful, scientifically accurate, and non-misleading. To help accomplish these goals, PhRMA has created its *Code on Interaction with Healthcare Professionals*² and *Guiding Principles on Direct to Consumer Advertisements About Prescription Medicines*.³ Thus, PhRMA was pleased to participate in FDA's public meeting, and we appreciate the efforts of FDA, especially CDER's Division of Drug Marketing, Advertising, and Communications (DDMAC), in seeking public input on the important issues involving communication about medical products over the Internet.

PhRMA and its member companies will work with FDA to help develop standards for responsible communication about medicines online by manufacturers. Accordingly, we propose that FDA adopt Internet-specific standards, including in the following areas:

- A universal symbol that could be used in space-constrained media to indicate a direct link to FDA-regulated risk and benefit information;
- Introductory warning information in sponsored search results and similar media with direct links to comprehensive risk and benefit information; and
- Microblogging of newsworthy regulatory events for medical products.

¹ 74 Fed. Reg. 48,083 (Sept. 21, 2009).

² Available at http://www.phrma.org/code_on_interactions_with_healthcare_professionals.

³ Available at http://www.phrma.org/direct_to_consumer_advertising.

Introduction

The Unprecedented Demand for Reliable Health Information Online

As demonstrated during FDA's informative two-day public meeting on this topic, patients and healthcare professionals are turning to the Internet to gather health information in unprecedented numbers. Internet users are using social networks, blogs, and other social media to gather healthcare information and to share their experiences with other users. These tools also benefit professionals and medical students by providing a forum to exchange information on medical research and topics of common interest.⁴ According to a 2009 survey by the Pew Research Center, 61% of American adults (83% of Internet users) now look online for health information.⁵ Pew found that online health research has "an impact on decisions or actions and there are clearly more positive experiences than negative ones." 42% of all adults, or 60% of e-patients, say they or someone they know has been helped by following medical advice or health information found on the Internet.⁶ In addition, one-third of Americans are now looking online for information about medicines.⁷ But according to Pew, "The internet does not replace health professionals." 86% still ask a health professional when they need health information.⁸

Access to truthful, reliable information on the Internet will improve public health. Given the extraordinary volume of dangerous, inaccurate, and unverified information about medicines on the Internet, it is imperative that FDA facilitate the availability of truthful, scientifically accurate and FDA-regulated information online. Patients increasingly use the Internet as a source of information when caring for themselves or others. According to data from comScore Inc., 78% of patients who are online visit a health-related site to learn more about their own condition (as well as 56% of Caregivers). In addition, the Department of Health and Human Services Healthy People 2010 report recognizes the power of the Internet to provide patients with health information.⁹ One of the goals of Healthy People 2010 is to increase Internet access, because "access to the Internet and subsequent technologies is likely to become essential to gain access to health information, contact health care organizations and health professionals, receive services at a distance, and participate in efforts to improve local and national health." Thus, FDA should facilitate access to truthful, scientifically accurate information provided by manufacturers about their medicines over the Internet and social media.

⁴ See, e.g., American Medical Association Facebook Profile, <http://www.facebook.com/AmericanMedicalAssociation> (last visited Oct. 23, 2009); Reach-MD Facebook Profile, <http://www.facebook.com/pages/ReachMD-the-Channel-for-Medical-Professionals/42225727881#>. (last visited Oct. 23, 2009); Open Medicine Wiki, http://wikisr.openmedicine.ca/index.php/Main_Page (last visited Oct. 23, 2009).

⁵ Susannah Fox & Sydney Jones, Pew Internet and American Life Project, *The Social Life of Health Information -- Americans' Pursuit of Health Takes Place Within a Widening Network of Both Online and Offline Sources* 4 (June 2009) ("Pew Survey").

⁶ *Id.* at 7 (emphasis added).

⁷ Manhattan Research, *Cybercitizen Health Study* (2009).

⁸ See Pew Survey at 15.

⁹ HHS, *Healthy People 2010* vol. 1, ch. 11, "Health Communication," available at <http://www.healthypeople.gov/document/HTML/Volume1/11HealthCom.htm>.

I. The Appropriate Role of Biopharmaceutical Research Companies

Biopharmaceutical manufacturers use the Internet to provide truthful and scientifically accurate information to healthcare professionals and patients about the medicines they discover, develop, and produce.¹⁰ Already, they provide the only FDA-regulated promotional information about medicines online. Given the importance of new media to healthcare professionals and patients, FDA should calibrate its regulation of the Internet and social media to facilitate the use of these communication tools by FDA-regulated biopharmaceutical manufacturers to provide truthful, scientifically accurate information.

