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Pharmaceutical Companies

Pharmaceutical companies fear that encouraging consumers to post publicly on social media sites will inundate them with reports of adverse drug experiences, which they may be required to file with the Food and Drug Administration or risk potential liability. Fears surrounding these reporting regulations and the FDA's lack of direction on the issue has prevented many pharmaceutical companies from taking real advantage of the spoils social media marketing has to offer today's brands. While awaiting the FDA's next moves, the authors write, we can expect that the majority of pharmaceutical companies will continue to navigate cautiously social media's waters, searching for more traditional opportunities to take a dip in when they advertise online, where greater controls on content are afforded to advertisers and regulatory scrutiny is more of a known entity.

Pharma Challenges: Adverse Event Reporting and Social Media

BY STUART L. FRIEDEL AND JOSEPH A. SENA JR.

In a world where consumers are increasingly bypassing the corner newsstand for the online App store and fast forwarding through television commercials has become a national pastime, a marketer's ability to successfully leverage popular social media platforms like Facebook, Twitter and YouTube can make or break a brand's marketing campaign. Most industries have embraced the unique opportunity afforded by social media to engage consumers in a two-way conversation, while continuing to feed them advertising content at a mere fraction of the cost of securing traditional print or broadcast media. Whether it be ''pinning'' photographs of a marketer's must-have fall fashion items to its Pinterest page or submitting summer vacation videos on a marketer's YouTube channel for a chance to win a trip around the world, brands are engaging and reengaging consumers via social media in record numbers. *So, why are pharmaceutical companies not making their fair share of tweets or developing the most talked about Facebook apps*?

Social media marketing poses unique risks for the highly regulated pharmaceutical industry. Whereas traditional internet marketing allows pharmaceutical companies to control the presentation of information on static web pages, social media functions much more interactively with consumers. Content on social media sites is unpredictable; primarily created and controlled by consumers, rather than the site-owning pharmaceutical companies that must abide by the industry's strict regulations. The pharmaceutical industry's primary regulator, the Food and Drug Administration (FDA), has yet to provide comprehensive guidance on how it would apply its regulations—most of which were created well before social media became prevalent or ex-

 ISSN

isted at all—to the marketing of prescription drugs in social media. Specifically, pharmaceutical companies fear that encouraging consumers to post publicly on social media sites will inundate them with reports of adverse drug experiences, which they may be required to file with the FDA or risk potential liability. Fears surrounding these reporting regulations and the FDA's lack of direction on the issue has prevented many pharmaceutical companies from taking real advantage of the spoils social media marketing has to offer today's brands.

This brief article will review the FDA's regulations regarding postmarketing reporting of adverse drug experiences and the consequences pharmaceutical companies may face for failing to comply therewith. Then, the article will consider what steps the FDA has taken, or still needs to take, to clarify the industry's responsibilities with respect to adverse drug experiences reported in the social media space. Lastly, this article will explore risk mitigation and monitoring issues that pharmaceutical companies must consider when deciding whether to market their brands via social media.

OVERSIGHT AND REGULATION

FDA's Responsibility to Ensure the Safety and Effectiveness of Drugs

The FDA is responsible for protecting the health and safety of the American public by ensuring, among other things, that drugs are safe and effective for their intended uses and are labeled accurately and in compliance with the law. Pursuant to its statutory mandate, the FDA regulates and monitors the approval, manufacture, processing, packing, labeling, and shipment in interstate commerce of drugs. The Food, Drug, and Cosmetic Act[1] (the FDC Act) requires that a drug manufacturer secure approval of a new drug application (NDA) from the FDA before it may commercially market the drug. In order to do so, the manufacturer must conduct investigations (e.g. clinical testing) that demonstrate that the drug is safe and effective for its intended uses and submit the results of such testing to the FDA for evaluation. The FDA evaluates the safety and effectiveness of a drug on the basis of this information, rather than its own testing. The FDA approves NDAs with the understanding that adverse reactions may become apparent only after a drug is marketed and used more widely, under more diverse conditions (i.e., concurrent use with other drugs) or prescribed for uses for which the drug was not approved (e.g., ''off-label'' uses).[2]

''Adverse Drug Experience'' and Reporting Requirements Under the FDC Act

The FDC Act requires that the FDA continue to evaluate the safety and effectiveness of drugs and, when appropriate, withdraw the NDA or change the drug's labeling based on information discovered *after* a drug is on the market and used by the general population of patients.[3] To do so, the FDA promulgated regulations,[4] which require pharmaceutical companies to submit expedited and accurate reports of postmarketing ''adverse drug experiences'' to the FDA at certain time intervals.

