Under the Watchful Eye

What Do FDA Warning Letters Tell Us?

By Kevin L. Ong, Joshua White, Eric Swanis, and Sara Deskins Tucker

Warning letters are being issued more frequently by the United States Food and Drug Administration (FDA). Failing to comply with FDA warning letters may lead to severe repercussions such as product seizures, withholding of regulatory approvals/clearances and even civil penalties. Warning letters may also be admitted as evidence in a product liability case. While the FDA's Quality System Regulations provide a comprehensive and systematic framework for companies to follow during device development, analysis of trends from warning letters issued by the FDA indicates that there are still areas for improvement.

Appropriate design controls improve the product development process, shorten development time and subsequently lower manufacturing costs. They also allow manufacturers to recognize potential problems earlier, to respond to the FDA's concerns, to make corrections and, ultimately, to meet customers' expectations. Finally, implementation of adequate design controls helps to avoid FDA warning letters in the first place, thereby avoiding FDA sanctions and limiting product liability exposure.

Evolution of Quality Assurance

As the American population ages, there has been a corresponding increase in healthcare needs, including the use of

drugs and medical devices, to improve quality of life. There has also been an increasing need for treatment options to address chronic conditions such as obesity and diabetes, which not only affect older generations, but are also becoming more common in younger populations. The prevalence of these conditions has spurred growth in the research and development of pharmaceutics, diagnostics, and medical technologies to treat these disorders. This has necessitated a corresponding increase in the regulation and oversight of these technologies.

The life sciences industry is highly regulated worldwide. In the United States, regulatory oversight is provided by the FDA for matters related to safety and efficacy and compliance with quality systems. Quality systems are guided by Quality System Regulations, which became effective in 1997 and replaced the previous 1978 Good Manufacturing Practices for medical devices. The updated regulation added design controls after the FDA found that 44 percent of quality issues leading to voluntary recall actions were attributable to errors or deficiencies in product design that may have been prevented by adequate design controls. The regulation was also revised to ensure consistency with international standards for quality systems. The Quality System Regulations provide a framework for companies to achieve quality requirements. Quality requirements relate to methods used in, and the facilities and controls used for, designing, manufacturing, packaging, labeling, storing, installing, and servicing of medical drugs and devices.

FDA Inspections and Quality Systems

One of the ways the FDA confirms compliance with quality regulations is through inspections and audits. The FDA inspects manufacturers of finished medical devices and drugs as well as suppliers of components, parts or accessories of devices. Inspections are not limited to domestic manufacturing sites, but also include foreign sites that produce FDA-regulated products or components that are imported into and sold within the United States, as well as domestic sites that import and distribute foreign-manufactured goods to be sold within the United States. Routine and periodic inspections are conducted, typically biennially, but can be performed at any time for the following reasons:

- "For cause" to investigate problems brought to the FDA's attention regarding product safety or commercial fraud
- Follow-ups to verify appropriate corrective actions have been taken
- In response to third party complaints
- Pre-approval/clearance inspection
- Initial inspections of new facilities or newly-registered establishments
- Initial inspections under new management and/or ownership.

During inspections, the FDA seeks to, *inter alia* determine the site's level of compliance with relevant regulations; determine if any corrective actions are needed to protect public health and safety; and/or gather facts in support of enforcement action. The FDA inspects facilities, documents, production processes, samples of products and labeling, and also interviews staff. The focus is on various quality system subsystems, which provide top-level guidance for various aspects of the design and manufacturing processes to ensure finished devices are produced in compliance with FDA regulatory standards and to ensure they are safe and efficacious for the general public. The quality system subsystems fall into five general categories:

Production and Process Controls. Production and process controls generally relate to establishing and maintaining procedures to document, monitor and verify compliance of the manufacture of the device. These processes are applied to all phases of production beginning with initial purchase and receipt of raw materials and/or parts and extending to the sale, distribution, installation and servicing of the finished product.

Corrective and Preventive Actions. Corrective and preventive actions generally relate to establishing and maintaining procedures for investigating non-conformances, identifying actions to address these, and verifying that these actions are effective.

Design Controls. Design controls generally involve the establishment and maintenance of procedures to control the design of the device to ensure that the specified design requirements are met.

Management Controls. Management controls refer to policies, organizational structure, resources, personnel and internal review of the quality system.

Document Controls. Document controls relates to procedures for documenting device and batch/lot-specific specifications and production processes, as well as for document approval, distribution and changes.

Warning Letters

Following an inspection, feedback is provided through Inspectional Observations, which are documented using Form 483. Although an inspector discusses significant findings and concerns with the company's management throughout an inspection, he/she will deliver a final Form 483 written report at the conclusion of the inspection. This

does not constitute a final Agency determination of whether any condition is in violation of the Food Drug and Cosmetic Act (FDCA) or any of its related regulations. Rather, Form 483 serves as a guide for corrective actions with a written response expected to the FDA within 15 working days. The company can respond to the Form 483 during discussions with the inspector in the midst of or at the conclusion of the inspection. The company's response may affect the FDA's determination of the need for follow-up action. Corrective actions or procedural changes that are accomplished immediately in the presence of the inspector are regarded as positive indications of the company's concerns and desire to voluntarily correct discrepancies. If the FDA does not receive an adequate response, or if a company's violations are serious enough in nature, the site may receive a warning letter from the FDA, have its non-conforming product sequestered or may be completely shut down.

