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Solving the Social Media Adverse Event Reporting Problem

Is It Just Too Much "Noise" to Sift Through?

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Pharmaceutical marketers often claim to be prevented from engaging in online conversations with consumers because of the difficulty and uncertainties involved in dealing with adverse events (AE) reported via social media. Many presenters at FDA's November 2009 public hearing on the Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools addressed this problem and offered solutions (see "Social Media Adverse Event Reporting Safe Harbors"; PMN Reprint #89-01; http://bit.ly/o4gAx). This article reviews the comments submitted to the FDA after the meeting.

The FDA asked for public comments regarding how pharmaceutical companies should monitor and process AEs on the Internet and social media sites. The questions it asked were:

1. How are entities with postmarketing reporting responsibilities and other stakeholders using the Internet and social media tools with regard to monitoring adverse event information about their products?
2. How is adverse event information from these sources being received, reviewed, and processed?
3. What challenges are presented in handling adverse event information from these sources?
4. What uncertainties are there regarding what should be reported from these sources to meet FDA adverse event reporting obligations?

AE Monitoring Policies

No drug company wants to be responsible for proactively monitoring the entire Internet for potential adverse events. Most agree that this kind of monitoring should only be done on company-owned sites and should follow the same rules that apply to other media; namely, "if a company representative becomes aware of an adverse event on a non-company related Internet site, that information must be evaluated for potential reporting to the FDA."

Johnson and Johnson (JNJ), in its comments to the FDA, said "Companies should have policies in place addressing how to evaluate their own websites for potential adverse events…" a sentiment shared by other pharma companies.

The *Pharma Marketing News* survey (PMN Survey), "WANTED: Answers to FDA's Questions Regarding Pharma's Use of Social Media," results of which were submitted to the FDA, asked respondents to choose one of the following responses regarding FDA's question about how adverse event information from social media sources are being received, reviewed, and processed by drug companies:

- Special group within the company is responsible for receiving, reviewing, and processing AEs (Internal Group)
- Receiving and processing AEs is outsourced to a specialized agency; review is handled in-house to determine which AEs need to be reported as required by law (Outsourced)
- The information is usually incomplete and does not meet the requirements for submitting a meaningful AER (not actionable)

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FDA Clarifies Pharma's AE Reporting Responsibilities

[Source: Notice of Public Hearing, Docket FDA-2009-N-0441, http://bit.ly/3O7MPE]

FDA's expectation is that "entities responsible for reporting will promptly review all adverse event information received or otherwise obtained, which potentially includes information from the Internet and social media tools."

According to FDA's March 2001 draft guidance for industry entitled Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines (available at http://bit.ly/DJwg5), adverse experience information that is submitted via the Internet to an entity with postmarketing reporting obligations under 310.305, 314.80, and 600.80 should be reported to FDA if there is knowledge of the four basic elements for submission of an individual case safety report, namely:

1. An identifiable patient
2. An identifiable reporter
3. A suspect drug or biological product
4. An adverse experience or fatal outcome suspected to be due to the suspect drug or biological product

The draft guidance also states that those entities should review any Internet sites *sponsored by them* for **adverse experience information**, but are *not responsible for reviewing any Internet sites that they do not sponsor*; however, *if they become aware of an adverse experience on an Internet site that they do not sponsor, they should review the adverse experience and determine if it should be reported to FDA*.

- We have no SOP (standard operating procedure) for receiving, reviewing, and processing AEs from these sources (No SOP).
- None of the above
- Don't Know

The choices of respondents are shown in Figure 1, below.

Technology Can Help

JNJ proposed that the technology of the Internet be used to assist in routing potential adverse events to the FDA. "In view of the nature of online communications," said JNJ, "FDA should consider an alternative, and potentially more effective, approach for company-owned sites that would use the technology of the Internet to greater advantage." One solution on a company site might be to direct adverse event reporting to an appropriate place by providing a "prominent link for reporting adverse events that will provide reporting forms and/or appropriate contact information for direct communication." JNJ was vague about who the appropriate contact should — FDA, a company's pharmacovigilance group, a 3rd party, etc.

Identifying the Reporter

Many comments addressed the problem of meeting all four of FDA's criteria for reporting AEs (see box, pg 2) when applied to events discovered on social media sites. The most-often cited problem was how to identify the reporter, which was a problem cited by 82% of respondents to the PMN Survey.

