

**Department of Health and Human Services**

**OFFICE OF  
INSPECTOR GENERAL**

**FDA WARNING LETTERS  
Timeliness And Effectiveness**



**JUNE GIBBS BROWN  
Inspector General**

**FEBRUARY 1999  
OEI-09-97-00381**

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# EXECUTIVE SUMMARY

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## PURPOSE

To determine how the Food and Drug Administration (FDA) uses warning letters and the extent to which they result in timely compliance with Federal laws and regulations.

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## BACKGROUND

The FDA is the Federal agency charged with enforcing the Federal Food, Drug, and Cosmetic Act and several related laws. At the headquarters level, FDA primarily is comprised of five centers and the Office of Regulatory Affairs. The Office of Regulatory Affairs coordinates FDA's compliance activities and oversees the activities of FDA's 5 regional offices, 20 district offices, and 130 resident posts.

The FDA's district offices and resident posts conduct almost all inspections of the firms that FDA regulates. When investigators find objectionable conditions, they are required to provide the firm with their findings using form *FDA-483*. If violations uncovered during an inspection meet a threshold of "regulatory significance," FDA also may issue a warning letter. Both FDA centers and district offices issue warning letters, depending on the type of firm and violation. Some warning letters issued by the district office require headquarters review and approval. The warning letter generally represents FDA's first official notification that it has found one or more products, practices, processes, or other activities that are in violation of the Food, Drug, and Cosmetic Act. The warning letter affords firms the opportunity to voluntarily correct violations prior to the initiation of formal enforcement action.

In fiscal year 1997, FDA issued 1,175 warning letters. This reversed a trend during which the number of warning letters decreased 36.2 percent from 1994 (1,626) to 1996 (1,037). District offices issue approximately 80 percent of all warning letters.

The General Accounting Office raised concerns about how FDA uses warning letters in two 1997 studies. Based on their findings, we determined that this inspection was warranted. We conducted on-site reviews at a stratified random sample of six district offices. At each district office, we reviewed warning letter and establishment files and tracked the outcome of all warning letters issued during fiscal year 1996. We also conducted interviews with FDA headquarters, all district offices, and 24 firms that received warning letters during 1996.

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## **FINDINGS**

### **Warning letters are an effective compliance tool**

When FDA conducts follow-up activities, it finds that firms have either corrected the violations cited in warning letters or have made significant progress toward doing so. Almost 90 percent of firms respond in writing to warning letters within 15 days of receiving them, detailing corrective actions that they intend to take.

### **The warning letter's effectiveness depends on conscientious follow-up**

The FDA completes appropriate follow-up in approximately 97 percent of cases. Follow-up may involve reinspecting the firm, soliciting documentation of corrections, or meeting with the firm to address compliance issues. In other cases, FDA does not need to follow up except to ensure that the firm responds to the warning letter. Follow-up inspections frequently uncover other violations, but FDA rarely has to initiate compliance actions. On average, follow-up inspections take place more than 9 months after the warning letter is issued.

### **Warning letters are not always timely**

Headquarters rarely reviews and concurs with warning letter recommendations within FDA's 15-day guideline. Even when headquarters review is not required, district offices frequently take more than a month to issue a warning letter.

### **Discrepancies between headquarters and district office data on warning letters are extensive**

Almost 20 percent of the warning letters in the district offices are not accounted for in the headquarters database. Conversely, 16 percent of the warning letters in the headquarters database do not appear in the district offices' files.

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## **RECOMMENDATION**

The warning letter is an effective tool in motivating firms to comply with Federal laws and regulations. To increase its effectiveness, FDA should (1) improve the timeliness of the warning letter process and follow-up activities and (2) revamp its warning letter data collection system to ensure accuracy.

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## **AGENCY COMMENTS**

We received comments on the draft report from FDA in which the agency concurred with our recommendation. Where appropriate, we have made revisions in the report in

response to these comments. We also have responded to several of FDA's comments in the appendix.