An ''adverse drug experience'' is defined as ''any adverse event associated with the use of a drug in humans, whether or not considered drug related, including the following: An adverse event occurring in the course of the use of a drug product in professional practice; . . . from drug overdose whether accidental or intentional; . . . from drug abuse; . . . from drug withdrawal; and any failure of expected pharmacological action.''[5] The FDA classifies adverse drug experiences into four types, each triggering different reporting requirements. Adverse drug experiences that are (i) *serious and unexpected* include those serious, but not provided for on the label (e.g., death, hospitalization, significant persistent disability/incapacity); (ii) *serious and expected* include those serious and listed on the current label; (iii) *non-serious and unexpected* include those non-serious and not provided for in the label, and (iv) *non-serious and expected* include those non-serious and already in the label.

Pharmaceutical companies are required to report information pertinent to the safety and effectiveness of the drug from any source within 15 days of initial discovery of any unexpected side effects or injuries associated with the drug not provided for on the label. All other adverse drug experiences must be reported to the FDA in quarterly periodic reports during the first three years following approval, and then, thereafter, at annual intervals.[6]

LIABILITY FOR NONCOMPLIANCE

Failure to comply with adverse drug experience reporting obligations constitutes a ''prohibited act'' under the FDC Act, subjecting the violator to potential liability as outlined below.[7] The FDA has broad authority to pursue violations of the FDC Act and its regulations; however, enforcement can generally be broken down into three types: (1) advisory action, (2) judicial action, and (3) administrative action.

Advisory Action

FDA's most common practice in response to a failure to adequately comply with adverse drug experience reporting obligations has been to issue a ''warning letter,'' citing the violation and requesting prompt and voluntary corrective action. The FDA relies on the issuance of warning letters to quickly and efficiently rectify breakdowns in adverse experience reporting requirements without incurring the costs of full scale judicial enforcement. By way of example, in May 2010, the FDA issued a scathing 12-page warning letter to Pfizer,[8] citing that the company's corrective actions to cure previously identified issues with the company's late adverse expe-

[1] Federal Food, Drug and Cosmetic Act of 1938, 21 U.S.C. §§ 301-99(d)(2011).

[2] *See* FDA Drug Safety Report, Advances in FDA's Safety Program for Marketed Drugs: Establishing Premarket Safety Review and Marketed Drug Safety as Equal Priorities at FDA's Center for Drug Evaluation and Research (April 2012), *available at* http://www.fda.gov/downloads/Drugs/DrugSafety/UCM300946.pdf (''No drug is risk-free, and it is not uncommon for new information to be discovered after a drug is on the market and being used by larger numbers of patients.'').

[3] 21 U.S.C. § 355(k).

[4] 21 C.F.R. §§ 314.80-.81 (2012).

[5] 21 C.F.R. § 314.80.

[6] 21 C.F.R. § 314.80(c).

[7] 21 U.S.C. § 331(e).

[8] Warning Letter from FDA to Pfizer Inc. (May 26, 2010), *available at* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2010/ucm215405.htm.

rience reporting and downgrading of experiences to non-serious without reasonable justification had been ineffective. The letter gave Pfizer 15 days to correct such deficiencies or potentially face judicial or administrative enforcement.

