

# PRO TE: *Solutio*

SOLUTIONS FOR YOU



## FDA Warning And Untitled Letters

*Using Historical Reference To Avoid  
Receiving Them In The Future*

## Healthcare Reform

*Actions That Can Be Implemented  
Today To Prepare For Changes*





DEAR CLIENTS:

Healthcare reform and burgeoning social media are only two of the challenges faced by today's pharmaceutical, medical device, and healthcare industry. This issue of *Pro Te: Solutio* offers suggestions for navigating the changing landscape of federal law and regulations.

The broadest, most discussed change this year is healthcare reform. Though the full impact of healthcare reform will not be felt for some time, physicians should begin the transition now, taking advantage of opportunities the law offers while avoiding potential pitfalls. *Healthcare Reform: Physicians Should Act Today to Save Tomorrow* shares information about steps physicians and physicians' practices can take right now in three major areas.

*You've Been Warned: FDA Warning and Untitled Letters* outlines what a company can do to avoid the surprise of receiving Warning letters and Untitled letters from the FDA — and when such a letter is delivered, how to avoid further actions. *Are Your Meta Tags Showing?* discusses the ins and outs of using the internet and social media to market FDA-regulated products.

The issue of whether state failure-to-warn claims against generics manufacturers are preempted by the Food, Drug, and Cosmetic Act remains unsettled. *Generic Preemption After Levine* looks at the reasoning of appeals courts following the United States Supreme Court's decision that such claims against branded manufacturers are not preempted and explores the possibility that the Supreme Court might soon revisit the issue with respect to generics.

Change comes from all directions. Butler Snow strives to keep our clients informed of change that impacts them, whether its genesis is in our regulatory, legislative, or judicial systems or the constant technological advances that alter the way we live. We hope this issue of *Pro Te: Solutio* will prove informative enough for you to share with others.



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# PRO TE: Solutio

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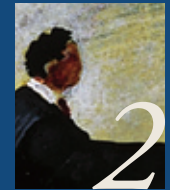
## SHARING SOLUTIONS

It's human nature to share problems. But how often is someone willing to share solutions? Butler Snow wants to do just that — provide scenarios and the solutions that turned a client's anxiety into relief and even triumph. That's why we created this magazine, *Pro Te: Solutio*, which explores how real-life legal problems have been successfully solved.

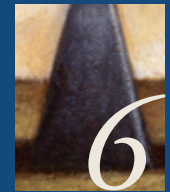
That's also why we at Butler Snow redesigned and expanded our unique health-oriented industry group, now comprised of two major sections that handle business and litigation. The Pharmaceutical, Medical Device, and Healthcare Industry Group has more than 50 multi-disciplinary attorneys who provide creative solutions for the complex issues of the healthcare industry. This group includes product liability and commercial litigators; corporate, commercial, and transaction attorneys; labor and employment attorneys; intellectual property attorneys; and those experienced in government investigations.

*Pro Te: Solutio* is a quarterly magazine available only to the clients of Butler Snow. If you have questions or comments about its articles, you're invited to contact Christy Jones and Charles Johnson, as well as any of the attorneys listed on the last page of this publication.

## TABLE of CONTENTS



HEALTHCARE REFORM



GENERIC PREEMPTION AFTER LEVINE



ARE YOUR META TAGS SHOWING?



YOU'VE BEEN WARNED: FDA WARNING AND UNTITLED LETTERS

# HEALTHCARE REFORM



## PHYSICIANS SHOULD ACT TODAY TO SAVE TOMORROW

HEALTHCARE REFORM IS NOW A REALITY, and those reforms create a very different medical practice environment. Although many of the changes will not be implemented immediately, physicians should begin now to position themselves to take advantage of opportunities the law offers and to protect themselves against potential pitfalls; they can act today on measures which will enable their practices to benefit from incentives that will become available as reforms are implemented. Attorneys can help strategically and with legal issues, but physicians can take steps to help themselves. This article focuses on steps that can be taken in three areas: fraud and abuse, creating value, and physician-hospital relationships.

### FRAUD AND ABUSE ENFORCEMENT

It is no secret that the government has identified fraud and abuse enforcement as a fundamental priority of the healthcare reform legislation. Fraud, waste, and abuse is one of the major components of the Patient Protection and Affordable Care Act (PPACA). The number of auditors and investigators has increased, and whistleblower actions arguably are more attractive. Violations of the Anti-Kickback Statute (AKS) and Stark Statute (Stark) now are subject to sanctions under both the Civil Money Penalties Law and the Federal False Claims Act (FCA).

Of particular interest to physicians, PPACA requires providers (and suppliers and health plans) to “report and refund” any “overpayment” within 60 days after the overpayment is “identified” or the date any corresponding cost report is due, whichever is later. An “overpayment” is defined as any funds received or retained under Medicare or Medicaid to which the provider, supplier,

or plan is not entitled after an “applicable reconciliation.” A provider also must specify “the reason for the overpayment.”

Reporting and repaying any overpayment is an “obligation” under the FCA, so failure to report and return an overpayment within the applicable deadline may constitute a violation. Potential monetary penalties range from \$5,500 to \$11,000 per claim, plus treble damages. PPACA also amends the Civil Monetary Penalty statute to establish monetary penalties for failure to report and repay overpayments. “Unpaid overpayments” also are grounds for Medicaid program exclusion. The new laws will apply to earlier overpayments that are only now discovered — not just those occurring after the effective date of PPACA.

PPACA does not provide specific guidance about when an “overpayment” is considered “identified” and, thus, the repayment deadline triggered. The OIG historically has taken the position in the self-disclosure context that an overpayment is not “identified” until a pro-

vider has completed its internal investigation of an overpayment. The treatment of this issue under PPACA is not yet clear.

This increased focus on fraud and abuse enforcement means that physician practices should ensure that their billing, documentation, credit balance review and repayment procedures, reports to government, as well as Stark, Anti-Kickback, and other financial relationships are in compliance with the new laws. Taking the following steps now will save time, energy, money, and administrative burden later when auditors appear or in the event of a whistleblower action:

1. Review the practice’s compliance program and make any recommended updates or corrections. If the practice does not have an effective compliance program (as defined by the OIG), adopt one and implement it immediately. Legal counsel can assist with adoption and implementation, but ultimately, it is the practice’s responsibility to ensure that the program is followed.

PHYSICIANS SHOULD TAKE ACTION TODAY ON THE MEASURES THAT WILL ENABLE THEIR PRACTICES TO BENEFIT FROM INCENTIVES THAT WILL BE AVAILABLE IN THE HEALTHCARE SYSTEM AS HEALTHCARE REFORMS ARE IMPLEMENTED.





PHYSICIANS ARE A MAJOR FOCUS OF THE HEALTHCARE REFORM LEGISLATION. PHYSICIAN PRACTICES CAN DO A GREAT DEAL TO IMPROVE THEIR CIRCUMSTANCES AND, AT THE SAME TIME, IMPROVE CARE TO THEIR PATIENTS. NOW IS THE TIME TO BEGIN PREPARING FOR THE CHANGES ON THE HORIZON.

2. Review the practice's internal compensation formula to confirm that it is Stark-compliant.

3. Make sure all financial relationships with referral sources are as close to an AKS safe harbor as possible.

4. Make sure all financial relationships with providers to which Stark-designated health services are referred, or from which referrals for Stark-designated health services are received, fall within a Stark exception.

5. Obtain a baseline audit of the practice's documentation accuracy. Legal counsel should assist with this task, and both counsel and the practice should take appropriate steps to evidence an intent that the audit work and the outcome be protected by the attorney-client privilege and/or treated as attorney work product.

6. Develop an annual auditing and monitoring schedule based on the identified risk areas for the practice.

#### MEASURING AND IMPROVING QUALITY

The healthcare reform legislation includes a national strategy to improve the delivery of healthcare services, patient health outcomes,

and population health through measurement, more transparency, and value-based purchasing. Quality measures are being developed by the government that will allow assessment of:

1. Health outcomes and functional status of patients;

2. Management and coordination of healthcare, including care transition across multiple care episodes and the continuum of providers, healthcare settings, and health plans;

3. The quality of information given to patients by healthcare providers, and whether and how that information is used in making healthcare decisions;

4. Meaningful use of health information technology;

5. The safety, effectiveness, patient-centeredness, appropriateness, and timeliness of care;

6. The efficiency of care;

7. The equity of health services (including addressing health disparities across populations and geographic areas);

8. Patient experience and satisfaction; and

9. Use of innovative strategies and methodologies.

By 2012, measures will be published to establish a Medicare payment modifier that provides for differential payment to physicians based on quality of care.

The physician practice must be able to measure its quality and costs if it is to demonstrate and improve quality in the future. Physician practices must adopt standardized clinical processes, to the extent possible, to succeed in the highly measured environment. Clinical integration within a practice allows the practice to become more efficient and standardized in patient care delivery. Acting now to integrate clinically and standardize care and to measure quality, outcomes, and costs will help ensure success when additional Medicare payments are available based on quality of care. Many of the following steps can also improve the practice's financial margins:

1. Consider possible methods of clinical integration within the practice.

2. Analyze existing behaviors and habits

among the physicians in the practice and in relationship to staff that do not directly and measurably contribute to improved quality, financial margins, or patient experience.

