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CURRENT TRENDS IN THE FDA'S ENFORCEMENT OF GMP REQUIREMENTS

Drugs and devices are "adulterated," as that term is used in the Food, Drug, and Cosmetic Act, if the drugs and devices are contaminated, impure, or diluted; deliver too much or too little of the active ingredient; or do not conform to mandatory specifications. A product can also be deemed "adulterated"—even in the absence of any such defects—if the manner in which the product was manufactured did not conform to the "Good Manufacturing Practice" or "Quality System" regulations (collectively known as the GMP regulations). Manufacturers therefore must not only avoid product defects but must also proactively undertake thorough measures designed to prevent defects. To enforce the adulteration, GMP, and other laws, the Food and Drug Administration ("FDA") conducts thousands of establishment inspections each year, issues thousands of "FDA-Form 483" observations alleging the adulteration of medical products, and issues hundreds of Warning Letters.

An analysis of recent Warning Letters and inspectional observation data reveals that, more than ever, most allegedly "adulterated" products work as intended and conform to all release specifications. Most Warning Letters, including most of those that focus on GMP issues, are not reactions to product failures. Rather, the bulk of the warnings reflect instead the FDA's increasing focus on the processes and procedures that are intended to prevent defects. For manufacturers, this means that there is no substitute for thoroughness and diligence, and that the process of manufacturing is as important as the results.

Although this *Commentary* focuses on medical products, food providers should note that enforcement of food GMP regulations is moving in the same direction. The FDA currently examines whether food processors—particularly processors of higher risk foods—are taking proactive steps to avoid contamination. Further, the FDA has recently released extensive proposed changes to the food GMP regulations. The new regulations, when finalized, will require almost all food processors to adopt stringent preventive controls.

TRENDS IN INSPECTION OBSERVATIONS

If an FDA inspector notes any regulatory violations during an establishment inspection, the FDA will issue an "FDA-Form 483." This form sets out the inspector's observations. Although the FDA does not publish most 483s,[1] the FDA does publish extensive summary statistics. This data set shows that the FDA cites inadequacies in the procedures for avoiding product defects far more often than actual product failures or responses to product failures.

This trend is most pronounced in the 483s issued to device manufacturers. The four most common observations are: failure to establish procedures for corrective and preventive action; failure to establish procedures for handling complaints; failure to develop, maintain, or implement adverse event reporting procedures; and failure to establish procedures to determine whether incoming materials and services conform to specifications. In all, 15 of the 25 most commonly cited violations involve a lack of established procedures (which could mean either that the written procedures are lacking or that a firm's employees fail to follow them). To be sure, the FDA also cites device manufacturers for inadequate documentation, failure to validate processes and designs, not investigating product failures, and other violations. But the FDA's emphasis on written procedures is striking.

The observations relating to drug facilities are more heterogeneous. Failure to establish written procedures is a persistent issue, and four of the seven most common violations fall into this category. Other common observations include: the responsibilities of the quality control unit are either not written or are not fully followed, the manufacturer failed to fully investigate out-of-specification batches (including both released and rejected batches), and laboratory controls are not validated.

For biologic facilities,[2] the FDA cites inadequate procedures three times as often as any other observation. Failure to investigate out-of-specification products is the second most common violation, and the next four each relate to inadequate documentation.

WARNING LETTERS, AND HOW TO AVOID THEM

A Warning Letter, although technically informal, signals that the FDA is prepared to begin a court proceeding unless violations are quickly corrected. Most Warning Letters demand that the recipient set out, within 15 working days, "specific steps [the] firm has taken to correct the noted violations, as well as an explanation of how [the] firm plans to prevent these violations, or similar violations, from occurring again." Warning Letters are public. After only a short delay, and with minimal redactions, the FDA posts all Warning Letters to its web site—and from there it is often not long before the letters come to the attention of the media, investors, and plaintiffs' lawyers.

A review of recent Warning Letters shows that there is no simple method for avoiding them. Rather, manufacturers should commit themselves to the hard work of bringing their processes into compliance before the FDA arrives. It is also crucial to provide a thorough response if an inspection reveals GMP issues, and to give serious attention to complaints from patients and medical practitioners.

Releasing a contaminated or out-of-specification product into the marketplace increases the likelihood of an inspection and often results in a Warning Letter. A handful of Warning Letters directly cite such problems as grounds for issuing the Letter. More frequently, the FDA will cite the underlying GMP violation, noting the eventual product defect as an example of the importance of maintaining or following appropriate procedures.

It is more common still for the FDA to issue a Warning Letter on GMP issues where there is no known problem with the released products, and there have been no complaints. As the FDA wrote in one Warning Letter, "the lack of current customer complaints alone is neither a verification of a robust quality system nor that you have appropriate process controls in place." Indeed, only a minority of recent Warning Letters indicate that the finished product failed to perform or is known to be out of specification. Even in the absence of an actual product defect, the FDA is unwilling to tolerate unreliable processes that *could* result in defects.