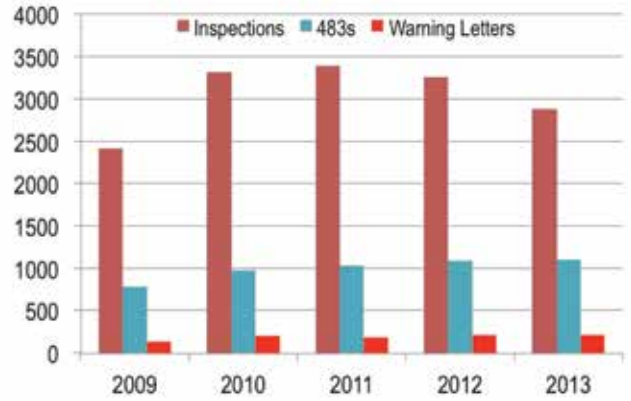
Unlike a Form 483, warning letters cite specific regulatory references for each violation. Warning letters also require a written response within 15 working days. Warning letters indicate violations of regulatory significance that could lead to enforcement actions if not promptly and adequately corrected. While they are not considered a final regulatory action by the FDA, they serve to establish prior notice. The public nature of warning letters, which are published on the FDA website, as well as the pending enforcement actions by the FDA, make warning letters one of the primary ways in which the FDA achieves prompt voluntary compliance by the manufacturer. The implications of the warning letter include potential impact on the company's requests for approval of export certificates and drug applications for pharmaceutical products.

For device manufacturers, premarket applications for Class III devices that may be affected by the violations listed in a warning letter will not be approved until these violations have been corrected. In some exceptional instances, the FDA may bypass the issuance of a warning letter and instead take immediate enforcement action. The circumstances that could potentially lead to immediate action include intentional or flagrant violations and violations that could lead to a reasonable possibility of injury or death. For example, following an FDA investigation, Schering Plough recently entered into a consent decree, agreed to pay a $500 million fine for quality violations at selected manufacturing facilities, its President/Chief Operating Officer resigned, the approval of a pharmaceutical product was delayed for almost a year, and the company's market value was estimated to have been reduced by more than $30 billion.

Trends in FDA Enforcement

Using the FDA's databases, we compiled and reviewed records of FDA Center for Devices and Radiological Health (CDRH) inspections, Form 483s, and warning letters, as well as the specific Quality System Regulations citations in the warning letters. The CDRH is the branch of the FDA that is responsible for the regulation of medical devices. Our analysis showed that in recent years, the CDRH has conducted over 3,000 inspections annually, a sharp rise from about 2,400 in 2009. This rise coincidentally followed the naming of a new FDA commissioner and the resignation of the CDRH Director in 2009. This increase in inspections was also paralleled by an increase in the number of issued 483s, which rose from 778 in 2009 to 1,099 in 2013. Furthermore, the number of quality system violations cited in warning letters also increased. In 2010, 45 percent of warning letters had quality system citations, while in 2011 to 2013 approximately 75 percent of warning letters included quality system citations. Additionally, in 2013, there was an average of 6.3 quality system citations per warning letter compared to 3.1 in 2010.

FIGURE 1



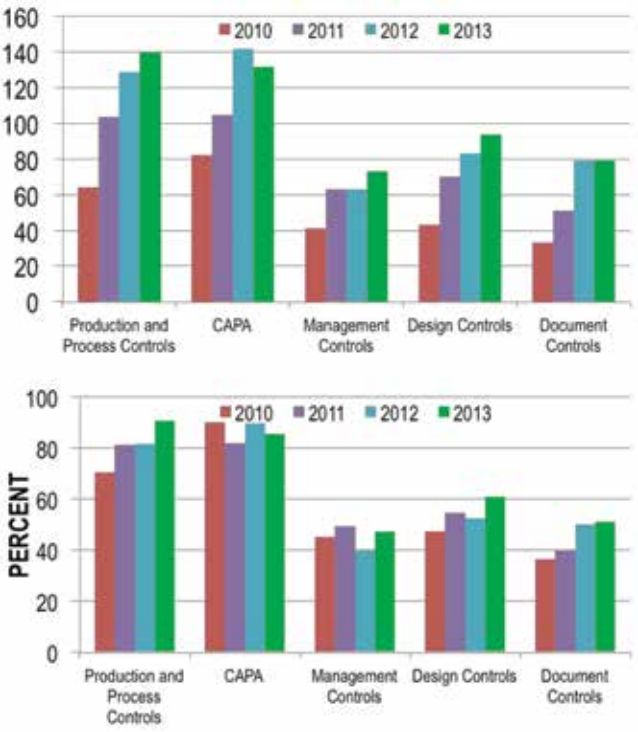
Number of FDA inspections, Form 483s, and warning letters between Fiscal Year 2009 and Fiscal Year 2013.

