



Medical Device Congress

Warning Letters: Strategies for Responding and their Impact in the Marketplace

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Topics We Will Address

- What FDA is Really Saying when it Issues a Warning Letter
- Responding Effectively to Warning Letters
- Whether to Publish a Warning Letter Response
- Corporate Warning Letters
- Impact of Warning Letters on Subsequent Litigation
- Key Takeaways

What FDA is Really Saying when it Issues a Warning Letter

What Does FDA's Decision to Issue a Warning Letter Really Mean

- FDA perceives violations to be of regulatory significance.
- FDA likely thought the 483 response was inadequate.
- FDA does not trust the company to correct problems sufficiently on its own.
 - By issuing a warning letter, FDA requires the Company to pay more attention to the issues.
 - By issuing a warning letter, FDA requires the manufacturer to explain how it plans to address the deficiencies.
 - FDA requires the company to deal aggressively with the issues by suspending product reviews and export certificates until corrections are made.

What Does FDA's Decision to Issue a Warning Letter Really Mean

- Warning Letters typically represent the first step if an inspection was classified as official action indicated (OAI).
- Warning Letter is often the last warning that failure to achieve prompt corrective action may result in enforcement action.
- FDA is not required to issue a warning letter before taking further legal action (e.g., injunction, seizure, criminal investigation).

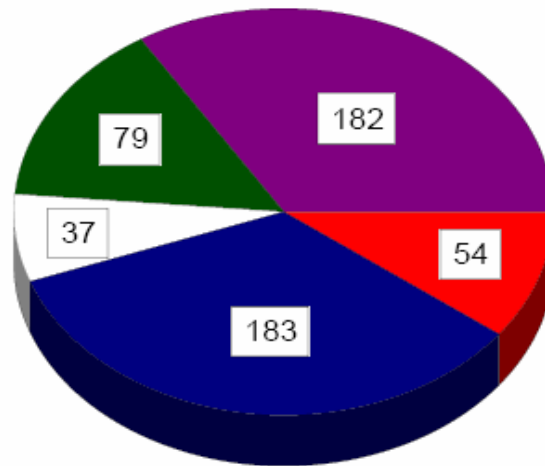
If you think a Warning Letter Might be Coming . . .






- A company's response to a Warning Letter often can begin before an anticipated Warning Letter is received.
 - Because a Warning Letter is likely to be based on an FDA inspection [and the items contained in the Form FDA 483], the 483 can be a guide in the early preparation of a draft response to an anticipated Warning Letter.
 - If a company anticipates that a Warning Letter may be issued because of the results of FDA's analysis of a sample of its product, it can prepare for the Warning Letter by gathering data showing that the product meets its specifications and labeling representations and can begin reviewing applicable FDA labeling requirements.