3. Require each physician in the practice to measure his or her own performance and make changes based on data.

#### PHYSICIAN-HOSPITAL RELATIONSHIPS

Physicians will be subject to value-based purchasing in Medicare beginning in 2012. Efficiency standards and performance measures will be established. It is likely that the measures adopted will be applied to performance data from 2011 (only a few months away). The physician value-based purchasing program will be coordinated with the hospital value-based purchasing program, which also begins in 2012. Hospitals and physicians have a short timeframe to agree on a common goal to improve their performance, with the ability to achieve and demonstrate improved quality and efficiency as the endpoint. On their side of the equation, physician practices can:

1. Review information regarding alternatives available for hospital-physician relationships;

2. Consider the best way to approach hospital representatives about solidifying the relationship in ways that will improve quality to the benefit of the physician practice, the hospital, and patients.

#### ANTI-KICKBACK AND STARK REVISIONS

PPACA also includes a number of changes to the AKS and Stark laws, some of which become effective soon. For example, when a physician refers a patient to an entity with which the physician has a financial relationship for MRI, CT, PET and other services still to be identified by DHHS, the referring physician must inform the patient in writing at the time of the referral that he or she may obtain services from another provider. In addition, the physician must provide the patient with a written list of providers in the area.

PPACA also amends the rural provider and "whole hospital" ownership exceptions to Stark. Future physician investment in hospitals, effectively, is barred. Hospitals with existing physician investment are grandfathered if a provider agreement is entered by December 31, 2010. A number of limitations apply to the grandfathered hospitals, however. For

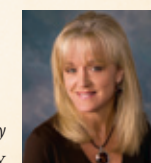
example, the aggregate percentage of physician investment in the hospital, or an entity with ownership in the hospital, cannot be increased. There are also restrictions regarding the expansion of hospital services or beds.

Physicians are a major focus of the healthcare reform legislation. Physician practices can do a great deal to improve their circumstances and, at the same time, improve care to their patients. Now is the time to begin preparing for the changes on the horizon.

<sup>1</sup> The United States Department of Health and Human Services (DHHS) Office of Inspector General (OIG) reported, in 2009, savings and expected recoveries of \$20.97 billion, including \$4 billion in investigative receivables.

<sup>2</sup> This statute may be invoked by the Inspector General without a referral to the Justice Department.

WRITTEN BY  
JULIE WATSON LAMPLEY





# Generic Preemption AFTER Levine

“THE EIGHTH CIRCUIT’S DECISION [AGAINST PREEMPTION] NOT ONLY THREATENS TO UNDERMINE THE PUBLIC’S CONFIDENCE IN GENERIC DRUGS; IT THREATENS THE LONG-TERM VIABILITY OF THE GENERIC PHARMACEUTICAL INDUSTRY IN THIS COUNTRY.”<sup>1</sup>

## INTRODUCTION

More than a year ago, the United States Supreme Court, in *Wyeth v. Levine*, held that state law failure-to-warn claims against brand-name drug manufacturers are not automatically preempted by the Food Drug and Cosmetic Act (FDCA). *Levine* applies only to branded pharmaceuticals, and the Court did not address the implications of its holding for generic drug manufacturers. Before *Levine*, a number of courts found that failure-to-warn claims against generic manufacturers were preempted by the Hatch-Waxman amendments to the FDCA.

The reasoning: because generic manufacturers were required to maintain the “same” label as the branded drug, generic manufacturers could not initiate label changes independent of the branded manufacturer. Generic manufacturers therefore argued that state law failure-to-warn claims could not succeed when the generic manufacturer complied with the FDCA and used the last approved label for the brand-name equivalent drug.

After *Levine*, the trend is for courts to find that failure-to-warn claims against generics manufacturers are *not* preempted by the FDCA. Both the Fifth and Eighth Circuits

have ruled against preemption.<sup>2</sup> A petition for certiorari was filed with the United States Supreme Court in *Mensing v. Wyeth*, and the Court has asked the Solicitor General to weigh in on the issue. The Court’s request for input from the Solicitor General suggests there may be enough interest from the Court to hear the appeal.

Appeals currently are pending before the Sixth and Ninth Circuits from decisions that found in favor of preemption.<sup>3</sup> The Sixth Circuit has asked the FDA to submit a brief explaining its view of generic preemption. That brief will be filed 14 days after the

Solicitor General files its brief in *Mensing*.

Set forth below is an overview of the reasoning employed by the Eighth and Fifth Circuits in finding against preemption, as well as a summary of the generic manufacturers' arguments in favor of preemption. Finally, the article includes general thoughts on the potential implications of a Supreme Court decision that finds either for or against generic preemption.

#### NO GENERIC PREEMPTION — FIFTH AND EIGHTH CIRCUITS

The Eighth Circuit was the first federal court of appeals to consider generic preemption after *Levine*. The court premised its finding against preemption on its conclusion that a generic drug manufacturer should alert the FDA to any new hazard affecting a drug. The Eighth Circuit noted that generic manufacturers follow the same adverse event reporting requirements as brand manufacturers, and it emphasized 1992 comments by the FDA that generic manufacturers must submit periodic reports of adverse events even if they have not received any adverse reports or initiated any labeling changes.<sup>4</sup> The court found “implicit” in this comment the FDA’s expectation that generic manufacturers will initiate label changes, and it concluded that such changes could be proposed to the FDA through the prior approval process. Because the court concluded that a generic manufacturer could at least propose a label change that the FDA could impose uniformly on all manufacturers, the Eighth Circuit declined to address whether generic manufacturers could change a label through the Changes Being Effected (CBE) procedure.

The Eighth Circuit concluded that in addition to initiating label changes through the prior approval process, a generic manufacturer could suggest that the FDA send out a warning letter to healthcare professionals. The court noted in a footnote that generic manufacturers could not unilaterally send out “Dear Doctor” letters, but offered no explanation for its conclusion that the authority regarding Dear Doctor

letters applicable to brand manufacturers applies equally to generics.

The Fifth Circuit in *Demahy* generally followed the Eighth Circuit’s reasoning, but it went further and concluded that a generic manufacturer could unilaterally make labeling changes through the CBE process.<sup>5</sup> The Fifth Circuit held that the requirement that a generic drug label be the “same as” the brand label is imposed inflexibly only at the initial application stage. The Fifth Circuit’s reasoning indicates that, once a generic drug is approved and marketed, the CBE process is available to generic manufacturers just as



AFTER *LEVINE*, THE TREND IS FOR COURTS TO FIND THAT FAILURE-TO-WARN CLAIMS AGAINST GENERICS MANUFACTURERS ARE *NOT* PREEMPTED BY THE FDCA.

it is to brand-name manufacturers. Presumably, the FDA then ensures uniformity by imposing label changes initiated by a generic manufacturer upon other manufacturers, including the branded manufacturer.