America's research-based biopharmaceutical companies already provide FDA-regulated information to patients and healthcare professionals in print and broadcast media. Given the extraordinary growth of the Internet as a source of health information -- and the enormous amount of inaccurate and non-regulated information about medical products online -- FDA should avoid chilling manufacturers' communication of medical information about their products in a responsible way, taking advantage of the same technologies that the FDA and the White House use, including blogs, video, search, and social networking sites such as Twitter™ (see page 7 of these comments for example). As demonstrated by the FDA's own use of Twitter, it is clear that information about medicines can be provided in a truthful, non-misleading manner. Of course, the critical dialogue between patients and their health care professionals necessarily supplements any general information provided by manufacturers, whether information is provided through the Internet or more traditional media. According to the Pew survey, 53% of respondents who stated that an Internet search had improved their own health or their care for someone else, also stated that the information they found online led them to ask a doctor new questions, or to get a second opinion from another doctor.¹¹

As Internet media evolve, the FDA should calibrate its regulation to allow manufacturers to use new technologies to communicate risks and benefits about medicines. Consumers on the Internet are accustomed to viewing pop-ups, rollover text, links, and other communication mechanisms that are unique to new media. FDA should recognize, as the Federal Trade Commission (FTC) has, that space limitations in certain formats warrant allowing certain long warnings to be accessed using a prominently labeled hyperlink. An FTC staff paper states that web sites "are interactive and have a certain depth—with multiple pages linked together and pop-up screens, for example—that may affect how proximity [of disclosures] is evaluated."¹² Significantly, the FTC's staff paper concludes that "[h]yperlinked disclosures may be particularly useful if the disclosure is lengthy." Certain technologies, such as microblogs, emphasize brevity, but they may provide more information by hyperlink. Moreover, consumers are increasingly accessing information on handheld devices with small screens. Thus, FDA should adapt to the use of such media and not apply regulatory paradigms created originally for brochures and other physical media.

¹⁰ In these comments, the term "manufacturer" means a holder of New Drug Application (NDA) or Biological License Application (BLA).

¹¹ Pew Survey at 7.

¹² FTC, Dot Com Disclosures: Information About Online Advertising 6 (2000), *available at* <http://www.ftc.gov/bcp/edu/pubs/business/ecommerce/bus41.pdf>.

II. Proposals for Maintaining Responsible Online Communications By Manufacturers

PhRMA's member companies are proud to serve as the most knowledgeable and reliable source of information about the lifesaving medicines they research, develop, and manufacture. To that end, PhRMA looks forward to continuing to work with FDA and stakeholders to identify ways in which biopharmaceutical manufacturers may communicate about their medicines online in a truthful, scientifically accurate, and non-misleading way.

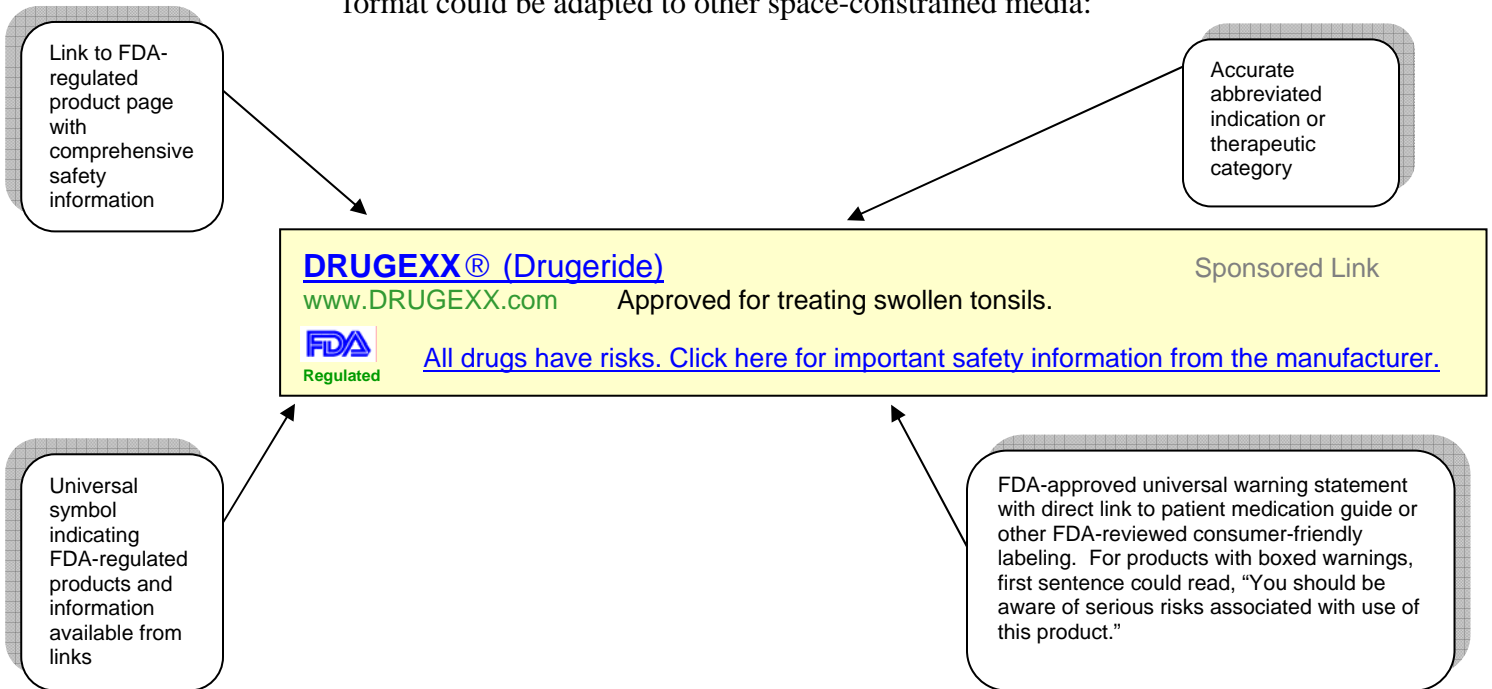
FDA should allow manufacturers to present brief "introductions" to health information in electronic formats, including brief but accurate indication descriptions, just as FDA now does in its own Twitter postings. These introductions are appropriate methods of conveying information within the space constraints of some new media (*e.g.*, search results, blog entry, tweets). Of course, such an introduction should also contain an affirmative statement about the risks of a medicine, even if initially abbreviated and continued in a pop-up or link. A condition of providing initial benefit and risk information in an abbreviated format could be that such entries contain prominent and clearly marked links indicating that users should view more comprehensive information such as full indication, full risk information, and more complete fair balance. The link label itself – perhaps with a universal graphic symbol as we discuss below – should provide appropriate balance to a truthful abbreviated indication statement, if the link: (i) is prominently marked, (ii) contains a definitive statement that use of the drug entails risk, and (iii) moves the user directly to a page containing a comprehensive statement of the indication and risk information. FDA's adoption of such a standard would be consistent with the FTC's standards as described above.¹³

