Pharma Marketing News

www.pharmamarketingnews.com

26 Jan 2012
Vol. 11, No. 1
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Published by
VirSci Corp.
www.virsci.com

FDA Guidance on Responding to Unsolicited Requests for Off-Label Information

The Social Media Guidelines Nobody Expected!

Author: John Mack

PMN111-02

Find resources cited this article online at:
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This article is part of the January 26, 2012 issue of *Pharma Marketing News*.

For other articles in this issue, see (after January 31, 2012):
http://www.news.pharma-mkting.com/PMNissue111Jan2012archive.htm

Published by:
VirSci Corporation
PO Box 760
Newtown, PA 18940
infovirsci@virsci.com

Two days after Christmas, on December 27, 2011, while most of us were still on vacation, the FDA quietly issued "Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices." Section VI. of this guidance addresses responding to unsolicited requests on public forums such as the Internet.

While this may not be the "social media" guidance many people were expecting (see "What We Expected Was This"; page 3), it does include guidelines for responding to unsolicited requests for off-label information encountered through "emerging electronic media."

A Bit of History

Back in June, 2011, I noticed that the FDA did not mention "social media" in its revised "Guidance Agenda: New & Revised Draft Guidances CDER is Planning to Publish During Calendar Year 2011." The previous agenda (2010) included "Promotion of Prescription Drug Products Using Social Media Tools."

Included in the 2011 agenda under the Advertising Category, however, was "Responding to Unsolicited Requests for Prescription Drug and Medical Device Information, Including Those Encountered on the Internet." And that is what the FDA managed to squeeze out before the end of the year.

"Responding to unsolicited requests" is not a social media issue per se nor was it one of the questions FDA asked at the November 2009, public hearing.

Pharma's Social Media Working Group

When I re-read the transcripts of the Public Hearing, I found only one mention of "unsolicited" and it was in the November 12, 2009, presentation made by Mark Gaydos, Senior Director of U.S. Regulatory Affairs, Marketed Products at Sanofi-Aventis.

Gaydos spoke on behalf of the Social Media Working Group, which included representatives from Amgen, AstraZeneca, Bristol-Myers Squibb, Millennium Pharmaceuticals, and Sanofi-Aventis U.S. (for more about this group, listen to this podcast: "Pharma's Social Media Working Group: Who It Consists of and What Its Objectives Are"; http://bit.ly/PMT095).

Gaydos spoke specifically about practical approaches for the pharmaceutical industry's "engagement in online communities or social media in a compliant manner."

Gaydos envisioned "specific scenarios where we're talking about unsolicited questions that are posed on a company-sponsored site." One specific scenario involveed questions about "off-label" use of a company's drug. Gaydos said, "with off-label questions there is already an accepted way for companies to in a

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Defining "Off-Label"

Source: Pharma Marketing Glossary

> FDA defines off label use as, "Use for indication, dosage form, dose regimen, population or other use parameter not mentioned in the approved labeling."
>
> "FDA recognizes that off label use of drugs by prescribers is often appropriate and may receive endorsement from published literature; they may also receive recommendations as 'Other standard uses - i.e., recommended by subspecialty societies, CDC, etc.'" -- FDA

Also:

> "An unlabeled use [off-label use] of a drug is a use that is not included as an indication on the drug's label as approved by the FDA." -- Medicare.

Also:

> Once a new prescription drug has been approved by the FDA, and prescriptions have been written and used by patients, patients and professionals may discover that there are additional symptoms or conditions the drug may treat effectively that were not among the reasons the drug was originally approved.
>
> Knowing about these different ways the drug may be effective, a doctor may decide to prescribe the drug for one of these alternative reasons. Such a prescription is considered to be "off-label." The drug does not need to go through the FDA process for the off-label prescription.
>
> In particular, generic drugs that have been in use for many years may be discovered to have alternative uses.
>
> In the US, it is legal for doctors to write off-label prescriptions. However, it is not legal for pharmaceutical companies to promote any drugs they manufacture for off-label use. They may promote the use of drugs only for the reasons the drug was approved.
>
> Source: About.com

See Article: "Guidelines for Off-label Communications"; http://bit.ly/pmn211-05

compliant fashion respond to those questions off-line," but "It's difficult to apply the same criteria here."