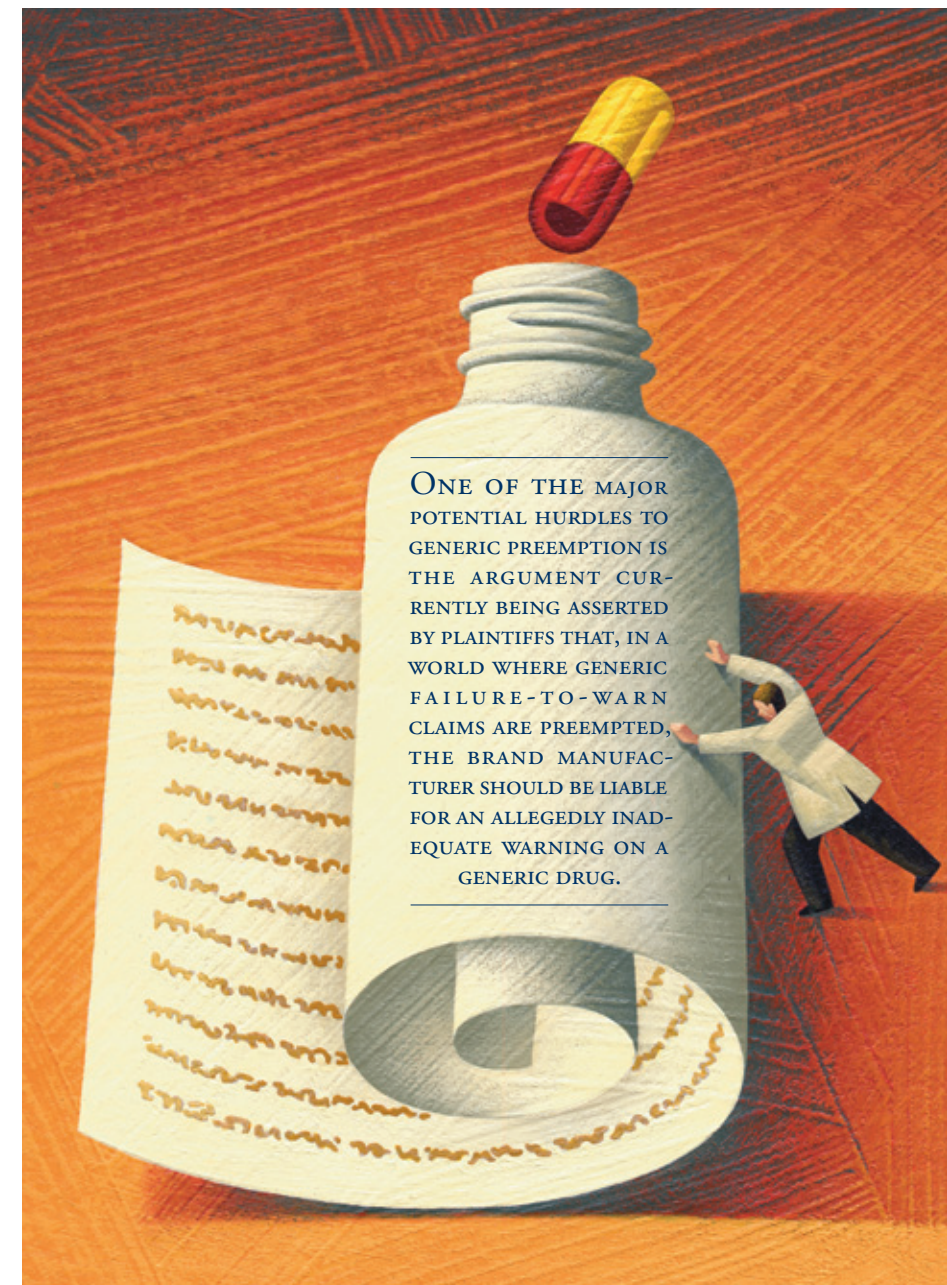
#### ARGUMENTS FOR GENERIC PREEMPTION

The arguments in favor of generic preemption — which are presently being made before the Sixth and Ninth Circuits and in support of the petition for certiorari in *Mensing* — generally focus on the Hatch-Waxman amendments’ intent to bring generic drugs quickly and cheaply to market. The mechanism for doing so was to require generic manufacturers to mimic the brand product in virtually all respects. Most importantly, the generic manufacturers rely on the requirement under 21 U.S.C. § 355(j)(2) that the labeling on a generic drug product be the “same as” the labeling the FDA previously approved for use on the brand-name equivalent. They argue that this

requirement makes it impossible to comply with the FDCA and any state law requiring that additional or different information should be in the label.

The generic manufacturers also distinguish the Supreme Court’s holding in *Levine* by emphasizing that *Levine* turned on the Court’s finding that the brand manufacturers were charged with “primary responsibility for their drug labeling” and for “crafting an adequate label and ensuring that its warnings remain adequate.” Generics, to the contrary, are charged with the entirely different task of insuring that their labels remain “the same as” the latest FDA-approved label for the brand-name equivalent product. The generic manufacturers argue that this distinction renders the analysis in *Levine* inapplicable in determining whether state law failure-to-warn claims against generic manufacturers are preempted.

Finally the generic manufacturers argue that, from a practical perspective, a finding against preemption will negate the entire purpose of the Hatch-Waxman amendments and undermine the affordability of generic drugs. The generic manufacturers highlight the laborious and expensive approval process for a new drug and note that, post-approval, the FDA makes decisions about labeling changes based on the original applicant’s clinical data, all the scientific literature about the drug, and all adverse events reported to the FDA since approval. Generic manufacturers are not required to compile and analyze this data, and they assert that the imposition of the requirement that they maintain the label could be achieved only through the cost of the generic drug rising to that of the brand-name drug’s price. One of the fundamental assumptions of the Hatch-Waxman amendments is that by streamlining the generic approval process, generic drugs will be brought to market quickly and at a lower price than the brand product. If the generic manufacturers are required to undertake the same steps required of the brand manufacturer to compile and analyze pre- and post-market data, the costs of generic drugs will undoubtedly increase.



#### CONTE AND GENERIC PREEMPTION

One of the major potential hurdles to generic preemption is the argument currently being asserted by plaintiffs that, in a world where generic failure-to-warn claims are preempted, the brand manufacturer should be liable for an allegedly inadequate warning on a generic drug. This argument gained notoriety in *Conte v. Wyeth*, 168 Cal. App. 4th 89 (Ca. Ct. App. 2008), where a California court held that a name-brand drug manufacturer owed a duty-of-care to an individual injured by a generic drug even when the plaintiff never ingested the brand manufacturer’s product. Although *Conte* has received much attention, it has gained little traction and has generally

been rejected by courts. Most courts have refused to follow *Conte* on the grounds that liability for injury caused by a product can be imposed only where the product causing the alleged injury was manufactured and/or supplied by the defendant.

One can posit that the resounding rejection of *Conte* by most courts is related to the seemingly growing conclusion that failure-to-warn claims against generic manufacturers are not preempted. It may be easier for courts to find against generic preemption than to leave the impression that a plaintiff is without a remedy. This is, of course, not to suggest that a ruling in favor of generic preemption will result in the widespread

adoption of the holding in *Conte*. Indeed, a holding from the Supreme Court in favor of generic preemption may do nothing to “resurrect” *Conte*. However, in the event the Court finds in favor of generic preemption, it seems likely that at least some judges will be tempted to follow *Conte* rather than give the appearance that they have left a plaintiff without a remedy. If that happens, then the progeny one can expect from *Conte* will soon be marching up the appellate ladder behind *Mensing*.

#### CONCLUSION

Although the post-*Levine* weight of authority appears to be against it, there are strong legal and practical arguments in favor of generic preemption. Those arguments are presently before the Supreme Court on a petition for certiorari, and the Court has at least expressed an interest in hearing what the government’s position is with respect to generic preemption. The Solicitor General will be weighing in on the issue soon, but it will likely be several months before the Court determines whether it will accept the appeal of *Mensing*. Acceptance of the appeal should resolve the issue. A refusal by the Court to hear it at this time will leave manufacturers waiting for decisions from the Sixth and Ninth Circuits and for the law to develop in other jurisdictions.

<sup>1</sup> Brief of the Generic Pharmaceutical Association as Amicus Curiae in Support of Petitioners *Pliva, Inc. et al.*, On Petition for Writ of Certiorari to the U.S. Court of Appeals for the Eighth Circuit, Nos. 09-993, 09-1039 (April 21, 2010) (supporting writ petition filed by defendant generic manufacturers from the Eighth Circuit’s decision in *Mensing v. Wyeth, Inc.*, 588 F.3d 603 (8th Cir. 2009)).

<sup>2</sup> See *Demahy v. Actavis*, 593 F.3d 428 (5th Cir. 2010); *Mensing v. Wyeth, Inc.*, 588 F.3d 603 (8th Cir. 2009).

<sup>3</sup> See *Smith v. Wyeth, Inc.*, No. 09-5460 (6th Cir.); *Gaeta v. Perrigo Pharms. Co.*, No. 09-15001 (9th Cir.).

<sup>4</sup> See *Mensing*, 588 F.3d at 609 (citing 57 Fed. Rep. 17950, 15965 cmt 53 (April 28, 1992)).

<sup>5</sup> See *Demahy*, 593 F.3d at 439-441.



WRITTEN BY ERIC HUDSON

# ARE YOUR META TAGS SHOWING?

## PROMOTION OF FDA-REGULATED MEDICAL PRODUCTS USING THE INTERNET AND SOCIAL MEDIA TOOLS

EARLIER THIS YEAR, the FDA issued the first enforcement action against a pharmaceutical company for its use of a social media sharing tool in marketing a prescription drug. A notice of violation letter directed Novartis Pharmaceutical Corporation to stop disseminating allegedly misleading promotional content utilizing the “Facebook® Share” social media widget (letter posted August 4, 2010 on the FDA website).<sup>1</sup> The letter recognizes that Novartis submitted its “website content” to the FDA, but Novartis did not submit the “shared content” that website visitors could access by clicking on the Facebook Share widget.<sup>2</sup>

Although the shared content actually was generated by the Facebook Share widget, Novartis’s website developer added the plug-in to the Novartis website and coded the meta tags and link(s) that were incorporated by the widget. The FDA determined that this content was completely controlled by Novartis because Facebook users could not modify the content.<sup>3</sup> The drug product information ultimately posted via the Facebook widget did not include any of the required risk disclosures. The FDA found that the communication was misleading even though the shared content contained a hyperlink to appropriate drug product safety information.<sup>4</sup>

Fortunately for pharmaceutical companies, the FDA letter to Novartis does not indicate that the FDA is concerned about promotion through social media marketing channels per se. There are no regulations that prohibit the use of certain types of media to promote drugs.<sup>5</sup> Rather, the letter focuses solely on compliance with existing FDA regulations in all media. But is the FDA ignoring the realities of internet usage and space-limited social media marketing tools?