In order to assure that biopharmaceutical manufacturers are able to utilize the Internet effectively and responsibly, PhRMA proposes that FDA permit communication under the following standards through new guidance, which could eventually be adopted in regulations. Significantly, the standards PhRMA is proposing consist of principles that are not dependent on any single technology. We note that the following proposals are not mutually exclusive:

- **Universal Symbol for Space-Constrained Media.** FDA should approve use of its own logo or a new universal graphic symbol to indicate direct links to FDA-regulated information in space-constrained media. Such a symbol could be used with microblogs and sponsored search, where there is not enough room to provide complete benefit and risk information. Such media postings would include a standard universal warning that would be approved by FDA (*e.g.*, "All drugs have risks. Click here for more information from the manufacturer"). The prominent graphic and link would take users directly to pages displaying the FDA-approved Prescribing Information (PI), Medication Guides, and/or FDA-reviewed important safety information. The use of FDA's own logo, or some other FDA-approved symbol, would increase the prominence of the link and also help patients and healthcare professionals identify the official manufacturer sites containing FDA-regulated benefit and risk information. While use of such a universal graphic symbol would require

¹³ See *supra* note 12 and accompanying text.

the cooperation of many parties, including Internet companies, PhRMA hopes that this proposal is one way to improve communication of the risks and benefits of medical products in new online media. An example of the use of such a symbol in a sponsored search result is provided below; however the format could be adapted to other space-constrained media:



Link to FDA-regulated product page with comprehensive safety information

Accurate abbreviated indication or therapeutic category

DRUGEXX® (Drugeride)

Sponsored Link

www.DRUGEXX.com

Approved for treating swollen tonsils.

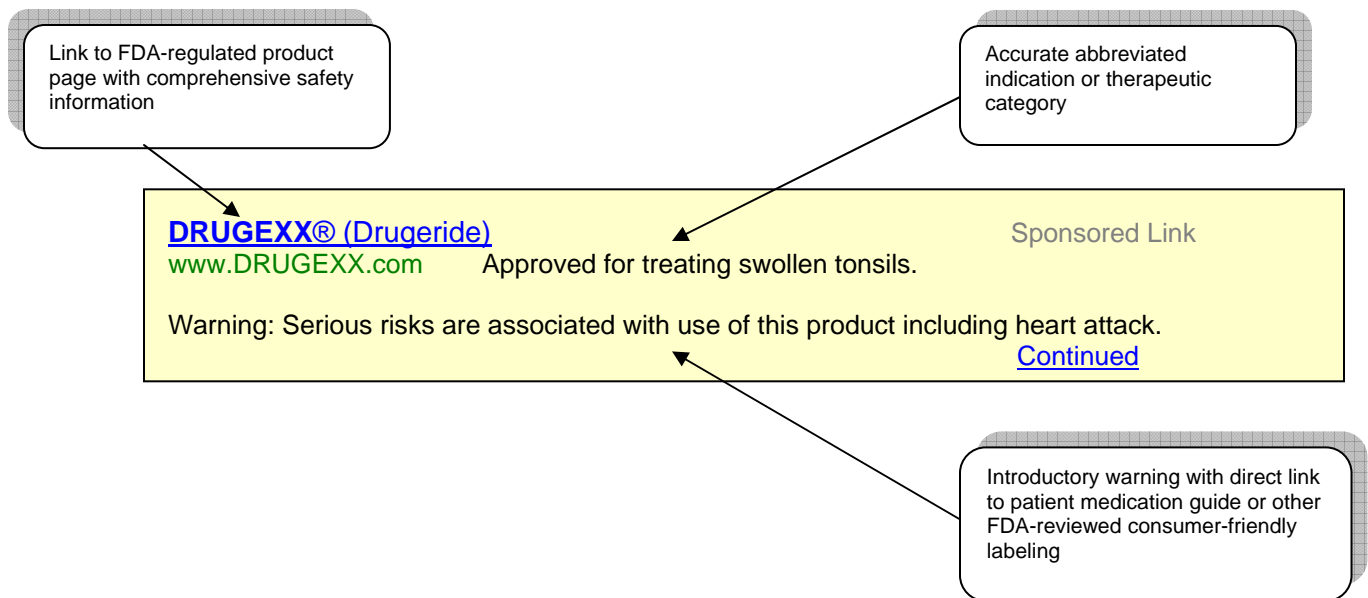


[All drugs have risks. Click here for important safety information from the manufacturer.](#)