Gaydos imagined the following scenario:

> "You can imagine, for instance, someone visits a company site, and there's a community hosted on that site, and they mention, oh, I'm taking your product for a specific condition, and that happens to be an off-label use of the product. However, it may have been deemed medically appropriate by their physician. Imagine how you would feel if you did something like that, and you were told by a company, that's an inappropriate use of our product, when, in fact, the doctor said it is appropriate."

That could harm the patient-physician relationship, said Gaydos.

FDA Responds

In response to a June 1, 2011, Pharma Marketing Blog post titled "FDA Drops Social Media from Its 2011 Guidance Agenda," FDA issued this notice:

> Policy and guidance development for promotion of FDA-regulated medical products using the Internet and social media tools are among our highest priorities. Despite our limited resources and increasing workload, we remain committed to this area in terms of both time and human resources.
>
> It is difficult to provide a timeframe for the issuance of our guidances due to the extensive work and review process, or "Good Guidance Practices" (GGPs), which ensures that FDA's stakeholders are provided well vetted guidances articulating FDA's current thinking on a topic.
>
> Taking into consideration input from within and outside FDA, including testimony and comments from the Part 15 hearing, we have identified the following issues that are important to address:
>
> - Responding to unsolicited requests
> - Fulfilling regulatory requirements when using tools associated with space limitations
> - Fulfilling post-marketing submission requirements
> - On-line communications for which manufacturers, packers, or distributors are accountable
> - Use of links on the Internet
> - Correcting misinformation
>
> We are developing multiple draft guidances to address these topics to benefit industry and the public by ensuring that these draft guidances are meaningful and well thought out when they are issued.

What We Expected Was This

No so long ago, there was much speculation as to when the FDA would publish its first guidance for the drug industry regarding promotion via the Internet and social media. At several conferences, FDA officials have stated that they expect to issue several guidances addressing specific questions that were addressed at the November 15, 2009 Part 15 public hearing.

Recall that there were FIVE questions that the FDA asked the public to comment upon:

1. For what online communications are manufacturers, packers, or distributors accountable?
2. How can manufacturers, packers, or distributors fulfill regulatory requirements (e.g., fair balance, disclosure of indication and risk information, postmarketing submission requirements) in their Internet and social media promotion, particularly when using tools that are associated with space limitations and tools that allow for real-time communications (e.g., microblogs, mobile technology)?
3. What parameters should apply to the posting of corrective information on websites controlled by third parties?
4. When is the use of links appropriate?
5. Questions specific to Internet adverse event reporting

Based upon the number of responses to each of the above issues at the public hearing and in comments submitted afterward, it was thought likely that the first guidance from the FDA would address the space limitation issue

At the November, 2009, public hearing, the space limitation question was addressed 43 times by speakers, more than any other question. The same was true of comments submitted to the FDA as part of the public docket (see Figure 1, page 4).

In a *Pharma Marketing News* survey of readers on this issue, there were 46 comments related to space limitations (see "Overcoming Space Limitations in Social Media"; http://bit.ly/pmn93-02).

In Best Interest of Public Health

Aside from pressure by drug industry working groups such as the Social Media Working Group, FDA felt the need to issue this guidance because it "recognizes that it can be in the best interest of public health for a firm to respond to unsolicited requests for information about off-label uses of the firm's products that are addressed