Novartis suggested that FDA include a NEW parameter in its planned guidance for regulation of social media use by pharma; ie, an identifiable reporter must be "privately contactable"; that is, it is possible to readily communicate directly with the reporter without posting questions to a public forum to obtain more information. "An email address without any further identifying information (such as a name, address, or phone number) should not constitute an identifiable reporter," argued Novartis, "and a lack of further information (such as age or gender or relationship to the reporter for an identifiable patient) should not constitute an identifiable patient."

Interestingly, AstraZeneca (AZ) does not seem to agree. For purposes of the Internet and social media, AZ proposed that the "FDA define a valid reporter as one who has provided an e-mail address or other effective form of contact information (such as a Facebook contact)."

Solicited vs. Spontaneous AERs

Novartis commented about the distinction between "solicited" and "spontaneous" adverse event reports. The distinction has a bearing on how these need to

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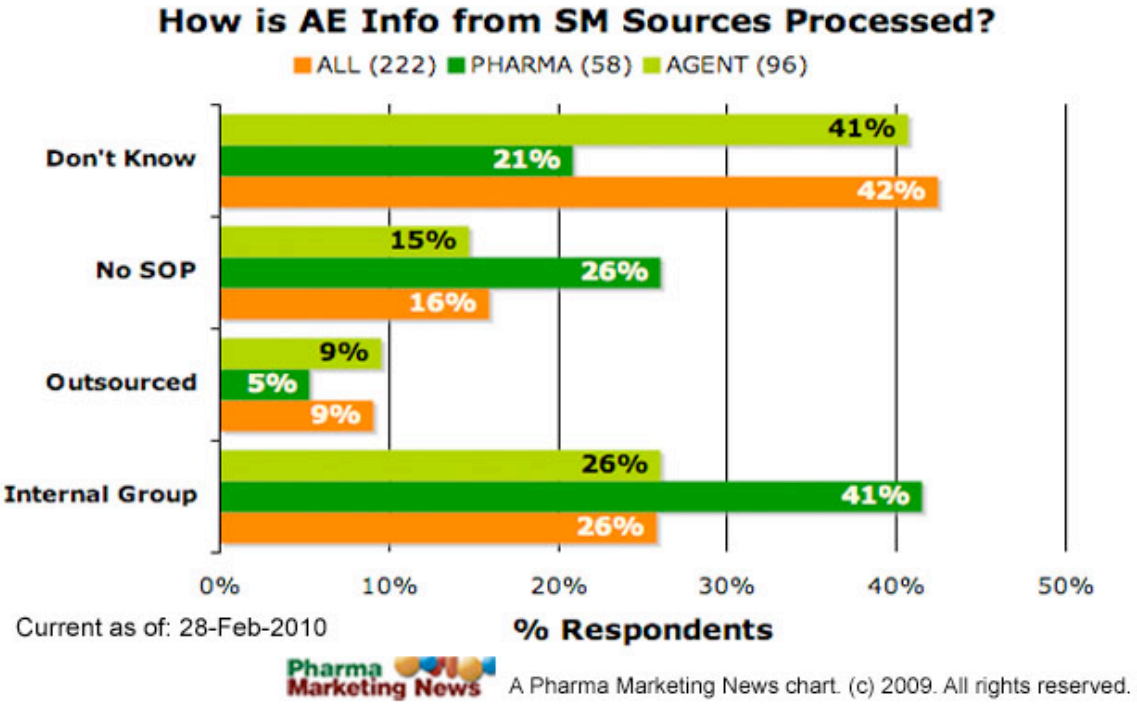

Figure 1. Results from PMN Survey regarding processing of AE information from SM sources.

be reported to the FDA. Novartis wants manufacturers to have the "flexibility to determine which category applies to individual social media programs." Basically, if a pharma company's social media program "actively encourages" patients to describe their experiences with a drug, then any adverse events posted should be considered "solicited."

Please see "Are J&J Agents Trolling for Adverse Events on the Internet?" (page 5) and determine whether or not the AEs unearthed in the process should be consid-ered "solicited" or "spontaneous."

AZ agrees with Novartis on the issue of "spontaneous" vs. "solicited" adverse event reports. It recommended that "solicited reports be limited to those collected from organized data collection systems including any information gathering systems that a sponsor uses. In contrast, we urge to agency to consider any unsolicited reports as spontaneous reports."