Universal symbol indicating FDA-regulated products and information available from links

FDA-approved universal warning statement with direct link to patient medication guide or other FDA-reviewed consumer-friendly labeling. For products with boxed warnings, first sentence could read, "You should be aware of serious risks associated with use of this product."

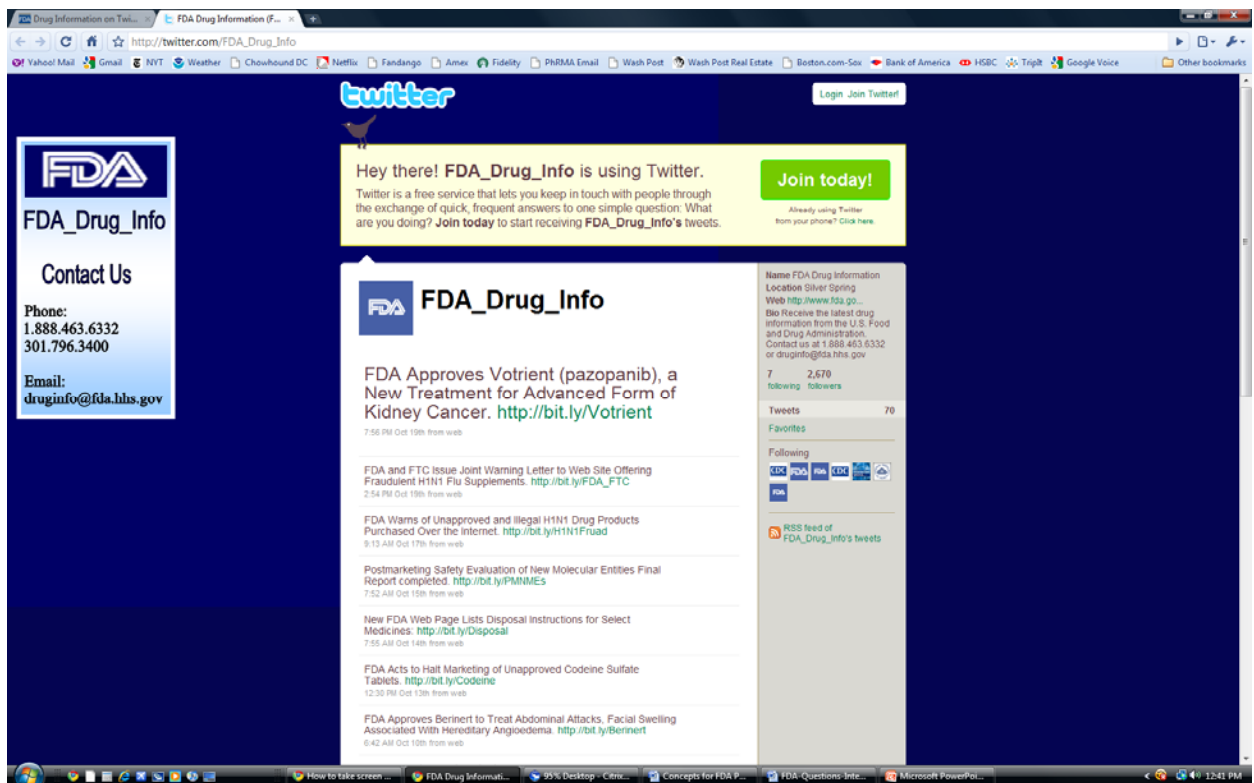
- Risk Information in Sponsored Search Results.** Biopharmaceutical manufacturers are committed to providing truthful and scientifically accurate information about their medicines. Given technological constraints, some media, such as sponsored search links, do not allow for manufacturers to provide complete benefit or risk information within allowed space. In such cases, FDA should allow manufacturers to provide the name of their medicine, an accurate summary of the FDA-approved indication and/or therapeutic area, and the beginning of a comprehensive description of risk information; on a directly linked landing page or pop-up box, the manufacturer would provide a continuation with comprehensive risk and benefit information.¹⁴ An example of the use of this format is provided below:



A direct link from “Continued” would contain comprehensive risk and benefit information including FDA-approved Prescribing Information (PI), Medication Guides, and/or FDA-reviewed important safety information. The introductory warning language that appears in a sponsored search result would be taken from FDA-reviewed risk information such as a Medication Guide. FDA should provide guidance regarding the specific information to be provided before and after the link.