*This report is the one of two reports on the FDA warning letter process. A companion report, "FDA Warning Letters: Trends and Perspectives" (OEI-09-97-00380), determined (1) why the number of warning letters has decreased in recent years, (2) what accounts for variations in district office warning letters, and (3) how firms view the warning letter process.*

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# INTRODUCTION

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## PURPOSE

To determine how the Food and Drug Administration (FDA) uses warning letters and the extent to which they result in timely compliance with Federal laws and regulations.

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## BACKGROUND

### The Food and Drug Administration

The Food and Drug Administration (FDA) within the Department of Health and Human Services is the Federal agency charged with enforcing the Federal Food, Drug, and Cosmetic Act and several related laws. At the headquarters level, FDA primarily is comprised of five centers and the Office of Regulatory Affairs.<sup>1</sup> The five centers are:

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

Each center promulgates regulations, oversees the review and approval for the marketing of new products, develops policy and compliance standards for regulated industries, and undertakes other initiatives to ensure the safety and effectiveness of products under FDA's purview. The Office of Regulatory Affairs coordinates FDA's compliance activities and oversees the activities of FDA's 5 regional offices, 20 district offices, and approximately 130 resident posts.

### On-site Inspections

Staff from FDA's district offices and resident posts conduct almost all inspections of the firms that FDA regulates.<sup>2</sup> Section 702(a) of the Food, Drug, and Cosmetic Act authorizes FDA to conduct inspections to enforce the provisions of that statute as well as other applicable laws. Inspections focus on manufacturing, laboratory, production, and/or

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<sup>1</sup> The FDA also operates the National Center for Toxicological Research in Jefferson, Arkansas and the Engineering and Analytical Center in Winchester, Massachusetts.

<sup>2</sup> The FDA contracts with State agencies to conduct some inspections, and headquarters staff sometimes participate in inspections of foreign or domestic firms.

storage processes but may include examining a firm's administrative practices and controls as well as collecting samples, labels, and promotional materials.

The FDA requires investigators to follow a standard protocol when conducting an inspection. Upon arriving at a facility, investigators issue a Notice of Inspection (Form *FDA-482*) to the top management official. The scope of the inspection generally is determined by the type of facility being inspected, the firm's history, general knowledge about the industry and its problems, and conditions found as the inspection progresses.

Investigators are authorized to collect samples or other physical evidence while conducting inspections. Examples include food, drugs, devices, or cosmetics. Samples also may include evidence of violative conditions, such as rodent droppings or any other evidence of noncompliance with Federal laws and regulations.

When investigators find objectionable conditions, they are required to provide the top management official with their findings on an Inspectional Observations form (Form *FDA-483*). The *FDA-483* should include any observed problems with the facility, equipment, processes, controls, products, employee practices, or records. Some examples of reportable observations include:

- ▶ filthy, putrid, or decomposed substances, unsanitary conditions, or evidence of contamination;
- ▶ careless handling of rodenticides or pesticides;
- ▶ results of field tests that reveal adulteration;
- ▶ observations of faulty manufacturing, processing, packaging, or holding of food, drug, or device products as related to Good Manufacturing Practice regulations;<sup>3</sup> and
- ▶ observations indicating noncompliance with medical device reporting requirements.

Some observations require that action be taken by the centers only. The FDA's Investigations Operations Manual instructs investigators to not report observations related to most labeling issues, promotional materials, the classification of a cosmetic or device as a drug, or the classification of a drug as a new drug on the *FDA-483*. These issues are referred to the centers for compliance action.

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<sup>3</sup> The Good Manufacturing Practice regulations specify FDA's expectations as to how firms should operate in manufacturing products regulated by the FDA. The regulation includes provisions related to personnel, quality control, facility design and maintenance, equipment, internal controls, production and process controls, packaging and labeling, storage and distribution, laboratory process, and reports and record keeping.



## Warning Letters

**What is a warning letter?** The warning letter generally represents FDA's first official notification to a firm or individual that FDA has found that one or more products, practices, processes, or other activities are in violation of the Food, Drug, and Cosmetic Act. The warning letter affords firms the opportunity to voluntarily take corrective action prior to the initiation of formal enforcement action.