Judicial Action

If the violation is egregious enough or if a violator fails to promptly rectify a warning letter's cited deficiencies, the FDA may pursue several types of formal judicial action to obtain resolution, punish the wrongdoing and/or compensate for loss. Judicial action includes pursuing injunctions, civil monetary penalties, criminal prosecutions, and seizing unsafe products.[9]

Judicial action in the pharmaceutical industry is a big revenue maker for the federal government, having recovered nearly $2.2 billion in civil damages in 2011.[10] This does not seem to be changing, as earlier this year the Department of Justice, on behalf of the FDA, announced settlement with global health care giant GlaxoSmithKline, which agreed to pay $3 billion to resolve claims arising from the company's allegedly unlawful promotion of certain prescription drugs, failure to report certain safety data, and false price reporting practices—the largest health care fraud settlement in U.S. history and the largest payment ever by a pharmaceutical company.[11]

Qui Tam Lawsuits Under the FCA and RCO/Park Doctrine

The federal government has expressed renewed interest in less frequently used judicial actions. Under the False Claims Act (FCA), private citizens who have knowledge of fraudulent activities against the government can initiate *qui tam* actions to hold companies accountable to reimburse the federal government for such fraudulent activity. Failure to report serious adverse drug experiences to the FDA can form the basis of a *qui tam* claim. Last year, a former employee of Takeda filed two whistleblower lawsuits accusing Takeda of knowingly hiding adverse drug experiences from the FDA and firing her after she raised inquiries thereto.[12] While the suits are still pending, the publicity around the case is believed to be attracting the attention of plaintiffs' attorneys seeking additional damages in negligence.

Judicial action has typically focused on the company; however, the FDA recently called for increased prosecution of ''responsible corporate officers'' (RCO) under the FDC Act. The RCO or *Park* Doctrine,[13] allows senior-level pharmaceutical executives to be charged with misdemeanors for violating the FDC Act, even where the individual neither knew of, nor participated in, the underlying misconduct. *Park* Doctrine prosecutions have been almost nonexistent in the past 20 years; but, in February 2011, FDA published guidelines outlining criteria it will follow in recommending corporate officer prosecutions under the *Park* Doctrine to the Office of Criminal Investigations.[14]

Administrative Action

Administrative action used by the FDA in regulating failure to report adverse drug experiences includes denying or withdrawing drug approval, and prohibiting submission of any future FDA drug applications, also known as ''debarring.'' The FDA also has the authority to debar individuals and corporations convicted of certain felonies or misdemeanors (i.e., under the *Park* Doctrine) from providing services in any capacity to a person or entity with an approved pending NDA. In addition, the FDA can withhold approval of requests for export certificates, listing the targeted facility until the violations are corrected.

Expansion of Civil Liability and the *Matrixx* Decision

Though there is no private right of action for violation of the adverse drug experience reporting requirements imposed under the FDC Act,[15] such violations may be considered evidence of negligence in civil litigation. In *Matrixx Initiatives Inc. v. Siracusano*,[16] the Supreme Court affirmed the Ninth Circuit's ruling that class action plaintiffs stated a claim for securities fraud by alleging that publicly traded pharmaceutical company Matrixx failed to disclose adverse drug experience reports to its investors suggesting that its product causes a loss of the sense of smell. Even though the adverse drug experiences may not be independently verifiable, they suggested a ''reliable causal link'' between the product and a loss of the sense of smell so that reasonable investors would have viewed the adverse-event reports as significant. *Matrixx* has forced publicly traded pharmaceutical companies to re-examine how and when to disclose in their public filings reports of adverse events.

SOCIAL MEDIA MARKETING AND REPORTING ADVERSE DRUG EXPERIENCES

Lack of Enforcement Guidance

Despite the myriad of enforcement mechanisms available to address failures to adequately report postmarketing adverse drug experiences, few or no enforcement actions have been relevant to such failures in the social media space, leaving pharmaceutical companies

[9] 21 U.S.C. § 334. Note: In the context of adverse reporting, seizure for failure to comply with Postmarketing Adverse Drug Experience Reporting Regulations would only be possible if the approval of the application for the product has first been withdrawn under the conditions cited in § 304(a)(1) of the FDC Act. Seizure would then be based on failure to hold an approved new drug application.