Eighty-two percent of American adults use a mobile communication device,<sup>6</sup> and six in ten now have wireless access to infor-

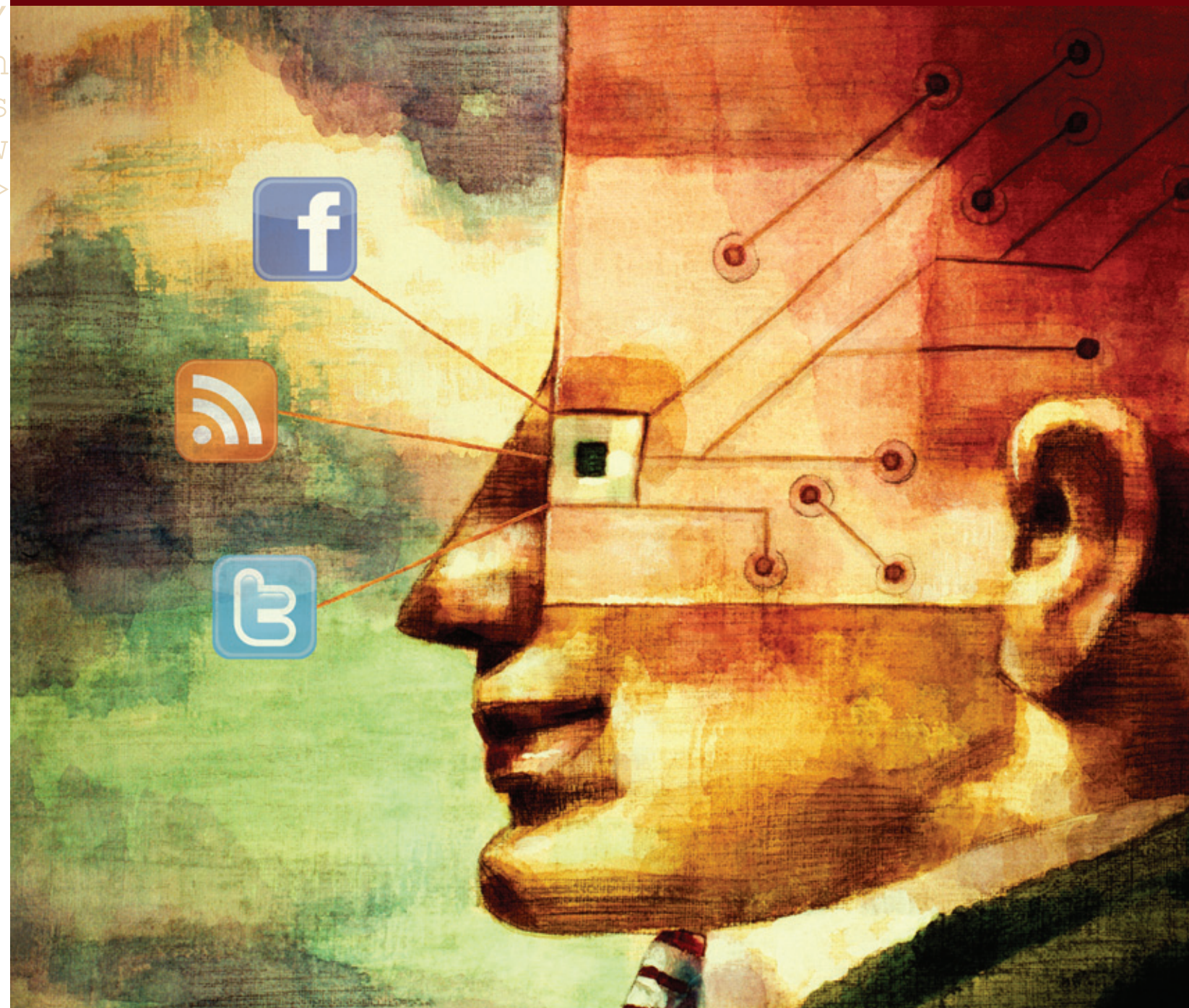
**FACEBOOK’S USER POPULATION IS NOW LARGER THAN THAT OF THE U.S., MEXICO, AND FRANCE COMBINED.**

mation (using either a laptop or cell phone).<sup>7</sup> Now that advanced wireless communication devices can fit in a pocket, access to interactive communication and information has become extremely portable. Susannah Fox, Associate Director, Digital Strategy with the Pew Research Center, believes that wireless access is causing a radical change in internet use: “Mobile devices are changing us [...] as internet users, making us more likely to share, more likely to access information on the go, and [...] erasing the digital divide.”<sup>8</sup>

As the internet’s ability to facilitate communication has evolved, a variety of advanced social media tools has emerged and been embraced by the public. In July of this year, Facebook announced that it reached a record half a billion users.<sup>9</sup> Facebook’s user population is now larger than that of the U.S., Mexico, and France combined.<sup>10</sup> Today, 61% of adult internet users use social networks (an increase of 33% since April 2009).<sup>11</sup> Moreover, Americans spend more than a third of their online time communicating and networking across social networks, blogs, personal email, and instant messaging.<sup>12</sup>

Patients in unprecedented numbers are turning to the internet to find health information: 61% of American adults (83% of internet users) report that they look online for health information.<sup>13</sup> “The convergence of media (computers, telephones, television, radio, video, print, and audio) and the emergence of the Internet create a nearly ubiquitous networked communication infrastructure. This infrastructure facilitates access to an increasing array of health information and health-related support services and extends the reach of health communication efforts.”<sup>14</sup>

In a national survey, sixty percent (60%) of online consumers said that social media is



“a trusted resource” they use when searching for health information online.<sup>15</sup>

“76% of online consumers want to obtain [health-related] information from other people who share the same medical condition; 73% from doctors or other healthcare providers; 66% from friends and family”<sup>16</sup>

The U.S. Department of Health and Human Services Healthy People 2010 (HP2010) report stresses the importance of internet access to provide patients with relevant health information.<sup>17</sup> One of the identified goals is to increase the proportion of households with access to the internet at home because “access to the Internet and subsequent technologies is likely to become essential to gain access to health information, contact health care organizations and health professionals, receive services at a distance, and participate in efforts to improve local and national health.”<sup>18</sup> Moreover, “[t]he health impact of interactivity, customization, and enhanced multimedia is just beginning to be explored, and already interactive health communication technologies are being used to exchange information, facilitate informed decision making, promote healthy behaviors, enhance peer and emotional support, promote self-care, manage demand for health services, and support clinical care.”<sup>19</sup>

As internet users spend more time engaged in social media, drug companies want to participate in the dialogue. However, the reality is that pharmaceutical companies are struggling to keep up with the media preferences of today’s healthcare consumer. Considering the legal and regulatory issues involved in direct-to-consumer advertising, it is no wonder that the pharmaceutical industry isn’t exactly sure how to take advantage of new communication technologies in a responsible way.

Interactive media has raised many questions about the application of existing FDA regulations to the newer media.<sup>20</sup> The FDA has yet to provide clear guidance specifically addressing regulated promotional communication using internet and social media tools. In the meantime, the “FDA has continued enforcement actions without these clear standards,” said Jeff Francer, a lawyer



**PATIENTS IN UNPRECEDENTED NUMBERS ARE TURNING TO THE INTERNET TO FIND HEALTH INFORMATION: 61% OF AMERICAN ADULTS (83% OF INTERNET USERS) REPORT THAT THEY LOOK ONLINE FOR HEALTH INFORMATION.**

at the Pharmaceutical Research and Manufacturers of America (PhRMA).<sup>21</sup>

Recognizing the massive expansion of new tools and technologies (including blogs, microblogs, podcasts, social network sites, online communities, video sharing, widgets, and wikis), the agency held a public hearing in November 2009 to discuss how the statutory provisions and regulations should be applied to digital and interactive marketing media. Written comments were accepted through February of this year. Based on its Guidance Agenda, it appears that the FDA intends to publish draft guidances on advertising by the end of this year, including “Promotion of Prescription Drug Products Using Social Media Tools.”<sup>22</sup>

Thomas Abrams, director of the DDMAC, has indicated that the agency may issue multiple, targeted guidances instead of a single

guidance document covering all forms of online promotion to give the DDMAC flexibility in addressing new technologies.<sup>23</sup> Further, Abrams said that such guidances will likely address specific issues or circumstances rather than a particular media or technology.<sup>24</sup> In the meantime, the Novartis notice of violation letter partially clarifies the FDA’s viewpoint on drug product promotion in the context of social sharing:

- The FDA did not prohibit the use of social media tools to promote drugs.
- The FDA applied the same standard to social media as it has to other forms of pharmaceutical promotional ads/communications.
- Appropriate safety information should be included in all direct-to-consumer promotional social media communications.
- The DDMAC will apply the “fair bal-

ance”<sup>25</sup> standard to metadata content, without exception for space-limited media tools.

- The FDA has rejected the “one-click” rule; hyperlinks to risk information are insufficient to mitigate omission of relevant information from the message.

- Because many common sharing tools create shared messages/content by combining and copying meta tags, the metadata code *on each page* of the website used by these tools should be carefully reviewed for compliance with all FDA regulatory requirements and submitted to the FDA as promotional material. Safety information must be included in meta tag descriptions if the copy will likely become generated content for promotional material.

- It is important to understand exactly how sharing tools and search engines function, how content will be developed, how meta tags may be used, and the form in which the content will be ultimately be disseminated.

- Until specific regulations or guidelines are issued, meta descriptions used by sharing widgets should not reference branded drug indications, or the meta descriptions should not be branded at all. Shared metadata/content should not exceed the character-count limitations of the social media widget.

- It may be necessary to select/develop sharing tools that allow customized control over the message without relying on metadata.

- Any and all company-controlled content intended for use by social share widgets must comply with regulations and should be submitted to the FDA as promotional material.