Since Warning Letters, at least those that focus on GMP issues, are seldom issued immediately following an inspection, a firm can take steps to prevent a bad inspection from developing into a Warning Letter. In almost every instance, the FDA first provides its criticisms through 483 observations and in-person meetings, and solicits the firm's responses. While the FDA can and does issue Warning Letters regardless of the response, more commonly the FDA does not issue one unless the FDA perceives both a serious GMP issue and a failure to respond properly.

Providing a *thorough* response to the 483 is critical. Most GMP-related Warning Letters note that the manufacturer did respond, but conclude that the response is inadequate. The FDA typically demands an investigation of the cause of the observed GMP violations, a proposed solution, implementation of the solution (including retraining relevant employees), an investigation into released lots that may have been affected, and documentation demonstrating all actions were completed.

Another recurring cause of Warning Letters is poor handling of complaints. Manufacturers are required to collect complaints, evaluate them, and report certain adverse events to the FDA. The FDA has issued numerous Warning Letters to companies that do not implement (or do not have) written complaint handling procedures. This issue is more common with small or foreign companies that may not be fully conversant with FDA requirements. A problem that trips up large and small companies alike, however, is a failure to properly investigate complaints. If complaints indicate that a product is defective or dangerous, the FDA will expect an investigation that determines the root cause of the observed problems and leads to corrective actions.

Of course, many Warning Letters do not relate, or at least do not primarily relate, to GMP problems. Some letters are aimed at companies that make no apparent effort to comply with their regulatory obligations. Some of these companies may not believe that their products are subject to regulation. Others know but do not appear to care. Warning Letters to these companies indicate that everything is amiss: no registration, no product approvals, no written procedures, no adverse event reporting, etc. Established companies are unlikely to receive such letters.

The FDA issues other letters in response to allegedly impermissible advertising claims. The FDA sometimes issues "cyber" Warning Letters without an establishment inspection, relying solely on company web sites or other marketing materials. Some recipients of advertising-focused letters are fly-by-night operations that make extravagant claims about dubious products. But the FDA (and in particular the Office of Prescription Drug Promotion) also warns legitimate companies that, the FDA believes, make claims that outstrip their product approvals, or cross the blurry lines separating dietary supplements or cosmetics from drugs.

Viewing the body of recent Warning Letters as a whole, there is no one GMP regulation, nor even a discrete set of regulations, that can be said to command the FDA's focus. Rather, the FDA will scrutinize the entire manufacturing process.

CURRENT AND FUTURE ENFORCEMENT OF FOOD GMPs

When the FDA inspects food facilities, the most common negative observation, by a considerable margin, is that the facility did not adequately control pests. Other insanitary conditions likewise draw inspection observations and Warning Letters. But the FDA also focuses on failures to take proactive steps to maintain sanitary conditions. For example, design flaws hindering the cleaning of a facility are cited (slightly) more often than actual failures to maintain a facility in a sanitary condition. Many fisheries, which are subject to stringent "HACCP" regulations[3] in addition to the general GMP requirements, receive warnings for failing to take mandatory proactive steps. Eight of the 15 regulations most cited in 483s to food establishments pertain only to fisheries. These regulations mandate establishing a plan for sufficient monitoring of sanitation conditions, implementing the plan, recordkeeping, and verification of various aspects of the HACCP plan.

The FDA's focus on preventive steps will only increase when the Food Safety Modernization Act ("FSMA") is fully implemented. The FDA views this 2011 law as a "sweeping reform" that will "ensure the U.S. food supply is safe by shifting the focus from responding to contamination to preventing it."

Among many other provisions, FSMA requires most food manufacturers to implement "hazard analysis and risk-based preventive controls" similar to the HACCP obligations that currently apply to only a subset of the industry. On January 4, 2013, the FDA released draft regulations that will implement this mandate and will overhaul and modernize the GMP regulations pertaining to environmental pathogens, food allergens, mandatory employee training, and sanitation of food contact surfaces. These regulations are not binding at present, nor are they in their final form. But when they go into effect, the FDA's focus on preventive steps will be redoubled.

CONCLUSION

There are no quick fixes for avoiding 483 observations and Warning Letters. Product failures may encourage the FDA to increase the frequency of inspection of a facility. But avoiding product failures will not prevent inspections, and even without product failures, the FDA will demand full compliance with GMP requirements.

LAWYER CONTACT

For further information, please contact your principal Firm representative or the lawyer listed below. General email messages may be sent using our "Contact Us" form, which can be found at www.jonesday.com.

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ENDNOTES

1 Form 483s are public; the FDA posts selected 483s to the FDA web site, and generally 483s can be obtained from the FDA through FOIA (Freedom of Information Act) requests. But the FDA does not post the vast majority of the 483s.

2 In this dataset, "biologic" facilities are largely facilities that handle blood products.

3 Hazard Analysis Critical Control Points. The HACCP regulations pertaining to processors of fish or fishery products are collected at 21 C.F.R. Part 123.