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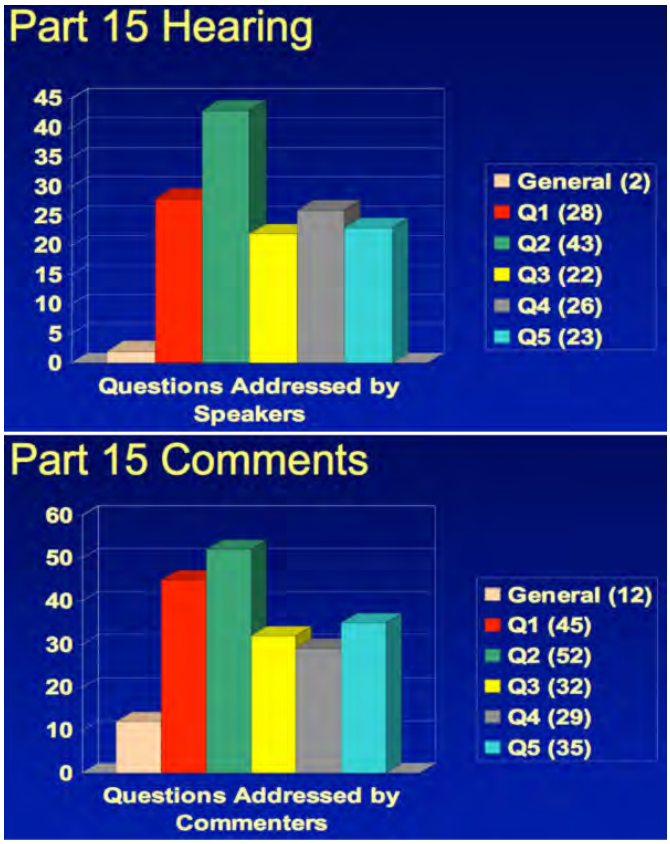

Figure 1. Comments Submitted to FDA. Source: FDA

to a public forum, as other participants in the forum who offer responses may not provide or have access to the most accurate and up-to-date information about the firm's products."

Not everyone will agree that it is the best interest of public health for drug companies to respond to unsolicited requests for off-label use of drugs. For one thing, many drug companies have engaged in illegal off-label activities such as giving doctors kickbacks for prescribing drugs off-label.

For example, in 2010, Novartis settled with the Department of Justice regarding its unlawful off-label marketing activities and bribery of medical professionals in connection with the anti-seizure drug Trileptal. Novartis agreed to pay $422.5 million to resolve the civil liability charges and the criminal charges brought against it under the whistle-blower provisions of the False Claims Act.

Also, there have been a number of surveys that indicate physicians (as well as the general public) have several other preferred sources of drug information, including off-label information (see, for example, "Are Pharma Reps Important to Docs or Not?"; http://bit.ly/pmn1017-06).

Review of Social Media Guidelines
But let's leave that issue aside for now and take a closer look at how the off-label guidelines apply to social media such as Youtube, Blogs, and Twitter.

As an aid to understanding the guidelines, Dose of Digital created a Flow Chart (see Figure 2, page 5).

Public vs. Private, Solicited vs. Unsolicited
The guidelines make a distinction between responding to PRIVATE versus PUBLIC requests for off-label information. As for handling private requests, the guidelines pretty much reiterate what the drug industry already knows.

The section regarding public requests, however, is what will be of most interest to the industry. Social media is in this category. Under that category are guidelines for handling "solicited" versus "unsolicited" requests. Of course, if requests are solicited—as defined by the FDA in these guidelines—then any response is considered promotional and subject to FDA regulations.

Youtube and Solicited Requests
The guidelines have something interesting to say about videos posted on Youtube. Specifically, it warns about responding to public comments that may be received in response to videos that a pharma company may encourage people to post about their own uses of the company's product. FDA gives this example:

> "A firm asks or otherwise encourages users to post videos about their own uses of its product on third-party video-sharing sites (e.g., YouTube), which may result in video postings about an off-label use of its product. If the firm's initial request for posting of videos results in any questions about off-label uses, or if any off-label video posting made in response to the firm's encouragement of video postings results in questions about the product's off-label use, these questions would be considered solicited requests."

FDA considers requests for off-label information that are prompted in any way by a manufacturer or its representatives to be solicited. If a company responds to such "solicited requests," it must be careful because such responses "may be used as evidence of a new intended use. Introducing a product into commerce for such a new intended use without FDA approval or clearance would, under these requirements, generally violate the law."

Will this open pharma's social media floodgates? That is, will pharmaceutical companies now be confident to open up comments on their Youtube and Facebook pages? I doubt it. Most pharma companies are still waiting to know how they should respond to potential adverse event reports they may receive via comments

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before they venture into opening up comments on Youtube or Facebook.