¹⁴ An initial presentation of risk information together with an abbreviated indication such as illustrated here appears to comply with FDA’s current regulatory standard for providing fair balance in promotional advertising. See 21 C.F.R. 202.1(e)(5)(ii) (“[N]o advertisement shall be considered to be in violation . . . if the presentation of true information relating to side effects and contraindications is comparable in depth and detail with the claims for effectiveness or safety.”).

- **Responsible Microblogging of Newsworthy Events.** FDA has set a responsible example in its use of Twitter to broadcast newsworthy events such as new drug approvals. Given the limited space constraints (*e.g.*, 140 characters) of such media, and consistent with FDA's own use of such media, the Agency should allow biopharmaceutical manufacturers to microblog about significant scientific and regulatory events (*e.g.*, approvals, new indications, recalls) for a medicine, provided that (i) all information provided in the initial entry is truthful and accurate, and (ii) the landing page contains a comprehensive description of product risks and benefits. As FDA's regulations recognize, scientific exchange of information which is neither advertising nor promotion can and should exist, and manufacturers should serve as responsible stewards of such information about the products they develop.¹⁵ An example of FDA's use of a microblog entry to describe a newsworthy event (a product approval) on Twitter is provided below ("FDA Approves ...")¹⁶:



¹⁵ See 21 C.F.R. 312.7(a) ("This provision is not intended to restrict the full exchange of scientific information concerning the drug, including dissemination of scientific findings in scientific or lay media.")

¹⁶ See http://twitter.com/FDA_DRUG_INFO (last visited October 19, 2009).

- **Correction of Inaccurate Information About Medicines.** Among the many values of social media is a focus on open and free-flowing communications from a wide variety of users. However, this free flow of communication also allows users to post inaccurate and misleading information about products, including medicines, that could actually harm patients (*e.g.* recommending unsafe drug uses). If a company becomes aware of such information, a prompt factual response or correction by the pharmaceutical manufacturer may enhance the public health. Biopharmaceutical manufacturers serve as the most knowledgeable source of information about the medicines they research and develop. Our manufacturers seek to continue to serve as responsible stewards of information about their medicines. Accordingly, FDA should confirm formally that, while it is not possible for manufacturers to monitor or correct all inaccurate information about their products on the Internet, such corrections by manufacturers in response to inaccurate postings will not be considered promotional labeling. FDA's adoption of such a policy would thereby allow manufacturers to correct inaccurate information about their medicines on the Internet or social media (*e.g.*, Wikipedia, Sidewiki, blogs, or other websites) if they should become aware of such information.

III. Public Health Dangers Posed By Illegal Internet Drug Sellers and Other Non-FDA Regulated Groups

Given the real public health dangers and lack of accountability posed by illegal Internet drug sellers and other non-regulated groups that provide information about prescription medicines online, FDA should encourage manufacturers' legitimate, FDA-regulated communication on the Internet as a source of reliable information. In addition, FDA and other government agencies should redouble enforcement efforts against Internet drug sellers that could be sources of counterfeit medicines, and could also be selling medicines to consumers without either a prescription or an adequate description of drug risks.

According to the Department of Homeland Security, "the Internet has become the primary tool for criminal organizations to advertise, communicate and conduct sales of counterfeit pharmaceuticals. The Internet has also become the primary mechanism for consumers to find, order and make payments for counterfeit pharmaceuticals."¹⁷ Warning the public against fake H1N1 treatments last fall, Commissioner of Food and Drugs Margaret A. Hamburg, M.D. stated, "Medicines purchased from Web sites operating outside the law put consumers at increased risk due to a higher potential that the products will be counterfeit, impure, contaminated, or have too little or too much of the active ingredient."¹⁸ FDA stated that it purchased and analyzed several products represented online as Tamiflu[®] (oseltamivir), which may pose risks to patients. According to FDA, "[o]ne of the orders, which arrived in an unmarked envelope with a postmark from India, consisted of unlabeled, white tablets taped between two pieces of paper. When analyzed by the FDA, the tablets were found to contain talc and acetaminophen, but none of the active ingredient oseltamivir."¹⁹

In addition, other non-FDA-regulated advertisers, bloggers, and content creators may provide inaccurate information about medical products and pose a significant public health risk as well. Given the dangers posed by illegal Internet drug sellers and other non-regulated content creators, it is even more important that FDA facilitate manufacturers' ability to provide truthful, scientifically accurate — and FDA-regulated — health information to healthcare professionals and patients.

¹⁷ Department of Homeland Security, U.S. Immigration and Customs Enforcement, ICE Efforts to Combat Counterfeit Pharmaceuticals (2006), available at http://www.ice.gov/doclib/pi/news/factsheets/counterfeit_pharms.pdf.

¹⁸ FDA, FDA Warns of Unapproved and Illegal H1N1 Drug Products Purchased Over the Internet (2009), available at <http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm186861.htm>.