Terms of Use

Sanofi-Aventis (S-A) proposed including a specific statement in a company's Terms of Use policy regarding adverse events. S-A proposed this wording: "This page is not intended for the reporting of side effects associated with the use of medical products. If you, or someone you know, have possibly experienced a side effect while taking [product], please contact our Drug Safety department at [toll-free telephone number, fax number, e-mail address]. You are also encouraged to report negative side effects of prescription drugs to the FDA. To do so, visit [Include appropriate FDA contact information – web site URL and toll-free number – for reporting adverse events]."

Recently, S-A had occasion to use such language in a disclaimer on its VOICES Facebook page, the wall of which accepts comments from the public. Unfortunately, a disgruntled patient who claims to have permanent hair loss after taking TAXOTERE, flooded the VOICES wall with posts and images of her bald head (see "Sanofi-Aventis Updates Facebook Site with Disclaimer, But Shirley Still Posting About Her Side Effects"; http://bit.ly/9xbRWB).

Tools for Monitoring AEs

S-A also commented on how adverse event information from social media sources should be received, reviewed, and processed. Respondents to the PMN survey suggested several techniques (see Figure 2, pg 6).

S-A said that monitoring of social media sites can be accomplished via "passive (conversation listening) or active (free flowing conversation) participation through in-house staff or contracted vendors." S-A takes the position that drug sponsors should monitor (through active participation) their own websites for potential adverse events. It also suggests the following monitoring parameters:

- Development of search terms (product/disease specific) and timeframes
- Development of process for identifying and transferring potential adverse events to the company's Pharmacovigilance department
- Training monitoring staff (in-house or vendor) on the aforementioned process
- Training vendors on company standard operating procedures (SOPs) for adverse event reporting
- Internal/vendor audits to assess compliance

Given S-A's recent Facebook experience, it's not likely that S-A is waiting for FDA guidance before fully implementing this plan. You can hear more about that by listening to a April 6, 2010 Pharma Marketing Talk podcast: "What Sanofi-Aventis Learned from Its FaceBook Experience & What the Experts Recommend It Do Now"; http://bit.ly/bkPq6y.

What Sites Should be Monitored?

Abbott appears to plan on monitoring the entire Internet and all social media sites for adverse events according to its comments to the FDA. "Companies should develop a monitoring framework/plan to monitor IN/SM [the internet and social media, inclusive] for mentions of their company and their products, which would include, for example, information related to product adverse events and complaints." Abbott, however, qualified that by saying "an important element of agency guidance is recognition that with any monitoring plan the IN/SM environment changes rapidly and can not be effectively monitored in its entirety."

Abbott also suggested that the FDA should make available a "user-friendly system through which web users may report events directly to the FDA as was suggested by speakers at the November 12-13, 2009 Part 15 hearing on this topic. For more on that, see "Social Media Adverse Event Reporting Safe Harbors"; PMN Reprint #89-01; http://bit.ly/o4gAx

AZ definitely does not believe that pharmaceutical companies should be responsible for monitoring the entire Internet/social media space for adverse events. "We do not believe that it is practical or helpful to attempt to monitor the entire Internet for possibly reportable adverse events," said AZ.

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Are J&J Agents Trolling for Adverse Events on the Internet?

John Mack
Published on Pharma Marketing Blog, September 22. 2009

An interesting post made on the Arthritis Foundation Forum by "Chris Braile" suggests that JNJ may have agents trolling the Internet to find negative comments about its products—including adverse event reports. "Chris Braile" claims he/she is a am a member of BzzAgent, an online networking site that offers free trials or products to people as a means of marketing. Here's the post:

> I am a member of BzzAgent, an online networking site that offers free trials or products to people as a means of marketing. They basically send you info and either coupons or free samples (or both) to help you convince other people to use the product in question (i.e. I did one for dog food and one for an OTC anti-histamine). Kind of like grassroots marketing. You only get offers targeted for your demographic group, of course.
>
> I just took a survey through BzzAgent for Johnson & Johnson, which basically was more of a "contract" where if chosen, I agreed to notify J&J if I became aware of any negative talk about their products. It was all couched in terminology implying that I would only be doing this as a representative of J&J, and only because it was "required by law" for all J&J employees to report any and all "adverse events" associated with use of J&J products. It mentioned that I would be under obligation to report anything I heard, even if on the internet, including contact information for the person stating the problem. Nothing about getting their permission to relay that information, which stuck out given the detailed, "legal" approach of the survey.
>
> So, basically - agreeing to be a "troll"

First, this may be part of the answer to FDA's first question about AER (Adverse Event Reporting; see pg 2). JNJ seems to take it very seriously, although we cannot be sure this is true—I cannot verify who the poster is or contact him/her to get verification. This illustrates the main problem with tracking AEs online: you often cannot identify the person making the report or the patient who suffered the AE (see FDA's question #4, pg 2).