It's not likely that pharma companies will engage in branded Youtube projects in the first place, although there has been a precedent (see " Web 2.0 Pharma Marketing Tricks for Dummies"; http://bit.ly/pmn68-02).

Blogger Example of "Solicited Request"
FDA cites this example of how a "solicited request" can be generated from a blogger:

> "If a firm sends out packets of information to known bloggers or online consumer reviewers and encourages them to write about an off-label use of its product on third-party sites and this then provokes a discussion about that off-label use, any requests inquiring about the product's off-label use as a result of these blogs, whether posted as comments to the third-party site or directed to the firm, would be considered solicited requests."

Although I have not heard of a pharma company "encouraging" bloggers to write about off-label uses, I do know that some companies have invited bloggers to vacation sites (see "A Call for Pharma Social Media Transparency Guidelines for Patient Bloggers"; http://bit.ly/ymv5Fx). What they discuss behind closed doors is not known to me or to the FDA unless there is a blogger "mole" present.

Proving Solicitation is Difficult
So, how would FDA prove that the company "encouraged" off-label discussion?

One way is to examine the contents of the "packets of information" sent to the bloggers. If that packet includes off-label information, then FDA can make a case that the company encouraged the blogger to write about it.

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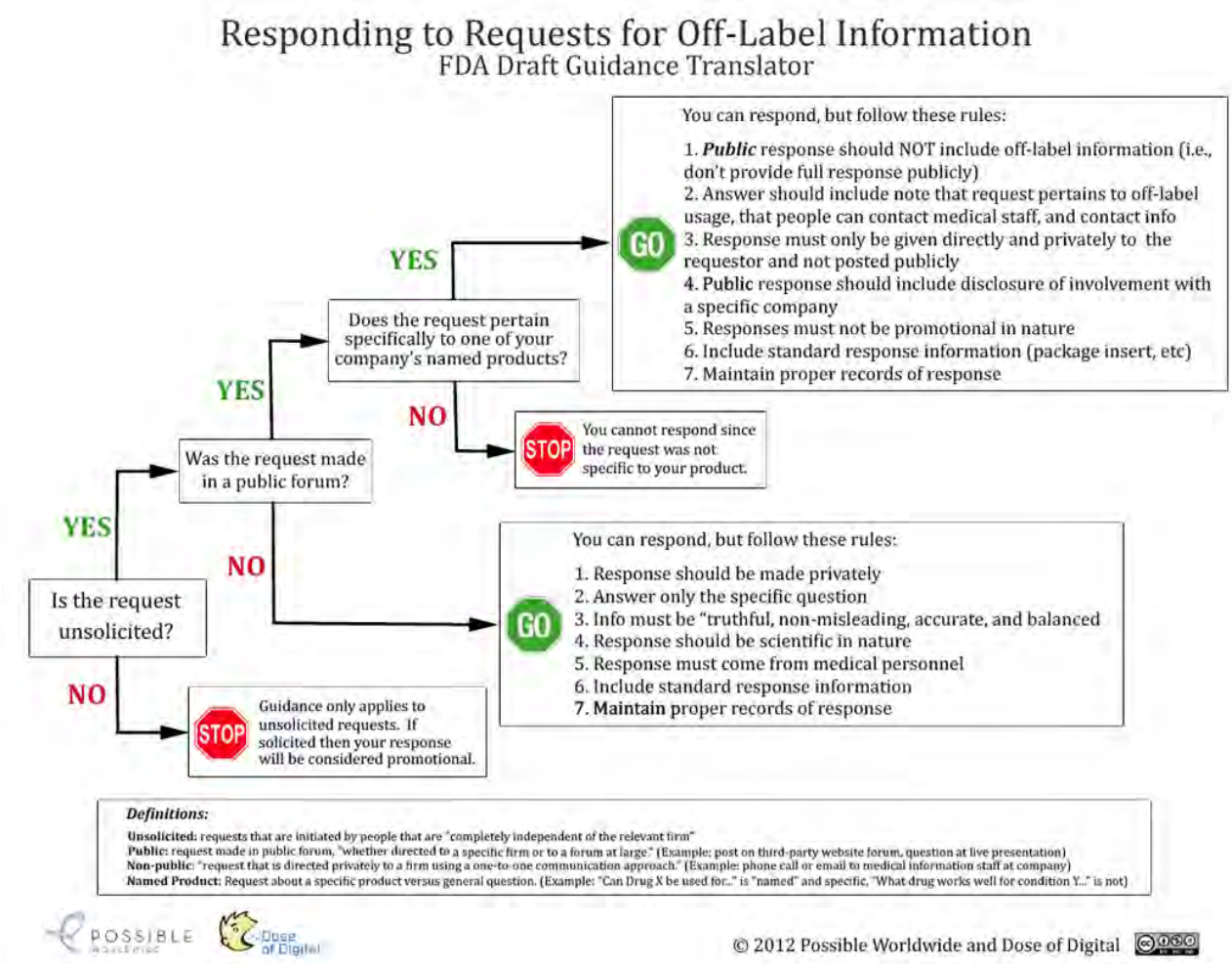