¹⁹ *Id.*

IV. Accountability of Manufacturers

FDA's notice poses a critical question during a time when all Internet users may now comment on or contribute content to almost any web page in numerous formats: "For what online communications are manufacturers, packers, or distributors accountable?"²⁰ Social media tools offer an unprecedented opportunity for third parties to speak about a manufacturer's products without the knowledge or control of the manufacturer. For instance, Wikipedia,²¹ an online encyclopedia featuring user-generated entries, includes pages describing many marketed drugs with information on the history of the drug, FDA-approved uses, lay media coverage, and investigational research. While some of the entry's content may repeat the manufacturer's own labeling or advertising, Wikipedia users can alter this content and post additional information. As a result, the final Wikipedia page may – through no fault of the manufacturer – fail to comply with FDA advertising and labeling rules were the page attributed to the company.²²

Social networking sites such as Facebook and Myspace™ allow users to create profiles through which they exchange pictures and videos, chat with friends, and send links to news articles. A user of Facebook could, for example, post a link to an article about an unapproved use of a drug and then write, inaccurately, that the drug's manufacturer was encouraging use of the drug in that manner. Likewise, microblogs such as Twitter present the opportunity for third parties to create problematic content. Twitter allows users to post and review other users' "tweets," 140 character messages that range in topic from the user's current feelings to current world events.²³ Twitter also permits users to conduct a "Twitter search" which produces a list of recent posts containing the search term. If one enters the name of a drug product, the results often contain entries describing individual users' experiences with the drug, anecdotal information about the drug, and users' opinions about the drug's efficacy. Even if a manufacturer were to post accurate, balanced information about its product, other "tweeters" can post unbalanced or inaccurate information in their posts, all of which would be displayed in response to a search for information about the product.

A biopharmaceutical manufacturer can only be accountable for a web site or other content that it controls, which should be defined as content — (i) that is controlled entirely by the manufacturer or its agents; (ii) where the manufacturer or its agents has authority to add or delete all content; and (iii) that is funded entirely by the manufacturer or its agents.²⁴ For purposes of enforcement, once FDA determines that content is controlled by a manufacturer, it must then determine whether the material may be regulated as promotional labeling or advertising under FDA's statutes and regulations. Importantly, not all manufacturer communications online

²⁰ 74 Fed. Reg. 48,083, 48,086 (Sept. 21, 2009).

²¹ Wikipedia, www.wikipedia.org (last visited Oct. 23, 2009).

²² Wikipedia, as just one example, is prone to vandalism and "editing wars" between users who disagree over the content that should appear in a particular entry. *E.g.*, Noam Cohen, *Wikipedia to Limit Changes to Articles on People*, N.Y. Times, Aug. 24, 2009, at B1.

²³ See Twitter, <http://www.twitter.com> (last visited Feb. 25, 2010).

²⁴ FDA has endorsed similar criteria in its Guidance on Industry-Supported Scientific and Educational Activities pertaining to continuing medical education (CME): "The agency will consider whether the [CME] provider has maintained full control over the content of the program, planning of the program's content, and over the selection of speakers and moderators." 62 Fed. Reg. 64,074, 64,097 (Dec. 3, 1997).

constitute promotional labeling or advertising about their products. For example, a press release describing clinical trial results or postings on www.ClinicalTrials.gov should not ordinarily be considered promotional by FDA. In addition, user-generated content posted by a third party on a site a manufacturer otherwise controls should also not be considered promotional labeling or advertising.

PhRMA's member companies recognize that they have an obligation to patients and healthcare professionals to provide scientifically accurate information about their medicines online. Thus, PhRMA proposes that employees or agents of a manufacturer who post content on the manufacturer's site, or other sites, as part of their employment should be required to disclose their relationship with the manufacturer in any posted content and make sure that content is truthful, scientifically accurate, and contains an appropriate balance between benefits and risks. Such a policy would be consistent with recent FTC guidance concerning compensated non-employee bloggers.²⁵

Attributing statements to a manufacturer that the manufacturer did not cause or control would, however, be untenable. Such third party statements simply do not fall within the definition of either labeling or advertising under the Federal Food, Drug, and Cosmetic Act (FDCA), one of which would be necessary to support a violation of law by the manufacturer.²⁶ Labeling is defined by the FDCA to include "all labels and other written, printed, or graphic matter (1) upon any article or any of its containers or wrappers, or (2) accompanying such article."²⁷ A third-party statement cannot reasonably be considered to accompany a drug merely because the statement refers to the drug. Rather, to be deemed labeling, the statement, at the very least, must be intended to be part of an integrated commercial transaction of the manufacturer.²⁸ Likewise, advertising, which is not defined by the FDCA, cannot reasonably be understood to encompass third-party statements simply because those statements reference a drug. The common meaning of the term envisions promotion for commercial sale, a motivation held only by the drug's manufacturer or its agents.²⁹ In sum, the statutory language of the FDCA provides no sensible basis to find a manufacturer liable if an unaffiliated third party misbrands a drug with no involvement by the drug's manufacturer, and we are unaware of any previous FDA enforcement action seeking to hold a manufacturer responsible for statements outside its control.

²⁵ Cf. 16 C.F.R. 255.5 example 7 (FTC guidance that non-employee blogger reviewing a product provided free of charge by a company should "clearly and conspicuously" disclose that he received the product free of charge).

²⁶ See 21 U.S.C. § 321(n).

²⁷ 21 U.S.C. § 321(m).