Notwithstanding FDA’s prior rejections of hyperlink solutions, industry stakeholders have requested that the agency reconsider the effectiveness of hyperlink disclosures in the case of technologies with severe space limitations, explaining that “[c]onsumers on the Internet are accustomed to viewing pop-ups, rollover text, links and other communication mechanisms.”<sup>26</sup> Another proposal would involve the use of an FDA-approved symbol and a standard universal warning in combination with hyperlinks and/or abbreviated descriptions in cases where it is not feasible to include complete safety information (*e.g.*, Twitter and other microblogs).<sup>27</sup>

Interactive health communication technologies are already being used to exchange information, facilitate informed decision making, promote healthy behaviors, enhance peer and emotional support, promote self-care, manage demand for health services, and support clinical care.<sup>28</sup> As the primary authoritative source of information about their prescription products, pharmaceutical companies can help ensure that scientifically accurate, meaningful, and balanced product information is disseminated to all social media audiences.

<sup>1</sup> Food and Drug Administration. Notice of Violation Letter to Novartis Pharmaceuticals Corporation. Division of Drug Marketing, Advertising and Communications, 7/30/10, 8/4/10. Available at <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLettersstoPharmaceuticalCompanies/UCM221325.pdf>>. Last accessed Oct. 7, 2010.

<sup>2</sup> Widgets, like the Facebook Share widget, are common sharing plug-ins that allow visitors to click a “button” to share/repost content to a social media site. This information may then be shared with other social media users in various ways (as in newsfeeds or wall postings).

<sup>3</sup> See Novartis Letter, *supra* note i, pp. 1, 2.

<sup>4</sup> See Novartis Letter, *supra* note i, p. 3.

<sup>5</sup> Food and Drug Administration, Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Federal Register, 181, Sept. 21, 2009, p. 48085.

<sup>6</sup> Lenhart, Amanda. “Cell Phones and American Adults.” Pew Internet & American Life Project.” Sept. 2, 2010. Available at <<http://pewinternet.org/Reports/2010/Cell-Phones-and-American-Adults/Overview.aspx>>. Last accessed Sept. 10, 2010.

<sup>7</sup> Smith, Aaron. “Mobile Access 2010.” Pew Internet & American Life Project,” July 7, 2010. Available at: <<http://www.pewinternet.org/Reports/2010/Mobile-Access-2010.aspx>>. Last accessed Sept. 12, 2010.

<sup>8</sup> Fox, Susannah. “The Power of Mobile, Commentary.” Pew Internet & American Life Project.” Sept. 13, 2010. Available at <<http://www.pewinternet.org/Commentary/2010/September/The-Power-of-Mobile.aspx>>. Last accessed Sept. 13, 2010.

<sup>9</sup> Johnson, Robert. Scaling Facebook to 500 Million Users and Beyond. July 21, 2010. Facebook.com. Available at <<http://www.facebook.com/notes/facebook-engineering/scaling-facebook-to-500-million-users-and-beyond/409881258919>>. Last accessed Sept. 10, 2010.

<sup>10</sup> Pepitone, Julianne. Facebook Hits 500 Million Users. July 21, 2010, CNN Money.com. Available at <[http://money.cnn.com/2010/07/21/technology/facebook\\_500\\_million/index.htm](http://money.cnn.com/2010/07/21/technology/facebook_500_million/index.htm)>. Last accessed Sept. 12, 2010.

<sup>11</sup> Madden, Mary. “Older Adults and Social Media. Social Networking Use.” Aug. 27, 2010. Available at <<http://pewinternet.org/Reports/2010/Older-Adults-and-Social-Media.aspx>>. Last accessed Oct. 7, 2010.

<sup>12</sup> “What Americans Do Online: Social Media And Games Dominate Activity.” The Nielsen Company. Aug. 2,

2010. Last updated Aug. 6. Available at <[http://blog.nielsen.com/nielsenwire/online\\_mobile/what-americans-do-online-social-media-and-games-dominate-activity](http://blog.nielsen.com/nielsenwire/online_mobile/what-americans-do-online-social-media-and-games-dominate-activity)>. Last accessed Sept. 12, 2010.

<sup>13</sup> Fox, Susannah and Jones, Sydney. “Pew Internet and American Life Project, The Social Life of Health Information—Americans’ Pursuit of Health Takes Place Within a Widening Network of Both Online and Offline Sources.” June 2009. Available at <<http://www.pewinternet.org/Reports/2009/8-The-Social-Life-of-Health-Information/02-A-Shifting-Landscape/1-Americans-are-tapping-into-a-widening-network-of-both-online-and-offline-sources.aspx>>. Last accessed Oct. 7, 2010.

<sup>14</sup> HHS, Healthy People 2010 vol. 1, ch. 11, “Health Communication.” Available at <<http://www.healthypeople.gov/document/HTML/Volume1/11HealthCom.htm>>. Last accessed Oct. 7, 2010.

<sup>15</sup> Rodale Inc. “Prevention Magazine Releases 13th Annual DTC Survey Results.” July 15, 2010. Available at <<http://www.rodaleinc.com/newsroom/ipreventioni-magazine-releases-13th-annual-dtc-survey-results>>. Last accessed Sept. 13, 2010.

<sup>16</sup> *Id.*

<sup>17</sup> See Healthy People 2010, *supra* note xiv.

<sup>18</sup> See Healthy People 2010, *supra* note xiv, Goal 11-1.

<sup>19</sup> See Healthy People 2010, *supra* note xiv.

<sup>20</sup> Food and Drug Administration, Promotion of Food and Drug Administration-Regulated Medical Products Using the Internet and Social Media Tools; Notice of Public Hearing, 74 Federal Register, 181 (21 September 2009), p. 48085.

<sup>21</sup> Heavy, Susan and Richwine, Lisa. “Outgunned FDA Tries To Get Tough with Drug Ads.” Sept. 3, 2010. Available at <<http://www.reuters.com/article/idUSTRE6821PN20100903>>. Last accessed Sept. 12, 2010.

<sup>22</sup> FDA. “Guidance Agenda: New Draft Guidances CDER is Planning to Publish During Calendar Year 2010.” Available at <<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079647>>. Last accessed Oct. 7, 2010.

<sup>23</sup> “DDMAC: Social Media Guidance Likely To Be Split Into Multiple Documents.” June 15, 2010. Available at <<http://www.thompson.com/public/newsbrief.jsp?cat=FOODDRUG&cid=2906>>. Last accessed Oct. 7, 2010.

<sup>24</sup> *Id.*

<sup>25</sup> In direct-to-consumer advertising, fair balance refers to the presentation of accurate and fair assessment of the risks as well as the benefits of the drug. See Federal Food, Drug, and Cosmetic Act, Part 202: Prescription Drug Advertising (21 CFR 202.1(e)(7)(viii)).

<sup>26</sup> Francer, Jeffrey K. “Pharmaceutical Research and Manufacturers of America, Statement of Promotion of FDA-Regulated Medical Products Using the Internet and Social Media Tools.” Nov. 12-13, 2009. Available at <[http://www.phrma.org/issues/fda\\_issues/phrma\\_comments\\_about\\_promotion\\_fda\\_regulated\\_products\\_using\\_internet\\_and\\_social\\_me](http://www.phrma.org/issues/fda_issues/phrma_comments_about_promotion_fda_regulated_products_using_internet_and_social_me)>. Last accessed Oct. 7, 2010.