Figure 2: FDA Guidance Translator. Find a full-page PDF version here: http://bit.ly/zuw0VO

(See "BI Masters the Art of WOM through Its 'Parrots,' er, Spokespersons"; http://bit.ly/zLSsOm, for a similar situation involving BI). The guidelines do NOT get into this level of detail, which is unfortunate and supports industry's claim that FDA guidance is often "unclear."

Twitter Example of "Solicited Request"
FDA cites this example of a "solicited request" made via Twitter:

> "If a firm announces results of a study via a micro-blogging service (e.g., Twitter) and suggests that an off-label use of its product is safe and effective, any comments and requests received as a result of the original message about the off-label use would be considered solicited requests."

Many pharma company Twitter accounts have been used to announce results of studies related to unapproved uses of Rx drugs. Some tweets may have made efficacy claims, but I am not aware of any that claimed the product was "safe." I am not sure from reading the guidelines how FDA would view such tweets.

With regard to solicited requests via social media, FDA's guidance does not offer any real world examples or anything that is not completely obvious to most pharma marketers.

Unsolicited Requests via the Internet
Of greater interest to the industry are the examples FDA gives for how drug companies should respond to "unsolicited" requests via social media. It should be noted, however, "unsolicited" adverse event reports, not "unsolicited" off-label comments have stymied the industry (see "Solving the Social Media Adverse Event Reporting Problem"; http://bit.ly/pmn93-04). We'll have to wait for further guidance to deal with that real world problem.

How should pharma respond to unsolicited requests received via public Internet sites and social media?

FDA puts limits on how to respond to such requests on public sites. FDA voiced this concern:

> "[public information] posted on websites and other public electronic forums is likely to be available to a broad audience and for an indefinite period of time [and] that firms may post detailed public online responses to questions about off-label uses of their products in such a way that they are communicating unapproved or uncleared use information about FDA-regulated medical products to individuals who have not requested such information. In this circumstance, communications to persons who have not requested information may promote a product for a use or condition for which FDA has not approved or cleared. FDA is also concerned about the enduring nature of detailed public online responses to off-label questions because specific drug or device information may become outdated (e.g., new risk information may become available)."

In general, FDA's position is that "a firm's public response to public unsolicited requests for off-label information about its named product should be limited to providing the firm's contact information and should not include any off-label information."

That eliminates a "loop hole" I often worried about; namely, an anonymous agent of a pharmaceutical company can post a request for off-label information and initiate a discussion that includes information posted by the pharmaceutical company itself.

FDA suggests that a drug company handle such public requests through private channels after the requester follows up to the contact provided with a private request that will then be handled "offline." FDA says:

> "The firm's public response should convey that the question pertains to an unapproved or uncleared use of the product and state that individuals can contact the medical/scientific representative or medical affairs department with the specific unsolicited request to obtain more information.
>
> "The firm's public response should provide specific contact information for the medical or scientific personnel or department (e.g., e-mail address, telephone number, facsimile) so that individuals can follow up independently with the firm to obtain specific information about the off-label use of the product through a non-public, one-on-one communication."