Violations related to production and process controls and corrective and preventive actions accounted for many of the citations, and in 2013, 91 percent of the warning letters with quality system citations included citations for production and process controls. Eighty-six percent of warning letters with quality system citations included citations for corrective and preventive actions. Furthermore, all quality system subsystems saw an increase in the number of citations over the years (Figure 2). However, only production and process controls (70 to 91 percent), design controls (47 to 61 percent) and document controls (36 to 51 percent) had a substantial increase in the percentage of quality system subsystem citations.

Across 2010 through 2013, 21 C.F.R. § 820.100(a) and 198(a) were the most commonly cited warning letter quality system deficiencies. These relate to corrective and preventive actions procedures and complaint file procedures, respectively. Furthermore, many of the same quality system citations appear as the most frequently cited deficiencies each year, which suggests that the FDA may emphasize specific aspects of the Quality System Regulations over others.

According to the FDA, in the mid-1990s, approximately 44

FIGURE 2



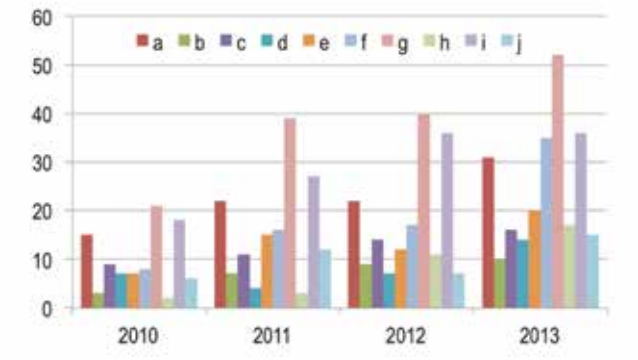
Number (top) and percent (bottom) of citations in each quality system subsystem between Fiscal Year 2010 and Fiscal Year 2013. The percent is based on warning letters with at least one quality system citation.

percent of the quality problems that led to voluntary product recalls were attributed to errors or deficiencies that were designed into particular devices and may have been prevented with adequate design controls. Two subparts of designs controls are consistently in the top ten quality system citations. As can be seen in Figure 3, there has been a general trend of increasing the number of design control citations for all subparts, which may highlight the increasing emphasis the FDA places on these criteria.

Legal Consequences of Warning Letters

Quality system citations contained in FDA warning letters could support a product liability lawsuit against the drug or medical device manufacturer. At minimum, FDA warning letters may be introduced as evidence in a product liability lawsuit. In civil litigation, plaintiff attorneys may cite this publicly available information regarding a company's alleged failure to comply with federal regulations as evidence of the company's knowledge of a product defect or failure to warn. For example, a plaintiff's attorney may try to use the warning letters to establish that the manufacturer was negligent, reckless and/or knew about a particular risk or product defect based on the information contained in the warning letter. Furthermore, a plaintiff's attorney may attempt to introduce the warning letters at trial to persuade the jury that the FDA endorses the plaintiff's claims.

FIGURE 3



Number of design control (21 C.F.R. § 820.30) citations in each quality system subsystem between Fiscal Year 2010 and Fiscal Year 2013. Subparts (a): general procedures; (b): design and development planning; (c): design input; (d): design output; (e): design review; (f): design verification; (g): design validation; (h): design transfer; (i) design changes; and (j): design history file.

If a plaintiff attempts to introduce a warning letter into evidence at trial, the defendant manufacturer can argue that the evidence is irrelevant, prejudicial and constitutes inadmissible hearsay. The relevance of the warning letter will often turn upon the date of the letter in relation to the date the plaintiff's injuries were allegedly sustained. Warning letters issued prior to the alleged injuries are more likely to be relevant to establish whether the manufacturer had notice of a product defect or particular risk. If the warning letter is deemed relevant, the manufacturer defendant can argue that it is unfairly prejudicial because its probative value is substantially outweighed by the danger of unfair prejudice, confusion of the issues, misleading the jury, undue delay, waste of time or needless presentation of cumulative evidence.

Generally, the defendant manufacturer will argue that admission of a FDA warning letter into evidence gives undue weight (i.e., the authority of the federal government) to a document that does not contain final Agency determinations and does not comport with due process considerations. Finally, the defendant manufacturer can argue that the warning letters are hearsay. Some courts have found that FDA warning letters and inspection reports do not fall under a hearsay exception as factual findings resulting from an investigation because evaluative opinions of agency staff members do not fall within the public records exception to the hearsay rule; however, courts vary in their rulings as to admissibility.

Failure to address the FDA's concerns stated in warning letters can lead to enforcement actions that have significant repercussions as well as product liability exposure. The increase in FDA warning letters and enforcement activities, highlights the importance of quality management in the pharmaceutical and medical device industries. LM

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