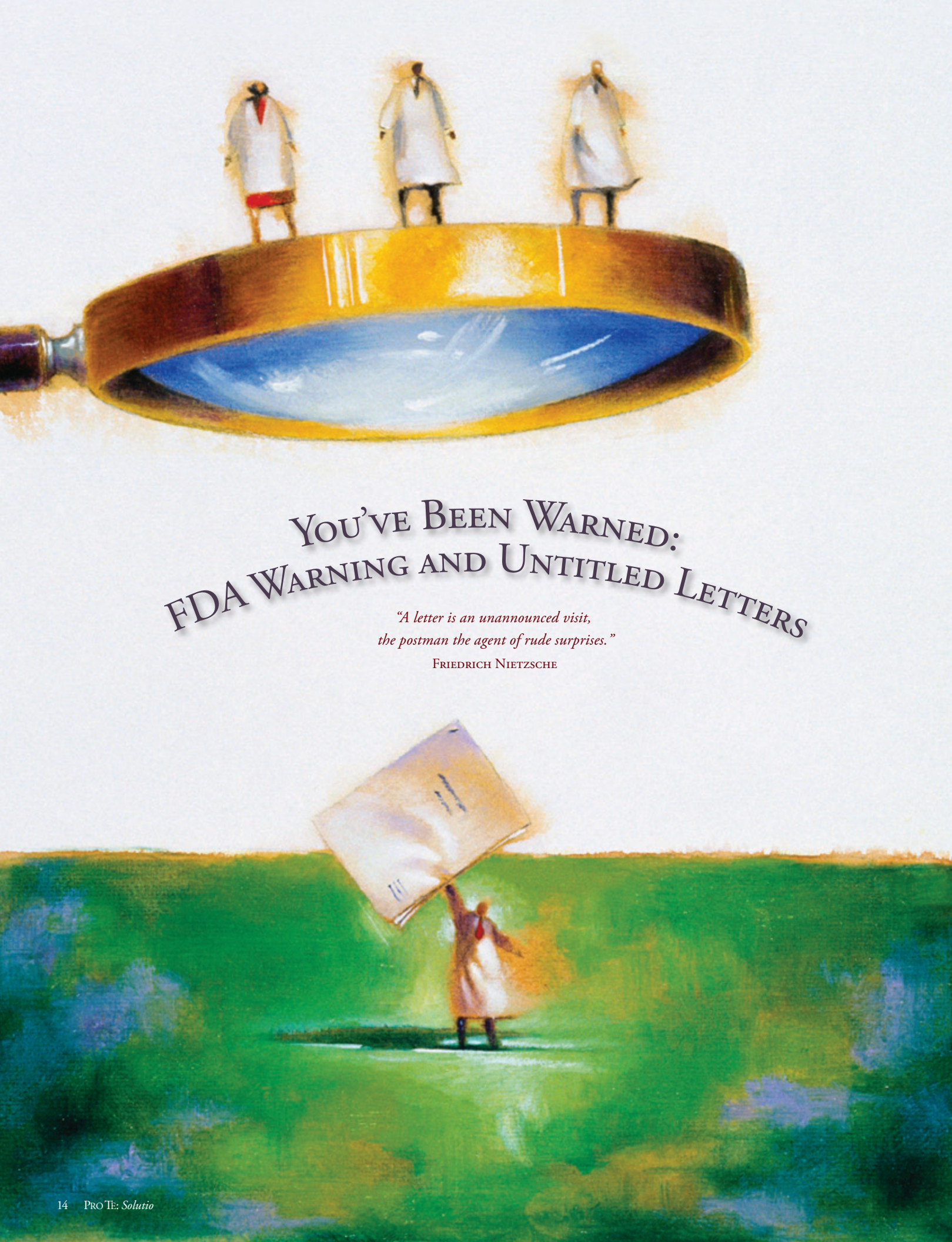
<sup>27</sup> *Id.*

<sup>28</sup> See Healthy People 2010, *supra* note xiv.



WRITTEN by HOLLIE A. SMITH





## YOU'VE BEEN WARNED: FDA WARNING AND UNTITLED LETTERS

*"A letter is an unannounced visit,  
the postman the agent of rude surprises."*

FRIEDRICH NIETZSCHE

JUST AS YOU ARE TAKING THE FIRST SIP of your second cup of coffee, the mail arrives, and you catch a glimpse of FDA letterhead. Certain that the FDA has finally approved the NDA for your company's breakthrough drug or has authorized that critical clinical trial, you abandon your cup of joe, snatch the letter from the pile, and begin skimming the text. Unfortunately, before you make it through the first sentence, you realize that this letter is not the harbinger of good news. Instead, the FDA has paid you an unannounced visit and delivered a rude surprise. Yes, you've been warned.

### I. WARNING LETTERS AND UNTITLED LETTERS

The FDA uses two different types of correspondence to warn of regulatory violations — the aptly named "Warning Letter" and the oddly titled "Untitled Letter," sometimes referred to as a notice of violation letter. While Warning Letters and Untitled Letters are frequently grouped together or confused (often by the press and internet bloggers rushing to draw attention to a company's violations), the letters convey distinct messages and impose different burdens on the recipient.

Warning Letters are the FDA's "principal means of achieving prompt voluntary compliance with the Federal Food, Drug, and Cosmetic Act" and are issued for significant regulatory violations. "Significant violations" are "violations that may lead to enforcement action if not promptly and accurately corrected." Warning Letters can vary in form and style, but all Warning Letters share the following elements:

- Clearly titled: "WARNING LETTER"
- Addressed to highest known official in the corporation and sent overnight by a trackable method;
- Establishes a response period — usually 15 days;
- References the dates of any inspections;
- Describes the violative condition, practice, or product in brief but sufficient detail to provide the respondent the opportunity to take corrective action;
- Cites the section of the law and, where applicable, the regulation violated;

- Acknowledges any corrections promised during an inspection, annotated on an FDA Form 483 Inspectional Observations report or provided to the district in a written response;

- Demands that prompt corrective action be taken;

- Advises that failure to achieve prompt correction may result in enforcement action without further notice; and

- Advises that other federal agencies will be informed of the Warning Letter so that they may consider it when awarding contracts.

Moreover, after the response period, the FDA requires a follow-up inspection to confirm implementation of corrective action.

Slightly less serious than a Warning Letter (but just as undesirable), an Untitled Letter is an "initial correspondence [...] that cites violations that do not meet the threshold of regulatory significance for a Warning Letter." See FDA Regulatory Procedures Manual, Chapter 4, Advisory Actions, 4-2 Untitled Letters. An Untitled Letter requests, rather than requires, a response within a reasonable amount of time — usually 30 days, does not advise that failure to take prompt corrective action will result in an enforcement action and does not evoke a mandated district follow-up.

The FDA posts all Warning Letters issued after December 11, 1996, on its website. Untitled Letters issued by the Division of Drug Marketing, Advertisement, and Communications (DDMAC) and the Center for Biologics Evaluation and Research (CBER) are also available on the FDA's website. Letters from recent years provide valuable

insight into the FDA's level of commitment to regulatory enforcement, the regulatory violations that currently capture the most attention, and the types of mistakes made by industry. Armed with such knowledge, a company can take steps to improve its own regulatory compliance and decrease the likelihood that it will receive a Warning Letter or Untitled Letter.

### II. RECENT TRENDS

During its 2001 fiscal year, the FDA issued 1,032 Warning Letters. Beginning in March 2002, the FDA's Office of Chief Counsel (OCC) began reviewing all Warning Letters before issuance in order to ensure "legal sufficiency and consistency with Agency policy." Thereafter, the number of Warning Letters issued plummeted, reaching a low of 445 for the 2008 fiscal year.

In 2009, FDA Commissioner Dr. Margaret Hamburg proclaimed that the FDA would be strengthening its enforcement strategies via additional inspections and compliance activities. One such enforcement strategy was to speed up the issuance of Warning Letters by limiting OCC review to "significant legal issues."

As a result of these enforcement initiatives, the number of Warning Letters issued by the FDA is on the rise. Approximately one month before the end of fiscal year 2010, the FDA has issued 563 Warning Letters — an increase of 19% from fiscal year 2009 and 26.5% from fiscal year 2008. At the center level, the Center for Drug Evaluation and Prevention (CDER) is the greatest champion of Commissioner Hamburg's

directive, issuing at least 28% more Warning Letters in fiscal year 2010 than in fiscal year 2009. The Center for Devices and Radiological Health (CDRH) takes second place with at least a 21% increase over the 2009 fiscal year. Collectively, the Center for Food Safety and Applied Nutrition and the Center for Veterinary Medicine account for an increase of 15%. If the Center for Biologics Evaluation and Research issues fewer than three Warning Letters before September 30, it will be the only center to record a decrease in the number of Warning Letters issued in fiscal year 2010.

Clearly the FDA's attention is focused on the pharmaceutical and medical device industries. Further analysis of the past two fiscal years indicates that the FDA has and likely will continue to target certain categories of violations: pre-market approval; current good manufacturing practices; drug marketing, advertising, and communication; medical device reporting; and clinical trials.

**1. Pre-Market Approval.** Both pharmaceutical and device manufacturers are experiencing continued scrutiny from the FDA in the area of pre-market approval. The number of Warning Letters issued by CDER for failure to obtain new drug approval has almost doubled that of fiscal year 2009 and accounts for 43% of all CDER Warning Letters issued in fiscal year 2010.

With approximately one month remaining in fiscal year 2010, the CDRH has issued 40 Warning Letters for failure to obtain pre-market approval of a device — the same number it issued in fiscal year 2009. As of September 2, 2010, these letters constitute 33% of all CDRH Warning Letters for fiscal year 2010.

**2. Current Good Manufacturing Practices.** Another area in which both pharmaceutical and device manufacturers have felt the impact of the FDA's crackdown is that of Current Good Manufacturing Practices (CGMP). Warning Letters for CGMP violations often follow a physical inspection, prior notice of violations via a FDA Form 483 Investigational Observations report,

and an inadequate response thereto by the manufacturer.

On the pharmaceutical side, CGMP violations accounted for 27% of all Warning Letters issued by CDER in fiscal year 2009. With one month remaining in fiscal year 2010, the CDER has issued 4 more CGMP Warning Letters than it did in fiscal year 2009.

With respect to device manufacturers, 51% of DCRH Warning Letters for fiscal year 2009 cited CGMP violations. Although it appears that CGMP violations issued by the CDRH have decreased during fiscal year 2010, to 33% of all CDRH Warning Letters, CGMP violations still account for the majority of CDRH Warning Letters issued.

— IN 2009, —  
**FDA COMMISSIONER  
 DR. MARGARET HAMBURG  
 PROCLAIMED THAT THE FDA  
 WOULD BE STRENGTHENING ITS  
 ENFORCEMENT STRATEGIES  
 VIA ADDITIONAL INSPECTIONS  
 AND COMPLIANCE ACTIVITIES.**

Within both industries, the FDA is generally focused on shortcomings in quality control, process validation, training control, and corrective/preventative action. Specifically, the FDA places emphasis on: (i) failure to have and/or follow written procedures for production and process controls, (ii) failure to investigate product specification lapses, (iii) failure to adequately clean and maintain manufacturing equipment or otherwise prevent contamination, (iv) failure to adequately train employees, and (v) failure to have and/or follow procedures regarding consumer complaints.