Private Responses and Serving the Public Interest
Regarding responding to public requests; eg, via social media, FDA says:

> "any substantive communication about off-label uses for the product, in response to the original unsolicited off label question, should occur solely between the firm and the individual who made the request," says FDA. "Regardless of the fact that the original, unsolicited off-label question may have been available to a very broad audience, the firm should not make its detailed response with off-label information publicly available within the same forum."

Unfortunately, although this may close the "loop hole" I mentioned above, this method of responding individually has a couple of negative implications.

First, private responses may not serve "the best interest of public health" because "public" means a bunch of people, not one person at a time. On the one hand, FDA believes responding to unsolicited requests for information about off-label uses of the firm's products

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serves the public interest because the firm has "robust and current information about their products." On the other hand, firms cannot distribute this information "publicly."

Second, responding privately requires more resources and expenses. Many people over the course of time may have the same questions. Instead of being able to use the power of the Internet to answer all these questions in a single message, each must be handled separately. See “The Burden of Responding”, right.

Sales and Marketing May be Seen, but Should NOT Be Heard From!

However the response is made, the FDA believes that

> "Responses to unsolicited requests for information should be generated by medical or scientific personnel independent from sales or marketing departments. FDA recommends that medical or scientific personnel have specialized backgrounds in responding to unsolicited requests for information, including important training, such as appropriately narrowing questions, tailoring responses only to the specific questions being asked, providing unbiased responses, and properly documenting responses.”
>
> "By contrast," says FDA, "because sales and marketing personnel are focused by training and experience on promoting a firm’s products, FDA recommends that sales and marketing personnel have no input on the content of responses to unsolicited questions or requests for off-label information."

The Burden of Responding

FDA estimates that approximately 400 firms respond annually to approximately 40,000 non-public unsolicited requests for off-label information made directly and privately to them as well as to public unsolicited requests for off-label information, including those that firms may encounter on emerging electronic media. FDA estimates that it will take firms approximately 4 hours to provide responses to each unsolicited request for off-label information as recommended in the draft guidance.

FDA also estimates that approximately 40,000 records will be maintained for all responses to non-public and public unsolicited requests for off-label information, and that each record will take approximately 15 minutes to prepare and maintain.

Docket Open for Comments

The FDA has opened a docket to accept comments to these draft guidelines. See [Docket No. FDA-2011-D-0868] (http://1.usa.gov/z1bi6E). Submit comments before March 29, 2012 on www.regulations.gov (specifically, here: http://1.usa.gov/wzMHP9).

It should be noted that in the *Pharma Marketing News* survey submitted to the FDA (http://bit.ly/ggz7o), there were quite a number of comments regarding how to handle off-label information posted online.

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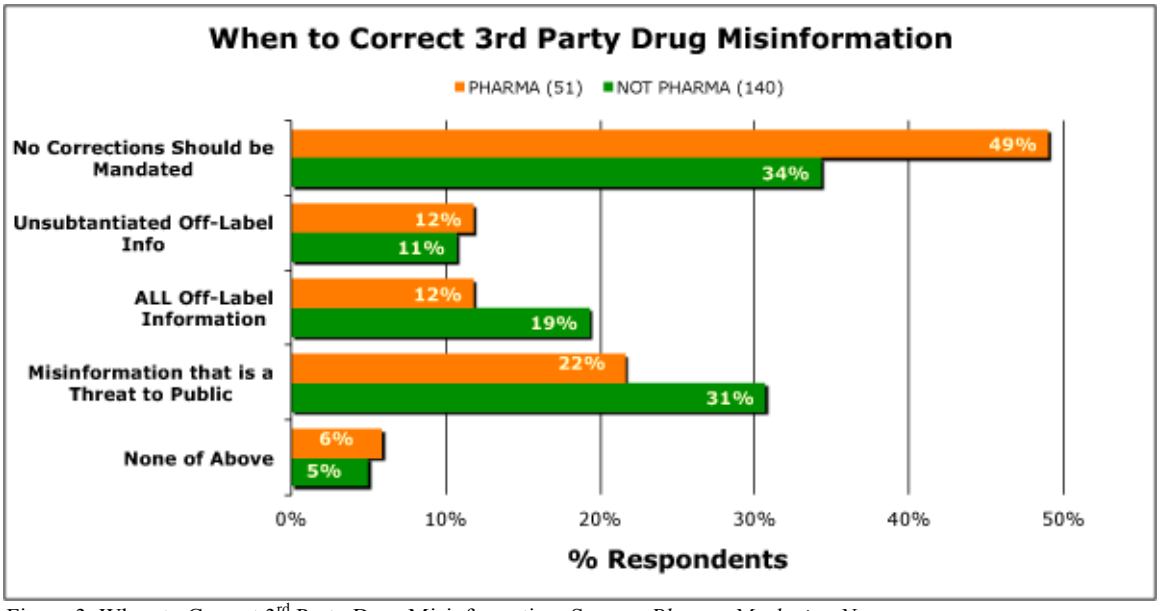