²⁸ *Kordel v. United States*, 335 U.S. 345, 350 (1948) ("The false and misleading literature in the present case was designed for use in the distribution and sale of the drug, and it was so used. The fact that it went in a different mail was wholly irrelevant whether we judge the transaction by purpose or result. And to say that the prior or subsequent shipment of the literature disproves that it is misbranded when introduced into commerce within the meaning of [section] 301(a), is to overlook the integrated nature of the transactions established in this case." (internal quotation marks omitted)). Accordingly, FDA regulations and guidance concerning labeling place obligations on the drug's sponsor and not on independent third parties. See, e.g., 21 C.F.R. § 314.81(b)(3) (requiring sponsors to submit advertisements and promotional labeling to FDA when such materials are made publicly available).

²⁹ Black's Law Dictionary 59 (8th ed. 2004) (defining advertising as "[t]he action of drawing the public's attention to something to promote its sale.").

Like other types of companies, manufacturers of biopharmaceutical products are not able to monitor the entire Internet for references to their products. Moreover, companies often will be unable to correct inaccuracies on sites that they find but whose content they do not control. Even when manufacturers take corrective measures, there is no guarantee that the company's alterations or posted information will remain in a correct state; users of Wikipedia, for example, may simply edit or delete the sponsor's corrective post. For such independent sites, manufacturers cannot be held responsible for all content. By definition, manufacturers cannot control the content of most independent blogs (including Sidewiki) and therefore cannot be held responsible for them.

PhRMA believes that a rule focusing on control of content properly addresses the challenges posed by new forms of media and also remains consistent with the traditional rules regarding a manufacturer's responsibility for its own statements. FDA does not consider manufacturers accountable for independent media reports on their products, which, like much Internet content, cannot be fairly described as promotional labeling. And FDA guidance concerning whether professional articles and educational events are considered promotional focus primarily on the manufacturer's ability to control or dictate what is said in these forums.³⁰ In the Internet context, using control as a metric of responsibility is even more important. Social media have expanded the opportunity for the public to publish their thoughts but have decreased the ability of manufacturers to identify and correct inaccurate information about their products.

³⁰

See supra note 24.

V. Adverse Event Monitoring

America's research-based pharmaceutical companies take extremely seriously their obligation to investigate and report potential adverse event (AE) information to the FDA. Accordingly, PhRMA and its members believe that manufacturers should monitor web sites they control for reportable AEs regarding their marketed products, and treat them as they would AE information taken from other media.

Given the highly interactive nature of the Internet and social media, patients, healthcare professionals, and manufacturers are exposed to an increasing amount of personal information about those who post; this can present significant challenges to manufacturers with respect to the scope of their obligation to report AEs to FDA. In order to help assure reliable AE information from online sources, and also to respect patient and reporter privacy, FDA should require manufacturer reporting of incidents discovered online only if online reporters are privately contactable (*i.e.*, it should be possible to communicate directly with the reporter without the need to post questions to a public forum to obtain more information). FDA should not force manufacturers to seek personal health information from patients or reporters in a public forum, such as a blog. Rather, if a manufacturer's employee (as part of his or her job) were to see evidence of an adverse event while on a blog or other public Internet forum, the manufacturer could post a public notice on the blog with company contact information, so that the company might try to conduct an appropriate, confidential investigation and make any necessary reports to FDA.

In addition, FDA could encourage companies to post on any company-controlled Internet sites directed to consumers a statement that reads: "ALERT: This site is not intended for reporting of adverse experiences with prescription drug products. Adverse events may be reported: to [company name] [contact information] or to the U.S. Food and Drug Administration [with a link to FDA's MedWatch site]."

A. Confirmation of Safety Reports

A fundamental approach to pharmacovigilance reporting is the confirmation of a safety report using the following minimum criteria: (i) identifiable patient; (ii) identifiable reporter; (iii) suspect drug; and (iv) adverse event. Additionally, in accordance with established regulatory guidance, an agreed 'start clock' for reporting deadlines is required.³¹ Moreover, information presented in aggregate does not constitute a valid case, because it does not contain an identifiable patient. We discuss these criteria in the context of online information below.

³¹ See FDA, International Conference on Harmonization (ICH) - Draft Guidance for Industry: E2D Post-Approval Safety Data Management: Definitions and Standards for Expedited Reporting § 3.2.1 (2003) ("Minimum required data elements for an ADR case are: an identifiable reporter, an identifiable patient, an adverse reaction, and a suspect product. Lack of any of these four elements means that the case is incomplete; however, MAHs are expected to exercise due diligence to collect the missing data elements.") available at <http://www.fda.gov/RegulatoryInformation/Guidances/ucm129457.htm> [hereinafter ICH E2D].

i. Identifiable Patient and Reporter

An individual that brings a potential AE case to a manufacturer's attention is the reporter. In an on-line environment, the individual that brings a potential AE case to a manufacturer's attention and the individual who posted the information on-line (the poster) are both reporters, and the standards of identity should be met for both reporters in order to have a valid case -- *e.g.* the identity of the person "finding" the AE case and the person "posting" the AE case on the web-based media must be identifiable.

