Responding to questions on off-label uses of medical devices and drugs without breaking the US rules on promotion

Kimberly Bessiere Martin explains why companies are concerned by the Food and Drug Administration's proposals on how they may respond to unsolicited requests for information on off-label uses of their products.

As GlaxoSmithKline's recent $3 billion settlement with the US government illustrates, the intersection of permissible off-label use of medications or medical devices by physicians with the impermissible promotion by a manufacturer of its drug or device for an off-label purpose presents challenges for companies[1].

While the Food and Drug Administration has recognised that "off-label use or treatment regimens may be important therapeutic options and may even constitute a medically recognised standard of care", manufacturers are prohibited from promoting their products for uses that are not approved uses as stated in the medication or device labelling. This is true even though physicians are allowed to prescribe medications and devices for off-label uses. As a result, drug and device companies often receive requests for information from physicians and consumers relating to off-label uses of prescription medications and devices. The FDA has recognised that manufacturers have scientific and medical departments that maintain large bodies of information on the company's products including information relating to off-label uses of its products.

As the GSK settlement illustrates, however, off-label promotion results in stiff criminal and civil penalties. Manufacturers must take care that responses to inquiries about off-label uses of their products do not cross the line into off-label promotion. Navigating these waters has always been a challenge for companies and it has become particularly more so with the advent of electronic and social media.

Concerns over the draft guidance

The FDA has provided guidance over the years as to permissible responses to off-label inquires. Most recently, in December 2011, it issued for consultation draft guidance entitled: Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices[2,3]. This draft guidance was intended to update and clarify the agency's policies on unsolicited requests for off-label information and to provide guidance relating to requests through electronic or social media. The FDA gave stakeholders until 29 March to comment on the draft document. Over 35 comments were lodged by biopharmaceutical companies, trade groups, physicians and other interested parties[4].

Respondents to the consultation raised several concerns. A key focus was the FDA's recommendation that questions raised in a public setting regarding off-label topics be answered only through non-public response. This recommendation, which had not previously been set forth in any regulatory document, emerged as a common area of concern because of the potential chilling effect it could have on scientific discourse and medical education[5-9]. Under the recommendation as currently worded, for example, a question about an off-label use by an attendee at a live presentation could not be answered orally by a speaker deemed to be speaking on behalf of the manufacturer. The draft guidance recommends that this type of inquiry be responded to in a one-on-one setting and in writing; thus, no provision is made for an oral response at a live presentation. As one respondent noted, "the applicability of the guidance is too broad, in that it fails to distinguish the venue in which the off-label request is made, and other circumstances regarding the request"[10].

The requirement that public questions regarding off-label topics be answered only through non-public responses raises the possibility that companies might not be able to correct misleading information or convey key safety data in public settings such as major medical meetings. As a result, under the currently worded guidance, an off-label inquiry posing a patient safety situation could not be publicly corrected to the group that heard the inquiry. The respondents requested that the FDA clarify the guidance such that it differentiates between requests in a commercial or non-scientific setting as opposed to requests during scientific exchange of information[11].

Likewise, there were concerns that the draft guidance would prohibit a company's ability to respond to non-public requests that occur in situations that are not one-on-one settings, such as where a manufacturer has a request to respond to one physician who intends to share the information with a group[12]. Again, the FDA has been asked to clarify that medical staff should be able to respond to questions posed by healthcare providers as a part of scientific exchange[13].

In addition, the ban on speech of this nature in a public setting has raised concerns relating to infringement on free speech rights under the First Amendment of the US Constitution. Specifically, because the draft guidance contains content- and speaker-based restrictions, concerns were raised that the restriction runs foul of the decision of the Supreme Court in *Sorrell v IMS Health Inc*, in which the court struck down a Vermont law prohibiting sales of prescription histories to pharmaceutical companies for promotional purposes but not to other interested parties. The FDA has been urged to reconsider its draft guidance in light of the *Sorrell* decision and to revise the document "to propose standards for responding to unsolicited requests for off-label information [that] are constitutional. . . "[14].

Avoiding prompting a request

Another recommendation in the draft guidance that causes manufacturers concern involves the definition of unsolicited request, which provides that the request must not be "prompted in any way" by the company. This definition could conceivably encompass inquires prompted by a scientific article detailing the unapproved uses of a product which was sponsored in some way by the manufacturer as a part of legitimate scientific exchange. In addition, off-label questions may arise as a result of on-label discussions between a company sales representative and a healthcare practitioner. The current draft guidance could result in such a question being interpreted as a result of or prompted by the on-label discussion with the sales representative. Several respondents requested that the FDA clarify the guidance to reflect that off-label requests arising in such situations are not solicited requests for information[15].

There has also been concern over a recommendation in the draft guidance that even a statement not made by the company and which the company cannot control, such as a posting to a third-party site such as YouTube, can result in liability to a company[16]. The draft guidance provided that if the company had encouraged users to post videos or comments about their use of the product and those posts resulted in the mention of an off-label use, then such a posting would be considered to have been prompted by the company. The prospect of companies being exposed to the risk of significant penalties for off-label promotion as a result of comments over which they have no control is an unsettling one, and many respondents believe such penalties are unnecessary to achieve the goals of the draft guidance. Numerous

requests have been made for clarification of this portion of the draft guidance. In its comments, the US drug industry association, Pharmaceutical Researchers and Manufacturers of America, has specifically called for the FDA to issue draft guidance devoted to the issue of social media as the FDA had announced it would in September 2009[17].

In all, the comments from companies to the draft guidance indicate that the document addresses some areas on which manufacturers had sought clarity; however, in several instances, the draft guidance creates additional questions and concerns. In particular, recognising the need for public response to requests for off-label information as a part of scientific discourse is a chief concern, which should be addressed in the final guidance.

In light of the penalties that manufacturers face for off-label promotion, the FDA's goal should be to provide a clear understanding of the permitted practices with regard to requests for off-label information and the use of social media in its final guidance.

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