According to the PMN Survey, 71% of respondents agree that "Usually, there is uncertainty regarding the true identity of the reporter" and 73% agree that "Usually, there is uncertainty regarding the true identity of the patient."

"Chris Braile" points out another problem: relaying personal information gathered on the Internet to a pharmaco by consumer agents may violate (or seem to violate) the privacy of the reporter. Chris seems to think it is sleazy to require him/her to do this (assuming there is any personal information to report).

It is not known whether the JNJ contract with Chris says that reports should be made ONLY if there is knowledge of the four basic elements for submission of an individual case safety report (ie, identity of the reporter, identity of the patient, identity of the drug, and certainty of seriousness of the event). You cannot expect a consumer hired by BzzAgent to know if all the requirements are met. Therefore, JNJ is asking these consumers to scoop up and report everything, which makes it necessary for JNJ to sift through these "trolled" reports to find any that meet the requirements for reporting to the FDA. No wonder many pharmacos find this too daunting a task and give up on getting involved in social media.

"Therefore," said AZ, "we recommend that FDA clarify in guidance that sponsor obligation for monitoring extends only to company-controlled, hosted online communications."

At least one company, Bayer Healthcare, let the Pharmaceutical Research and Manufacturers of America (PhRMA) speak for it regarding adverse events. PhRMA essentially takes the position that manufacturers should only be required to monitor web sites they control for reportable AEs regarding their marketed products. "Manufacturers are unable to monitor every web site, blog, or chat room for adverse events," said PhRMA, "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."

Patient Privacy Issues Cited

PhRMA also mention patient privacy concerns in its comments. "In order to help assure reliable AE information from online sources, and also to respect patient and reporter privacy," said PhRMA, "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."

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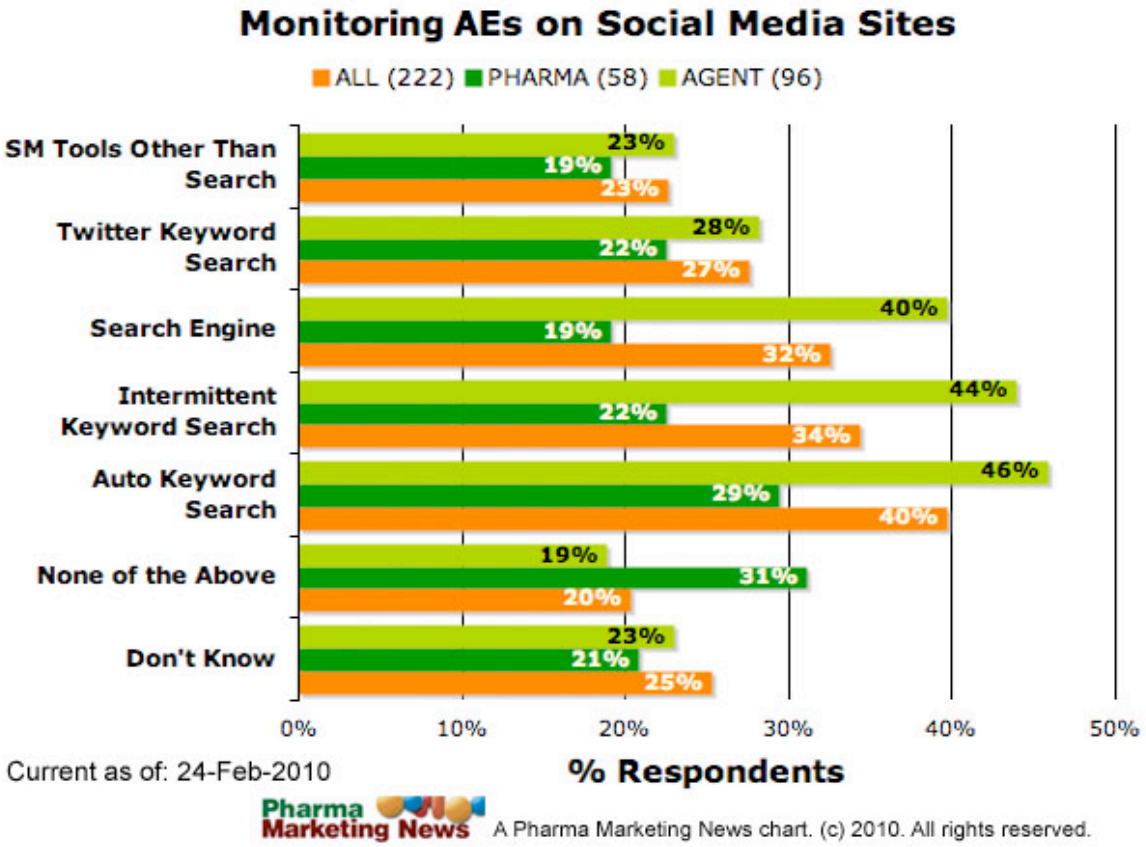