[10] Press Release, Dept. of Justice, Justice Department Recovers $3 Billion in False Claims Act Cases in Fiscal Year 2011 (Dec. 19, 2011), *available at* http://www.justice.gov/opa/pr/2011/December/11-civ-1665.html.

[11] Press Release, Dept. of Justice, GlaxoSmithKline to Plead Guilty and Pay $3 Billion to Resolve Fraud Allegations and Failure to Report Safety Data (July 2, 2012), *available at* http://www.justice.gov/opa/pr/2012/July/12-civ-842.html.

[12] *United States ex rel. Ge v. Takeda Pharm. Co.*, No. 10343 (D. Mass. Jan. 25, 2012).

[13] *United States v. Park*, 421 U.S. 658 (1975).

[14] The criteria make up a newly added section of FDA's regulatory procedures manual called ''Special Procedures and Considerations for Park Doctrine Prosecution.'' *See* FDA, Regulatory Procedures Manual § 6-5-3 (2011), *available at* http://www.fda.gov/ICECI/ComplianceManuals/RegulatoryProceduresManual/ucm176738.htm. OCI then makes the decision on whether to refer cases to the Department of Justice for potential prosecution.

[15] *See Ellis v. C.R. Bard Inc.*, 311 F.3d 1272, 1284 n.10 (11th Cir. 2002) (''[N]o private right of action exists for a violation of the FDCA.'').

[16] *Matrixx Initiatives Inc. v. Siracusano*, 131 S. Ct. 1309 (2011).

without much of an impression as to how the FDA may chose to enforce its regulations in this media.

One of the FDA's earlier online advertising-related enforcement actions came in April 2009, when it issued a series of advisory letters to companies alleging that advertising of their drugs' efficacy via ''sponsored links'' without including appropriate risk information misbranded the applicable drugs.[17] Since these ads allowed for only three lines of text, the pharmaceutical companies provided the risk information ''one click away'' on the applicable brand's website, as had become customary for many industries in traditional online banner advertising where space is also limited. FDA's rejection of the ''one click away'' practice does not shed light on adverse experience reporting via social media, but it does make clear that the pharmaceutical industry cannot make assumptions about FDA's application of its regulations online.

In 2010, the FDA issued an enforcement letter to Novartis for its use of the Facebook Share function to enable consumers to ''share'' a link to the Tasinga brand page on their personal Facebook pages.[18] The FDA cited Novartis for omitting risk information, broadening indications of the drug, and failing to substantiate superiority claims, but was careful to point out that these violations did not stem from patient-generated online comments, the main cause of concern for pharmaceutical companies over adverse drug experience reporting.

Lack of Administrative Guidance

What the FDA has done to address adverse drug experiences encountered online is, in March 2001, issue a draft guidance entitled ''Postmarketing Safety Reporting for Human Drug and Biological Products Including Vaccines,'' directing pharmaceutical companies with postmarketing reporting obligations to report to the FDA any adverse drug experiences that they learn about on internet sites that they sponsor if they have knowledge of the following four data elements:

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.

FDA's draft guidance neither provides further insight as to what exactly constitutes ''identifiability'' of a patient or a reporter, nor does it shed further light on the specificity and evidence of a causal link required to consider a drug experience reported online to be ''adverse.'' However, the draft guidance does clearly limit a pharmaceutical company's obligations to review for adverse drug experiences to only those internet sites it sponsors. This leaves the industry somewhat off the hook for reviewing internet sites that they do not sponsor, provided that, if a pharmaceutical company becomes aware of an adverse drug experience on a nonsponsored internet site, it should review the adverse drug experience and determine if it should be reported to FDA.