2005 Warning Letters

Warning Letters Fiscal Year 2005

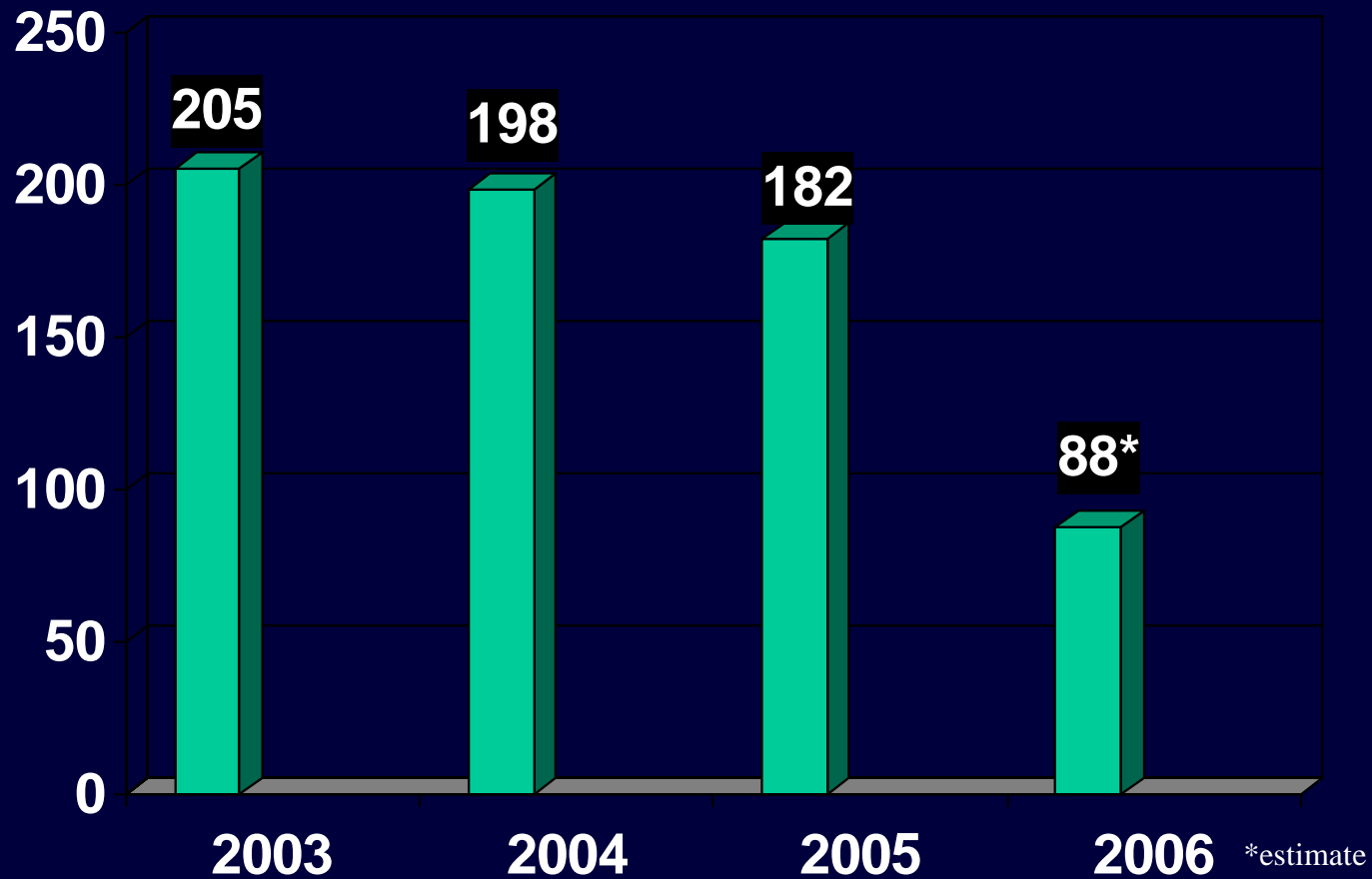
By FDA Center



-  Center for Devices and Radiological Health
-  Center for Drug Evaluation and Research
-  Center for Biologics Evaluation and Research
-  Center for Food Safety and Applied Nutrition
-  Center for Veterinary Medicine

Total Warning Letters = 535

CDRH Warning Letters 2003 - 2006



Responding Effectively to Warning Letters

The **DOs** of Effectively Managing the Response to a Warning Letter

- **DO** Respond within the timeframe unless you request an extension.
- **DO** Request a meeting with FDA if 483 response resulted in continued disagreement regarding correct path forward.
- **DO** State your commitments upfront, both those that are global and those that are particular to 483 observations.

The **DOs** of Effectively Managing the Response to a Warning Letter

- **DO** Tell the story by following a chronology of events, and by sticking to the facts.
- **DO** Compare the Warning Letter to the 483 to look for any differences in what was cited.
 - If you are unclear on reasons for differences, contact the District or Center.
- **DO** Consider hiring an outside expert, known to FDA, to assist in formulating a comprehensive plan to address FDA's concerns.

The Warning Letter Response: To Publish or Not to Publish

Publishing a Warning Letter Response

- FDA will post a Warning Letter response if requested by the company;
- Posted responses are redacted to the extent permitted by the Freedom of Information Act;
- FDA reserves the right not to post certain Responses, such as when posting likely would mislead the public about the safety or efficacy of a regulated product;
- Only 15 responses to CDRH Warning Letters have been posted since 2003.

Corporate Warning Letters

What is a Corporate Warning Letter

- Issued very rarely-3 to date, including:
 - Boston Scientific Corporation
 - Cordis Corporation
- Generally reflect an assessment by FDA that the company has corporate-wide, systemic deficiencies;
- Ordinarily not limited to a particular facility, but are focused on problems occurring across business units;
- Signed by the Director of the Product Center, in addition to the District Office Director; and
- Generally focus on failures at the highest levels of management to correct deficiencies across an organization.

The Potential Impact of a Warning Letter in Subsequent Litigation

Impact of Warning Letters in Subsequent Litigation with FDA

- Failure to adequately address deficiencies and violations cited in a Warning Letter can lead to future enforcement action by FDA, including:
 - Seizures
 - Injunction
 - Civil Penalties
 - Criminal Prosecution

Impact of Warning Letters in Subsequent Litigation in the Mass Tort Arena

- Warning letters provide strong ammunition to plaintiffs' lawyers in the mass tort arena:
 - Allow plaintiffs' attorneys to claim that FDA has judged that the company's actions were in violation of FDA's laws and/or regulations;
 - Strengthen design defect claims; and
 - Give claims of improper marketing greater legitimacy than they would otherwise have.
- Consider the warning letter issued relating to marketing of Vioxx.