Consistent with the ICH standard, "Patient and reporter identifiability is necessary to avoid case duplication, detect fraud, and facilitate follow-up of appropriate cases. The term "identifiable" in this context refers to the verification of the existence of a patient and a reporter and the ability for a manufacturer to make contact. One or more of the following automatically qualifies a patient as identifiable: age (or age category, *e.g.*, adolescent, adult, elderly), gender, initials, date of birth, name, or patient identification number."³² Accordingly, FDA's definition of reporter identity should be augmented for an on-line environment to include the requirement that the reporter is privately contactable (*i.e.*, it is possible to communicate directly with the reporter without the need to post questions to a public forum/environment to obtain more information) while adhering to patient privacy standards. Moreover, given the frequent use of screen names that provide for reporter anonymity, and the inherent difficulties such anonymity poses for making contact with reporters, FDA should provide guidance on the number of contact attempts necessary to constitute diligence.

ii. Suspect Drug

Consistent with existing AE reporting requirements, there should be a clearly identifiable product marketed by the manufacturer for safety information to be reportable.

iii. Adverse Event

Untoward medical occurrences such as a sign, symptom, disease term, or lack of effect is a fundamental requirement for an adverse event, consistent with existing pharmacovigilance standards.

iv. Clock Start

The regulatory reporting "time clock" starts on the date when the manufacturer first receives a case report that fulfils minimum criteria as well as the criteria for expedited reporting in an on-line environment. The clock start for reporting to FDA would only be initiated when minimum criteria for reporting exist, including an identifiable reporter.

³² *Id.* at 8.

B. Screening Web Sites

PhRMA supports the international standard that FDA and its sister agencies have adopted as part of the International Conference on Harmonisation (ICH).³³ Under FDA's existing draft guidance, ICH E2D, manufacturers "are not expected to screen external websites for ADR information. However, if [a manufacturer] becomes aware of an adverse reaction on a website that it does not manage, the [manufacturer] should review the adverse reaction and determine whether it should be reported. [manufacturers] should regularly screen their websites for potential ADR case reports."³⁴ Manufacturers are unable to monitor every web site, blog, or chat room for adverse events, but they can monitor sites that they control within a reasonable period of time. The standard for identifying an adverse event found on the Internet should be premised upon the existence of the four required elements: an identifiable patient, an identifiable reporter, use of a drug or biologic, and an adverse event. In the absence of these four elements no adverse event should be identified requiring follow-up or other action.

i. Manufacturer Controlled Web-Based Media

For safety reports on web sites controlled by manufacturers, PhRMA recommends that FDA require that companies review the content and process any safety information in accordance with the guidance for spontaneous reports. For safety information left on the manufacturer's website, the intent of the reporter is to share the safety information with the manufacturer, and the reporter demonstrates the volition to find the web-based media and take action to report safety information. FDA should require that manufacturers monitor web-based content that they control and should have the ability to follow-up with reporters who intended to report information to the company. The manufacturer may establish dialogue to attempt to establish a complete medical report including causality relation. The value of this information would be expected to be relatively high as it may provide insight into new safety signals for a product.

ii. Independent or Manufacturer-Supported Web-Based Media

The majority of healthcare websites are independent of biopharmaceutical manufacturers. Some sites may be financially supported but not controlled by manufacturers. Healthcare professionals and/or patients may have the opportunity to describe safety information with other members or viewers of such sites. Given the nature of such sites, any descriptions of safety events would not be intended as AE reports *to the manufacturer*, even though personnel of the manufacturer might observe individuals' posted information about a medicine (which often contains no information regarding the causal relationship of the event to the product). Consistent with the ICH standard discussed above, manufacturers should not be required to routinely review the content and process safety information on such third-party web sites that they do not control.

³³ FDA's draft guidance was created as an international standard of the International Conference on Harmonisation (ICH), which brings together the regulatory authorities of Europe, Japan and the United States and experts from the pharmaceutical industry in the three regions.

³⁴ ICH E2D at § 2.5.1.3 .

Manufacturers may simply observe (as a third party) dialogue between two participants on a web site not controlled by the manufacturer; if the four basic elements of an AE report are available then the clock start would be the first time of observing the safety information and confirming the reporter identity as described above. Follow-up of such cases should also adhere to any privacy or confidentiality requirements of the Web-based media or national law.

The potential value of safety information taken from third party web sites contributing to a benefit-risk assessment of a medicine is likely to be low when compared with other sources of data including randomized controlled trials, observational data and spontaneous data. Therefore, these data should be managed and assessed separately from those of other data sources, because these data are likely to be of low medical quality and difficult to substantiate through follow-up processes. This low quality safety data is also likely to increase baseline reporter "noise," based upon the inclusion of information that does not have the scientific rigor necessary for inclusion in the core safety analysis of the drug. This noise could prevent a signal from being identified from the spontaneous reporting system. FDA's development of its critically important Sentinel project for active drug safety surveillance would also appear to decrease the relative benefit of collecting low quality data from third-party online sources.

Conclusion

In conclusion, PhRMA appreciates FDA's significant efforts in determining how best to regulate information about prescription drugs on the Internet and social media. PhRMA intends to continue to serve as a constructive partner. Please do not hesitate to contact us if you have any questions about our comments.

Respectfully submitted,



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