In November 2009, nearly a decade after the FDA published its Postmarketing Safety draft guidance, FDA held a two-day public forum,[19] asking interested parties to weigh in on the use of social media by the pharmaceutical industry, including the issue of adverse drug experience reporting. While there seemed to be consensus that there can be no regulatory expectation of a pharmaceutical company policing the entire internet for adverse drug experiences, the industry was left with a lot of questions and only the promise of forthcoming guidance from the FDA. Late last year, the FDA published the internet focused ''Guidance for Industry Responding to Unsolicited Requests for Off-Label Information About Prescription Drugs and Medical Devices,'' but, as the title suggests, this document only addressed unsolicited requests for off label information online. Nearly three years after the FDA's public forum more than a decade since publication of FDA's Postmarketing Safety draft guidance, pharmaceutical companies are still left mostly in the dark as to how expansive their obligation is with respect to adverse drug experience reporting via social media and their own interpretations of what constitutes each of the four data elements defining an adverse drug experience reported online.

Obstacles Imposed by Social Media Platforms

Not only is the lack of comprehensive and updated guidance from the FDA frustrating for pharmaceutical companies wanting to rev up their activity in social media, social media's platform providers are not making life much easier. Facebook had initially granted pharmaceutical companies the option to block public commenting due to the industry's highly regulated nature and its fears over adverse drug experience reporting requirements. In August 2011, Facebook revoked that exception and, as a result, several notable pharmaceutical companies (e.g., Johnson & Johnson, AstraZeneca) took their Facebook pages down altogether.

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[17] *See, e.g.*, Warning Letter from FDA to Biogen Idec (March 26, 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies/UCM166071.pdf; Warning Letter from FDA to Sanofi Aventis (April 2009), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettertoPharmaceuticalCompanies/UCM166248.pdf. Additional warning letters concerning pharmaceutical companies' use of ''sponsored links'' can be found on the FDA's website. U.S. Food and Drug Administration Website, *Warning Letters 2009* (scroll to letters released 4/2/2009) (last visited Oct. 2, 2010), http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettersto Pharmaceutical Companies/ucm055773.htm.

[18] Warning Letter from FDA to Novartis Pharm. Corp. (July 29, 2010), *available at* http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersand NoticeofViolationLetterstoPharmaceuticalCompanies/UCM221325.pdf.

[19] Transcript of FDA Public Hearing, Promotion of FDA-Regulated Medical Products using the Internet and Social Media Tools (Nov. 12-13 2009), *available at* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM193462.pdf (Day 1) *and* http://www.fda.gov/downloads/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/UCM193463.pdf(Day 2).

  ISSN

Practical Considerations: Social Media Monitoring of Adverse Drug Experiences

Some argue that the pharmaceutical industry's concern about patients inundating them with adverse drug experiences postings to social media sites is misplaced. These parties believe, and some research supports, that actionable adverse drug experience reported via social media is and would actually be quite rare. In 2008, the Nielsen Company published results of a study[20] that analyzed 500 randomly selected healthcare-related messages on non-pharmaceutical social media sites and found that only one satisfied the FDA's four standard adverse event reporting requirements (specific medication, adverse experience, identifiable patient, and identifiable reporter). The theory is that social media posts will often fail to provide the first two required data elements of a reportable event due to the anonymity of membership to most social media sites. Users often use a pseudonym or user name that typically does not include personally identifiable information to engage others on these sites. Without a patient's real name and other identifying facts, the posting will likely not have been made by ''an identifiable person reporting the event.'' Similarly, posts made about the experiences of others will often fail to include an ''identifiable patient,'' as social media users discussing sensitive health information of others are even more likely to retain anonymity.

Risk Mitigation Considerations

There are ways to potentially mitigate risks related to adverse drug experience reporting if a pharmaceutical company decides the benefits of social media marketing are too great to pass up. Pharmaceutical companies can craft website policies with commenting guidelines that advise patients not to mention the specifics of events or personally identifiable information, both of which may otherwise serve to trigger reporting requirements, or clearly direct patients with this information to the FDA. For example, when visiting Merck's *Be Well* Facebook page,[21] users are confronted with blue ''Commenting Guidelines'' and purple ''Adverse Event Reporting'' click boxes. The Adverse Event Reporting statement encourages reports to be made offline or to the FDA directly by stating: ''In order to monitor the safety of Merck products, should any of your comments mention an adverse event to a Merck product, we encourage you to report this to Merck's National Service center at 1.800.672.6372 . . . . You may also report any adverse event directly to your healthcare provider or to the U.S. Food and Drug Administration (FDA) by calling 1-800-FDA-1088 or visiting http://www.fda.gov/Safety/MedWatch. Similarly, implementing a process, if available, where approval by the pharmaceutical company must be required before any public comments can be posted to the social media site creates a way for the company to retain control of content associated with its sponsored social media sites.