**3. Drug Marketing, Advertising, and Communication.** The Division of Drug Marketing, Advertising, and Communication (DDMAC) accounts for a small percentage of the overall Warning Letters issued by the CDEP but, relatively speaking, is

making a lot of noise in the enforcement arena. Thomas Abrams, head of DDMAC, confirmed that the DDMAC is “trying to get the point across to industry that we want them to comply with the law because it affects public health [...]. If you don't comply with the law, we are going to take action. We are not going to tolerate having consumers or healthcare professionals misled.”

The number of DDMAC Warning Letters increased 18% in calendar year 2009. With four months remaining in 2010, DDMAC has issued 11 Warning Letters — the same number it issued for all of 2008. If DDMAC continues to issue warning letters at its current rate, the number of letters issued during calendar year 2010 could potentially double the number issued in 2009. Even more noteworthy is the increased number of Untitled Letters issued by DDMAC. In calendar year 2008, DDMAC issued just ten Untitled Letters. In calendar year 2009, the number rose to 28 — an increase of 180%. With four months left in 2010, DDMAC has issued 31 Untitled Letters — three more than it issued in 2009 — laying the foundation for another prolific year.

DDMAC Warning Letters are based primarily on reviews of promotional materials aimed at healthcare professionals and consumers including product detailing aids, direct-to-consumer advertisements (print and television), manufacturer's websites, advertising banners on internet search engines, and social media links such as Facebook Share. For the fourth consecutive year, omission and/or minimization of risk information was the most frequently cited violation — appearing in 90% of Warning and Untitled letters issued thus far in fiscal year 2010. Allegations regarding overstatement of efficacy have risen one spot to claim second place, now comprising 71% of all Warning and Untitled Letters. The third most cited violation by DDMAC in fiscal year 2010 is unsubstantiated superiority claims at 59%. Other frequently cited violations include broadening of indication (the second place finisher for fiscal year 2009), omission of material facts, and failure to submit material for approval.



**4. Medical Device Reporting.** The number of Warning Letters citing violations of medical device reporting (MDR) requirements skyrocketed from three in fiscal year 2009 to 40 as of September 2, 2010. It is possible that much of this dramatic increase can be written off as an anomaly since 29 of the 40 letters were sent to medical device user facilities for failure to develop MDR procedures. However, the fact that nine warnings have been sent to device manufacturers thus far in 2010 — three times the number sent in fiscal year 2009 — is significant. The most cited violation was failure to develop, maintain, and implement written MDR procedures for internal systems that provide for timely and effective identification, communication, and evaluation of events that may be subject to MDR requirements, as required by 21 CFR §803.17. Additionally, device manufacturers were repeatedly cited for failure to timely report device-related injuries, or potential for device-related injuries, to the FDA.

**5. Issues Related to Clinical Trials.** Violations relating to clinical trials account for 10% of Warning Letters sent by CDER and CDRH thus far in fiscal year 2010. Based on the current rate, the actual number of clinical trial related Warning Letters issued by CDER in fiscal year 2010 likely will be consistent with the number issued in fiscal year 2009, while the number of letters issued by CDRH in fiscal year 2010 will increase by 50%.

The majority of letters sent by each center were to clinical investigators following an inspection of the trial site. The most frequently cited violations are: (i) failure to conduct the investigation according to the signed agreement, the investigational plan, and/or FDA regulations; (ii) failure to maintain accurate and complete records of each subject's case history; (iii) failure to maintain other required records; (iv) failure to adequately obtain informed consent from trial subjects; (v) failure to promptly report changes in the research activity to the institutional review board; and (vi) failure

to ensure proper monitoring of the clinical investigations.

**III. TIPS FOR AVOIDING UNTITLED LETTERS AND WARNING LETTERS**

While not an exhaustive list, the following tips can help reduce the likelihood that your company will receive an Untitled Letter or Warning Letter:

- **Generally:** Be proactive — do not wait on the FDA to come to you. Continue to learn from others. Take a more in-depth look at the Warning Letters and Untitled Letters previously submitted to members of your industry. Use the specific details in those letters as a roadmap for your actions.
- **Pre-Market Approval:** Do not market, promote or sell your product until you have confirmed that FDA approval is not required or have received appropriate approval by the FDA. Keep abreast of the FDA's ever-evolving treatment of products to understand how changes in approval requirements impact your product.



- **CGMP:** Invest in the development of continuous and dynamic quality control systems, validation systems, corrective/preventative systems, and training programs. Document all procedures in writing, and follow them without fail. Keep records and make sure all records are detailed, accurate, complete, and up to date. Undertake prompt and comprehensive corrective action following an inspection. Submit a detailed and complete response to any FDA Form 483 Inspectional Observations report within 15 days of the report's issuance even though there is no regulatory requirement to respond. In her January 2009 presentation *Writing an Effective 483 Response*, Anita Richardson, Associate Director of Policy for the FDA Office of Compliance & Biologics Quality, provides rationale for submitting a 483 response and tips for making the response effective.

- **DDMAC:** Support all claims, including comparative claims, with "substantial evidence." As explained by the FDA to consumers: "Substantial evidence refers to the data needed to support claims about an advertised drug. Before the FDA approves a drug for marketing, drug companies must complete studies to show that the drug does what they say it does. These studies are also required to support advertising claims about the drug. Drug companies need to have at least two studies to support these claims." Do not omit or downplay risks. Do not distract the consumer from the presentation of risks when using audio or visual media. Do not overstate efficacy. Do not imply increased efficacy by suggestion or omission. Do not fail to indicate limitations of the drug or otherwise gloss over drug limitations. Do not rely on fine print, referencing or attaching labeling, or brief disclaimers to offset inaccurate/unsupported claims. Use caution with social networking sites and other internet technology as they are uncharted territories. The Food and Drug Law Institute has published a "comprehensive guidebook on the use of social media in the food and medical products area" entitled *Using Social Media in FDA-Regulated Industries: The Essential Guide* which may prove

helpful in navigating these new areas.

- **Medical Device Reporting:** Make written plans. Timely notify the FDA of adverse events in accordance with applicable regulations.

- **Clinical Investigators:** Obtain proper informed consent from trial subjects. Follow all procedures and protocols. Monitor the trial. Keep detailed, accurate, complete, and current records. Report any deviations to the IRB.

#### IV. WHAT TO DO IF YOU RECEIVE A WARNING OR UNTITLED LETTER

If your company receives a Warning Letter or an Untitled Letter, you must respond promptly and appropriately. At a minimum, you should undertake the following steps to address the FDA's concerns and prevent the warning from escalating into an enforcement action:

- Take the letter very seriously even if, due to the lack of OCC review, it does not address significant legal issues or is legally deficient. Recently, FDA legal expert Arnold Friede noted that "people in the [pharmaceutical industry] aren't paying attention to these letters" and wondered "how far up against the wall industry will push the FDA before [increasingly severe] actions are taken." Even if others have dodged FDA enforcement actions after ignoring a letter, do not set your company up to be the straw that breaks the camel's back.

- Read the letter very carefully. Calendar any deadlines (and sufficient pre-deadline reminders).

- Compile a list of each and every violation alleged and determine the corrective action(s) required and/or requested for each.

- Respond within the applicable time-frame or request an extension.

- Consider engaging legal counsel or an FDA regulatory expert to chart a course of action and to assist with drafting the detailed response.

- Contact the listed FDA agent with any questions.

- Consider requesting a meeting with the FDA to discuss the letter, confirm

your understanding of the FDA's concerns, receive additional comments and insight from the FDA, and inquire as to the sufficiency of proposed the corrective action.

- Prepare a thoughtful and thorough response.
- Convey your company's position fully yet succinctly through a factual response.

If the Warning or Untitled Letter follows on the heels of a Form 483 Inspectional Observations report, look back at the Form 483 to see if it describes the violations more fully. If so, use the Form 483 as a guide to structure your letter. If there are differences between the Form 483 and the letter that trouble you, contact the FDA to discuss. Also, review your response to the Form 483, and make sure the response to the Warning or Untitled letter does a better job of answering the FDA's allegations.

- Address each and every concern raised by the FDA.

- Do not downplay the importance of the violations or attempt to justify them as industry practice.

- Clearly state in detail what action(s) your company has taken or will take to address the FDA's current concerns and to prevent future similar violations.

- Do not promise a corrective action unless it can be achieved.

- Try to complete the corrective action prior to the response deadline. If the corrective action is completed before the deadline, the response should include documentation showing that the correction has been achieved.

- If corrective action cannot be completed before the response time, explain the reason(s) for the delay and set forth a time frame within which corrective action will be completed.

- If disputing the FDA's findings and/or if your company will not agree to any corrective action, explain in detail the rationale behind the position and submit any supporting documentation. Carefully consider the ramifications of taking such a defensive position.

- Consider whether you want the FDA to post your company's response on its website. (Since May 2000, only 84 responses



have posted for all categories of FDA Warning Letters.)

- Follow through with all promised actions.
- Keep records of corrective actions to facilitate a prompt response to any follow-up by the FDA. If the corrective action is completed after the initial response deadline but before FDA follow-up, send written notification to the listed FDA agent and include supporting documentation.