Figure 2. Results from PMN Survey regarding monitoring AEs on SM sites

Eli Lilly made an important point regarding exposure of personal health information on public sites when attempting to perform adverse event reporting due diligence. “National and international privacy laws … may preclude sponsors from attempting to obtain follow-up information,” said Lilly. “Public opinion must also be taken into consideration, as many people may have an expectation that discussions that take place in social media remain anonymous, and any attempts to request personal information create significant mistrust in any company or other entity attempting to obtain that information.”

Reporter “Noise”

PhRMA contends that 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. 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. 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.”

Pharmaceutical companies will be forced to deal with a lot of “noise” on social media sites such as askapatient.com, a social network site where people can rate the medicines they are taking. The site is a virtual treasure trove of adverse events reported by patients! Over 1,000 patients taking BONIVA, for example, gave the drug a rating of 1.3 on a scale of 1 (Low) to 5 (high) and submitted comments (ie, “noise”) such as this:

"I am filling this out because my Mom took Boniva for many years. I now realize her death was in part due to her taking Boniva. She had so many of the side affects listed and I wish I had known while she was alive that they were caused by Boniva, so I could have taken her off of this poison.I suggested that she go on this-I feel so guilty. I hope this report helps others recognize what this drug does to your body. It certainly did not make my mother's bones stronger. She had so much muscle pain all over, but especially her back, broke her pelvis and had fratures in 4 vertebrae while taking Boniva."

You can read more about this on Pharma Marketing Blog (“What If, God Forbid, Sally Field Broke Her Leg?”; http://bit.ly/9aHDh5).

How Frequently Are AEs Mentioned in Social Media?

PatientsLikeMe (PLM)—an online community for people with "life-changing conditions"—submitted comments to the FDA about its experience with adverse events reported by its members. In short, PLM found that 7% of 500 randomly selected posts from the 364,000 posts contributed by patients within the PatientsLikeMe Forum during 2009 incorporated all four elements required for reporting an adverse event (an identifiable patient, a specific medication, an identifiable reporter and a reaction). This is 35 times the rate in a frequently cited Nielson study, which found only one such message in its random sample of 500 posts.

PLM said its study data "would extrapolate to approximately 20,000 events per year in our Forum alone. If we were to include data collected from all other sources (e.g. symptoms, treatment evaluations, side effects, annotations, private messages, research surveys) within PatientsLikeMe then the volume would be much higher. Given our current membership of approximately 55,000 patients representing only 15 diseases among hundreds that we plan to build, the contribution to drug safety and public health could be substantial."

PLM also reported that if patients were given the right tools that facilitate access to their personal medical data, the time required to report an AE to the FDA could be reduced by as much as 44% (from 36 minutes down to 20 minutes). In a pilot program in its 10,000 plus member Multiple Sclerosis community, 195 AERs were generated in one year. PLM found that "75% of these voluntary patient reports contained the four required elements for an adverse event and 24% reported a serious outcome."

Is this good or bad news for pharma companies hoping to cash in on the social media bonanza? Surely, many were bouyed by the Neilson data, which held out hope that AE's reported by patients on company-controlled or sponsored SM sites were not an insurmountable problem. The PLM data could bash those hopes.

“Social media environments that engage in promoting FDA-regulated medical products should take responsibility in partnership with pharmaceutical clients to proactively provide effective adverse event data to FDA as well as enhance consumer understanding of adverse events and drug safety issues,” said PLM.

