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.

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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 timeframe 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.

[1] *See* FDA Regulatory Procedures Manual, Chapter 4, Advisory Actions, 4-1-1 Warning Letters.

[2] *Id.*

[3] *See* FDA Regulatory Procedures Manual, Chapter 4, Advisory Actions, 4-1-10 Warning Letter Format.

[4] *See Id.* at 4-1-8 Warning Letter Follow-Up.

[5] *Id.*

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

[7] *See* FDA Regulatory Procedures Manual at Exhibit 4-1 (Mar. 2009).

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

[9] 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.

[10] *Id.*

[11] 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.

[12] *See* http://www.fda.gov/ICECI/EnforcementActions/WarningLetters and http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCompanies.

[13] 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>. Last accessed Oct. 19, 2010.

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[15] 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.

[16] 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.

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