Make lemonade from lemons. Use the letter as an opportunity to improve your company and reduce likelihood of future Warning Letters and/or Untitled Letters.

## V. CONCLUSION

In fiscal year 2011, members of the pharmaceutical and device industry can expect, yet again, to feel the full weight of the FDA's recommitment to regulatory enforcement. However, once equipped with an understanding of recent FDA Warning and Untitled Letters, you can formulate a proactive compliance strategy for your company, avoid rude surprises from the FDA and

maybe even enjoy a cup of coffee without dreading the arrival of your friendly neighborhood postman.

<sup>1</sup> See FDA Regulatory Procedures Manual, Chapter 4, Advisory Actions, 4-1-1 Warning Letters.

<sup>2</sup> *Id.*

<sup>3</sup> See FDA Regulatory Procedures Manual, Chapter 4, Advisory Actions, 4-1-10 Warning Letter Format.

<sup>4</sup> See *Id.* at 4-1-8 Warning Letter Follow-Up.

<sup>5</sup> *Id.*

<sup>6</sup> See FDA *The Enforcement Story* 2001. Enforcement Statistics. Available at <<http://www.fda.gov/ICECI/EnforcementActions/EnforcementStory>>. Last accessed Oct. 19, 2010.

<sup>7</sup> See FDA Regulatory Procedures Manual at Exhibit 4-1 (Mar. 2009).

<sup>8</sup> See FDA Enforcement Story 2008. Enforcement Statistics. Available at <<http://www.fda.gov/ICECI/EnforcementActions/EnforcementStory>>. Last accessed Oct. 19, 2010.

<sup>9</sup> Hamburg, M.D., Margaret. *Remarks at the Food and Drug Law Institute*. Aug. 6, 2009. Available at <<http://www.fda.gov/NewsEvents/Speeches/ucm175983.htm>>. Last accessed Oct. 19, 2010.

<sup>10</sup> *Id.*

<sup>11</sup> Heavey, Susan. *FDA Ad Chief Says Drugmaker Warnings Double*. Reuters. Jan. 30, 2010. Available at <<http://in.reuters.com/article/idINTRE60S63J20100129>>. Last accessed Oct. 19, 2010.

<sup>12</sup> See <http://www.fda.gov/ICECI/EnforcementActions/WarningLetters> and <http://www.fda.gov/Drugs/Guidance>

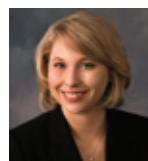
ComplianceRegulatoryInformation/EnforcementActivities byFDA/WarningLettersandNoticeofViolationLetters toPharmaceuticalCompanies.

<sup>13</sup> Richardson, Anita. *Writing an Effective 483 Response*. Presentation, 5th Annual FDA and the Changing Paradigm for HCT/P regulation, University of Rhode Island and Pharma Conference. Jan. 2009. Available at <[www.fda.gov/downloads/BiologicsBloodVaccines/.../UCM102921.pdf](http://www.fda.gov/downloads/BiologicsBloodVaccines/.../UCM102921.pdf)>. Last accessed Oct. 19, 2010.

<sup>14</sup> FDA. *Drug Advertising: A Glossary of Terms*. Last updated June 24, 2009. Available at <<http://www.fda.gov/Drugs/ResourcesForYou/Consumers/PrescriptionDrugAdvertising/ucm072025.htm#S>>. Last accessed Oct. 19, 2010.

<sup>15</sup> Comer, Ben. "DDMAC Regulatory Letters Could Double in 2010." *Medical Marketing & Media*. July 22, 2010. Available at <<http://www.mmm-online.com/ddmac-regulatory-letters-could-double-in-2010/article/175154/>>. Last accessed Oct. 19, 2010.

<sup>16</sup> Lookabaugh, Mark. *Responding to FDA 483s and Warning Letters*. Presentation, Parenteral Drug Association. May 17, 2006. Available at <<http://www.pda.org/MainMenuCategory/Chapters/New-England/Presentations/Responding-to-a-Form-483-or-Warning-Letter.aspx>>. Last accessed Oct. 19, 2010.



WRITTEN by KIM COGGINS

## TOTAL NUMBER OF FDA WARNING LETTERS SENT BY FDA FISCAL YEAR (October 1 – September 30)

	FY 2005	FY 2006	FY 2007	FY 2008	FY 2009	FY 2010 (as of 9/2/10)
TOTAL NUMBER	535	538	471	445	474 (6.5% increase from 2008)	602 (27% increase from 2009 and 35% increase from 2008)

## WARNING LETTERS BY FDA CENTER (Including district offices)

	FY 2005	FY 2008	FY 2009	PERCENT INCREASE FROM 2008 TO 2009	FY 2010 (as of 9/2/10)	PERCENT INCREASE FROM 2009 TO 2010
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH	182	152	137	-9%	172	26%
CENTER FOR DRUG EVALUATION AND RESEARCH	79	87	127	46%	179	41%
CENTER FOR BIOLOGICS EVALUATION AND RESEARCH	37	11	19	73%	16	-16%
CENTER FOR FOOD SAFETY AND APPLIED NUTRITION	237	195	191	-2%	235	23%
CENTER FOR VETERINARY MEDICINE						
TOTAL	535	445	474	6.5%	602	27%



While Warning Letters and Untitled Letters are frequently grouped together or confused (often by the press and internet bloggers rushing to draw attention to a company's violations), the letters convey distinct messages and impose different burdens on the recipient.

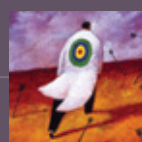
BREAKDOWN OF WARNING LETTERS BY PRIMARY SUBJECT AREAS

CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

	FY 2009	FY 2010
CURRENT GOOD MANUFACTURING PRACTICES (CGMP)	71 (52% of CDRH letters)	61 (35 % of CDRH letters)
PRE-MARKET APPROVAL	40 (29% of CDRH letters)	40 (33% of CDRH)
MEDICAL DEVICE REPORTING	3 (2% of CDRH letters)	41 (24% of CDRH)
ISSUES RELATED TO CLINICAL TRIALS	11 (8% of CDRH letters)	17 (10 % of CDRH)

CENTER FOR DRUG EVALUATION AND RESEARCH

	FY 2009	FY 2010
(CGMP)	34 (27% of CDER letters)	40 (22% of CDER letters)
UNAPPROVED NEW DRUG; MISBRANDING	36 (28% of CDER letters)	80 (45% of CDER letters)
DIVISION OF DRUG MARKETING, ADVERTISING AND COMMUNICATIONS (DDMAC)	13 (10% of CDER letters)	14 (8% of CDER letters)
ISSUES RELATED TO CLINICAL TRIALS	21 (17% of CDER letters)	21 (12% of CDER letters)



The FDA posts all Warning Letters issued after December 11, 1996, on its website. Untitled Letters issued by the Division of Drug Marketing, Advertisement, and Communications (DDMAC) and the Center for Biologics Evaluation and Research (CBER) are also available on the FDA's website. Letters from recent years provide valuable insight into the FDA's level of commitment to regulatory enforcement, the regulatory violations that currently capture the most attention, and the types of mistakes made by industry. Armed with such knowledge, a company can take steps to improve its own regulatory compliance and decrease the likelihood that it will receive a Warning Letter or Untitled Letter.

DDMAC WARNING LETTERS AND UNTITLED LETTERS BY CALENDAR YEAR  
(NOT including district letters)

	CY 2005	CY 2006	CY 2007	CY 2008	CY 2009	PERCENT INCREASE FROM 2008 TO 2009	CY 2010 (as of 10/12/10)	ESTIMATED PERCENT INCREASE FROM 2009 TO 2010 (based on current issue rate applying through September)
WARNING	15	14	11	11	13	18%	11	46% (72% from 2008 to 2010)
UNTTLED	14	8	9	10	28	180%	33	89.2% (430% from 2008)
TOTAL	29	22	20	21	41	95%	44	75% (243% from 2008)

BREAKDOWN OF DDMAC WARNING AND UNTITLED LETTERS BY SUBJECT  
(Note: A single letter may address multiple subjects)

	CY 2007	CY 2008	CY 2009	CY 2010 (as of 10/12/10)
INADEQUATE PRESENTATION OF RISK INFORMATION	15 (75%)	16 (76%)	35 (85%)	38 (90% of letters issued to date)
BROADENING OF INDICATION	4 (20%)	11 (52%)	20 (49%)	11 (26% of letters issued to date)
OVERREPRESENTATION OF EFFICACY	9 (75%)	9 (76%)	17 (85%)	30 (71% of letters issued to date)
INADEQUATE SUBSTANTIATION FOR COMPARATIVE SUPERIORITY CLAIMS	8 (40%)	4 (19%)	8 (20%)	25 (59% of letters issued to date)
OMISSION OF MATERIAL FACT	2 (10%)	5 (24%)	0	8 (19% of letters issued to date)
FAILURE TO SUBMIT PROMOTIONAL MATERIAL FOR APPROVAL	2 (10%)	0	0	7 (17% of letters issued to date)

Statistical data for 2009 and 2010 compiled from a review of the FDA's listing of Warning and Untitled Letters posted on <<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters>> and <<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies>>.



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