But if drug safety is important for pharmaceutical companies, then they should welcome the oppor-

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tunity that sites like PLM offer to improve the safety of their products. "Sites that integrate data collections systems and processes to capture the richness of patient experiences with drug products have an unprecedented opportunity to improve safety and outcomes for everyone who uses these products," said PLM in its comments to the FDA.

Biopharma company UCB and PatientsLikeMe have partnered to create an online, open epilepsy community that captures real-world experiences of people living with epilepsy in the U.S. Part of this partnership includes a pharmacovigilance program to monitor the site for adverse events and report directly to the FDA adverse events associated with UCB products (see "Finally, a Drug Company Embraces Social Media, AEs Included!"; http://bit.ly/RwXyi).

Not All AERs Are Equal

Merck put forth the argument that the "amount of information from these sources [Google, Youtube, Yohoo!, Flickr, etc.] is too vast, reiterative and ever expanding to be processed for ADR reporting meaningfully and economically. The rapid, indiscriminate dissemination that occurs via social media could cause a single adverse event to be reported exponentially with enough serial distortion that would render the determination of duplicity impossible. This then provides the very real potential for signal dilution and false positive signal generation.

Merck is also concerned about "many instances where persons have deliberately spread misinformation about adverse events because of their personal beliefs, desire for notoriety, or even because they hope to benefit financially." Just ask Sanofi-Aventis about that!

Merck presents a framework to mitigate or resolve the AE repor6ting issues it discussed:

1. For company-sponsored web-based media within the sponsor's control, we propose:
   - A) Sponsors should screen areas of websites under their control for identification of suspected ADRs.
   - B) To identify any pattern related to the safety of the product from chats entered on a message board on a company controlled website, a periodic review of the message board (monthly or quarterly) should be conducted as part of the company routine signal detection process, but this information would be considered non-validated until the event can be confirmed through contact with the reporter. The definition of identifiable reporter should be "an individual that is privately contactable" (e.g. provides associated email address).
   - C) Reports from social media should be managed and assessed separately from other sources of data (e.g., randomized controlled trials, observational data, scientific literature, and spontaneous data) obtained through traditional reporting mechanisms.
2. For web-based media not under the sponsors' control, we propose:
   - A) Sponsors should not be required to monitor any web-based media not within its control.
   - B) not be required to monitor any web-based media not within its control.
   - C) Any safety data discovered by the sponsor during review of independent web-based media should be considered non-validated until the event can be confirmed through contact with the reporter. The definition of identifiable reporter for independent sites should be "an individual that is privately contactable" (e.g. provides associated email address).
   - D) During review of independent web-based media, sponsors should not be required to screen video or audio postings for adverse event reporting purposes. If the source of the video or audio posting is privately contactable (e.g., meets the definition of an identifiable reporter) then the sponsor should follow-up with the reporter and provide a toll-free telephone number and an ADR form for the relevant adverse event information to be reported.

Lilly's Pilot Study Yields Nada

Lilly also suggested that FDA create "a separate category that defines reporting requirements for internet/social media events ... that takes into consideration the value versus cost/resource burden (including opportunity costs of performing other pharmacovigilance/risk management activities), recognizing the potential significant implications for sponsors and regulatory authorities alike."

To demonstrate the value vs. burden of monitoring and processing AEs found on social media sites, Lilly undertook a pilot project with a marketed product with an established safety profile where it "listened" to blogs and social media to identify what was being said about this specific product. For purposes of the pilot ("to allow for better integration into the company's safety database") the requirements for an

identifiable reporter were modified to allow any information, including a screen name, to meet valid case criteria. When the product was mentioned it was considered a "hit". The hits were then reviewed by the pharmacovigilance and product complaint (PC) departments for assessment of qualifying AEs/PCs.

Posts related to the product from December 2008, January 2009, and the first 2 weeks of September 2009 were evaluated and produced 521 hits. Of these, there were 151 cases reporting 283 AEs.

Lilly reported that “the preparation for this pilot, case entry into the database, and safety surveillance activities consumed over 500 person hours and resulted in no new safety signals for the compound.”

No Comment from Pfizer, Sepracor

Sepracor did not spend much time commenting on adverse events. It said that “some of the other patient safety initiatives being pursued at the FDA are more likely to result in picking up signals of previously unrecognized risks.” Pfizer made no comments regarding adverse event reporting.

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