Costs and Timeliness Involved in Social Media Monitoring

Mitigating risk, however, will not absolve pharmaceutical companies operating in the social media space from monitoring patient-provided content on its sponsored sites, as the FDA requires pharmaceutical manufacturers to ''promptly review all adverse drug experience information obtained or otherwise received by the applicant *from any source.*''[22] Monitoring can be a costly and time intensive endeavor in the social media space for a number of reasons. The social media landscape is so expansive, and even limited participation by a pharmaceutical company can provide a substantial amount of copy to review. Consider that each pharmaceutical company may have its own brand to market, as well as each of its product's brands to market. For each of these brands, there are numerous social media platforms, which may host each brand's online presence. As the presence of these brands online exponentially increases, so does the opportunity for consumers to interact with them and provide postings and other user generated content. Compiling all this information is one issue; finding and compensating properly trained personnel to do so is an additional consideration.

Furthermore, cutting costs and time by automating a brand's social media online monitoring is nearly impossible with respect to adverse drug experience reporting. The entire premise for reporting an adverse drug experience is that these ''adverse experiences'' are unpredictable and unknown, therefore pharmaceutical companies would be unable to pre-populate textual search fields to automatically collect all references to an adverse experience as they may be able to do in some other circumstances, such as a search for certain profane or offensive words. The various forms of media a patient can post to each social media platform further complicate a company's ability to engage in automated monitoring. Patient anecdotes and stories may be delivered in the form of video, audio, or photographs, none of which can be searched by a simple automated tool, even if a pharmaceutical company could develop the appropriate search terms.

Where do pharmaceutical companies wanting to utilize social media go from here? Concerns over exposure to liability for monitoring adverse experiences and the internal resources necessary to manage the resulting workflow will force many to remain on standby for the much-anticipated social media guidance from the FDA before taking decisive action. Others will find the benefits of social media too attractive for their brands to forego and pioneer the field. Depending on their success engaging patients online, the FDA may be forced to communicate its interpretation of the industry's obligations to report adverse drug experiences in social media by more pointed enforcement activity. While we all await FDA's next moves, we can expect that the majority of pharmaceutical companies will continue to navigate cautiously social media's waters, searching for more traditional opportunities to take a dip in when they advertise online, where greater controls on content are afforded to advertisers and regulatory scrutiny is more of a known entity. And importantly, in light of the potentially dire consequences of not timely reporting adverse drug experiences to the FDA, those entities

[20] Melissa Davies, Nielsen Online, Listening to Consumers in a Highly Regulated Environment: How Pharmaceutical Manufacturers Can Leverage Consumer-Generated Media 2-3 (Aug. 2008), *available at* http://blog.nielsen.com/nielsenwire/wp-content/uploads/2009/11/Nielsen-Online-Healthcare-Practice_Social-Media-Adverse-Event-Reporting_nov09.pdf.

[21] Merck Be Well Facebook Page (last visited Oct. 2, 2012), www.facebook.com/MerckBeWell.

[22] 21 C.F.R. § 314.80(b) (emphasis added).

who take on the responsibility (and hence liability) for monitoring social media for a pharmaceutical client should take particular care to the extent and form such obligation will take.

Regardless of the FDA's pace, patients are increasingly interacting with pharmaceutical companies and each other via social media to share their product experiences. FDA's reluctance to clarify how its regulations may apply to social media is stifling the pharmaceutical industry's engagement with social media, thereby denying the FDA of a potentially helpful mechanism to receive the information necessary for it to carry out its duty of ensuring marketed drugs are safe and effective for the American public.

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  ISSN