Merck Warning Letter (9/17/01)

- Accused Merck of delivering messages that were false, misleading and lacking in fair balance during:
 - promotional audio conferences, a press release, and in oral statements by sales reps
- Promotional campaign “minimizes the potentially serious cardiovascular findings that were observed in [a company] study and thus misrepresents the safety profile for Vioxx”
- Promotional activities “minimize the Vioxx/coumadin drug interaction, omit important risk information, make unsubstantiated superiority claims against other NSAIDs, and promote Vioxx for unapproved uses and an unapproved dosing regimen.”
- “Your misrepresentation of the safety profile for Vioxx is particularly troublesome because we have previously, in an untitled letter, objected to promotional materials for Vioxx that also misrepresented Vioxx’s safety profile”

Merck Warning Letter (9/17/01)

- Physician-led audio conferences minimized drug interactions, omitted risk information, made unsubstantiated superiority claims, and promoted Vioxx for unapproved uses and dosing regimens.
 - How did FDA know what was said?
- Press release stating that Vioxx has a favorable cardiovascular safety profile “is simply incomprehensible, given the rate of MI and serious cardiovascular events compared to naproxen.”
- Sales reps made false and misleading statements to DDMAC reviewers at professional meetings that minimized the potentially serious MI results observed in a company trial.

Merck Warning Letter (9/17/01)

- FDA required the following corrective actions:
 - ceasing dissemination of all violative promotional activities;
 - issuing a Dear Doctor letter, to be approved by FDA, to all HCPs that might have received the violative messages;
 - a written response to FDA, including a comprehensive action plan to disseminate corrective messages; and
 - dissemination of corrective messages to the audiences who received the information.

Did the Warning Letter Re-appear?



CASE STUDY 1: VIOXX TARGETING DOCTORS WITH DECEPTIVE MESSAGES ABOUT POTENTIALLY FATAL RISKS

most important drugs, with \$2.5 billion in sales in 2003 alone.⁷² Merck withdrew Vioxx from the market in September 2004 after clinical data unequivocally demonstrated serious heart risks with its use. During its five years on the market, millions of people took Vioxx, resulting in an estimated 88,000-139,000 heart attacks of which some 26,000-55,000 were likely fatal.⁷³

two professional conferences.

The Vioxx letter and surrounding story involves several key features of the deceptive marketing problem, but it makes a good showcase for one in particular: doctors are being heavily targeted with potentially deadly false messages about risks.

because we have previously, acted to promotional materials x's safety profile." (FDA

Warning Letter addressed were n which a doctor gave a Merck- itation to colleagues; a press y Merck sales representatives at

Targeting Doctors

In September, 2001, the FDA wrote to Merck regarding its promotion of Vioxx. The Warning Letter described several different types of promotional activities that minimized the serious risks associated with Vioxx use—the same heart attack risks that Merck is now being sued for failing to warn about—

Did the Warning Letter Re-appear?

Defective Drugs adrugrecall.com

This site provides news and legal information about defective drugs which may cause serious side effects.

Vioxx Recall
Alert
Alternative
Attorney
Caution
Claim
Class Action

been heeded much sooner than the recall of this dangerous pain medication. Vioxx was approved by the FDA in 1999 as an effective treatment for chronic pain conditions like rheumatoid and osteoarthritis and menstrual cramps. No Vioxx warning statements were made to the public by the FDA or the drug's maker, Merck, to educate patients about the potential risks associated with this defective drug.

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Warning
Withdrawal
Contact a lawyer

gastrointestinal effects of Vioxx and naproxen, a traditional NSAID. The results, published in 2001, showed a significant risk of stroke, heart attack, and other serious side effects among the Vioxx trial participants.

Arguably, this Vioxx warning should have prompted an immediate investigation of the risks associated with Vioxx. Instead of taking the Vioxx warning seriously, Merck decided to downplay the risks and argue that these clinical findings were not worthy of further investigation. In September 2001, two years before the Vioxx recall, a member of the FDA sent a Vioxx warning letter to Merck, expressing concern over their advertising practices and lack of actionable concern in response to the VIGOR study.

In this Vioxx warning letter the FDA representative expressed serious concern about Merck's practices. The letter stated that, after a review of their promotional activities and materials, the FDA, "has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of federal law." The Vioxx warning from the FDA tells Merck that they have "engaged in a campaign that minimizes the potentially

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In this Vioxx warning letter the FDA representative expressed serious concern about Merck's practices. The letter stated that, after a review of their promotional activities and materials, the FDA, "has concluded that they are false, lacking in fair balance, or otherwise misleading in violation of federal law." The Vioxx

Key Takeaways: Actions you can Take to Prevent Warning Letters and Further Enforcement Action

- Spend time to provide a comprehensive response to an FDA 483.
- Undertake timely and comprehensive corrective action.
- Ensure sustainable quality systems are developed
 - Implement appropriate policies and Standard operating procedures to ensure compliance.
 - Conduct firm-wide training to inform employees of company policies and procedures.

Key Take-Aways: Global Messages for Ensuring Compliance

- Take employee and FDA complaints seriously.
- Don't let your regulatory compliance situation progress to the point of receiving a Warning Letter - devote time and resources to correcting problems at the earliest stages.
- Invest in regulatory and quality - too often these areas are the first to be cut because ROI can't be done to justify the costs.
- The cost of FDA enforcement action are far more expensive than the cost of a robust compliance program.