Figure 3. When to Correct 3rd Party Drug Misinformation. Source: *Pharma Marketing News* survey.

In relation to Q #3: "What parameters should apply to the posting of corrective information on Web sites controlled by third parties?", survey respondents were given a number of specific "misinformation scenarios," including 2 that related specifically to off-label comments.

Some comments from survey respondents included:

> "Unfortunately comments about a products benefits, it side effects , adverse events and /or off label use are taking place now anyway "offline". Now with online access to comments, at least the comments can be monitored for action and response if information is incorrect or unbalanced or illegal (off-label)."
>
> "Companies should be responsible for the communications they produce and pay for. They cannot be responsible for user-generated content. If it is user-generated content on digital media they host or financially support, companies should monitor this content carefully and perform due diligence with regard to user-generated off-label content or potential safety issues."
>
> "Create a reporting system to alert/address serious off-label use cases, consumer protection hotline style."
>
> "Imminent danger issues should be determined by FDA or other independent group; not the company. They should be corrected. Off-label claims should be corrected, but the forum for such correction is the challenge. Basically, if the drug companies want to play in the social media arena, they need to devote human resources to truly participating in those places. This will include discussion, correction, and other dialogue."
>
> "Not sure that off-label claims need to be corrected so much as pointed out that the indication is not FDA approved."
>
> "Who would decide what is of real or imminent danger? Regarding off-label claims supported by peer review, Medicare and many insurance companies accept this info for funding many new drugs, particularly in oncology, so why should a company try to correct this. Finally, it would be difficult for a company to know of all the potential off-label claims and uses that occur every day, several of which occur when drugs are used in combination therapy and it is another drug that is being used off-label, thus making both products' use off-label. As well, there is every time a different dose is used based on the treating physician's judgment. It would be impossible to monitor this, let alone take corrective action."
>
> "Example: Pharmaceutical Company X makes drug B that cures Y. The site has links to Y support group. On the Y support group one member writes "did you know drug B also works to cure Z. That's what members in a support group do they talk openly. Is Company X sell off label? No. Is company X responsible? No. Can the member get the drug to cure Z? Maybe. From a doctor? Not without consent. Should the links be allowed yes."

Legal Challenges

Some drug companies (eg, Pfizer) would have preferred new legally-binding regulations rather than guidelines (see, for example, "Pfizer Asks for New FDA Regulations, Not Guidance, for Social Media"; http://bit.ly/cqzWPJ). The industry might also challenge these guidelines on legal grounds (see, for example, "Pharma Turns Up the Heat on Off-Label 'Free Speech' Chilled by FDA - Implications for Social Media Marketing"; http://bit.ly/pmn1017-05 and "FDA Social Media Guidelines May Be Moot If This Court Decision Holds Up"; http://bit.ly/pmn111-03).

These guidelines are just the first attempt by the FDA to address some of the issues mentioned in the above comments. Obviously, the guidelines have not answered all the questions and taken account of all the possible scenarios where off-label information is published online. The example where a drug company links to a forum that may contain off-label information is a case in point.

As with all guidances, FDA warns "Firms may choose to respond to unsolicited requests for information about off-label uses of their approved or cleared products in a manner other than that recommended in this draft guidance. Such activity would not constitute a per se violation of the law, but could potentially be introduced as evidence of a new intended use."

Pharma Marketing News