The FDA is not required by law to warn firms or individuals that they are in violation of the law prior to initiating a formal regulatory action.<sup>4</sup> The FDA believes, however, that:

...documentation of notice of violative conduct strengthens the agency's position in regulatory actions by establishing that responsible individuals continued violative conduct despite warnings by the agency.<sup>5</sup>

**Who issues warning letters, and what time frames exist?** The FDA centers and district offices issue warning letters. In general, district offices issue warning letters to domestic firms based on inspections. Some centers issue warning letters for advertising and promotional violations or to foreign firms that market products in the United States. Others, such as the Center for Veterinary Medicine, issue few or no warning letters at all.

At the district office level, although some warning letters can be issued at the discretion of the district director without center or other headquarters review or concurrence, FDA's Regulatory Procedures Manual lists numerous specific program area violations that require review by the appropriate center. The Regulatory Procedures Manual also states that when a warning letter is warranted, a district office should issue it to the firm or submit a recommendation for headquarters review within 15 days of the end of the inspection. When center review is required, centers are supposed to review and approve the issuance of a warning letter within 15 days of receipt. If a center disagrees with a warning letter recommendation, it must provide a justification to the district office within 30 days.

The following table illustrates how many warning letters the centers and district offices issued from fiscal years 1994 to 1997. The district office tally includes all warning letters sent under district directors' signatures, including those that underwent center review:

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<sup>4</sup> One exception to this statement is a requirement that when acting under the authority of the Radiation Control for Health and Safety Act, FDA is required by law to provide a written notification to manufacturers when the agency discovers products that fail to comply with a performance standard or that contain a radiation safety defect.

<sup>5</sup> FDA Regulatory Procedures Manual, Chapter 10, Subchapter — Prior Notice.

*District offices annually issue approximately  
80 percent of all warning letters*

Year	Total	District office-issued	Center-issued
1994	1,626	1,282 (78.8%)	344 (21.2%)
1995	1,501	1,175 (78.3%)	326 (21.7%)
1996	1,037	841 (81.1%)	196 (18.9%)
1997	1,175	1,003 (85.4%)	172 (14.6%)

In fiscal year 1997, FDA issued 1,175 warning letters. This reversed a trend during which the number of warning letters decreased 36.2 percent from 1994 (1,626) to 1996 (1,037). More warning letters are issued for devices and radiological products than for any of FDA's other product areas. In fact, from 1994 to 1997, the Center for Devices and Radiological Health issued more warning letters than any district office. The district offices issuing the most letters in 1997 were San Francisco (96), Florida (88), and Dallas (74). The district offices issuing the fewest warning letters in 1997 were Boston (16), Detroit (19), and Nashville (20).

**What does a warning letter say?** The warning letter instructs the firm to correct the issues noted and to respond in writing within 15 days of receipt of the letter. District offices coordinate with the appropriate center to determine whether a firm's response to a warning letter is adequate. If the district or appropriate center deems the firm's response adequate, it will notify other appropriate agency units. This may require a reinspection of the firm.

The FDA issues warning letters for regulatory violations, not for violations of nonregulatory guidance documents. It states that "the threshold for determination of what constitutes 'regulatory significance' is that failure to adequately and promptly achieve correction to the warning letter may be expected to result in enforcement action."

### **Follow-up and Subsequent Compliance Actions**

The FDA's Regulatory Procedures Manual states that the district offices and/or centers should verify that corrections have been achieved. This generally involves conducting a follow-up inspection. If more appropriate, however, districts may require that a firm document corrections or may undertake educational efforts with the firm to address the issues. Continued noncompliance can result in administrative or regulatory actions. Administrative actions include detentions, civil penalties, and requesting voluntary recalls.

Regulatory actions include license revocations, license suspensions, citations, prosecutions, judicial civil penalties, injunctions, and seizures.<sup>6</sup>

## Related Work

The General Accounting Office (GAO) issued two studies in 1997 that questioned the consistency of FDA's inspection and compliance activities:

- ▶ In "Blood Supply: FDA Oversight and Remaining Issues of Safety" (GAO/PEMD-97-1, February 1997), GAO found that FDA issued warning letters to blood suppliers inconsistently. The GAO also reported that some inspections yielded multiple *FDA-483* observations but did not result in a warning letter, while other inspections with relatively few or minor observations resulted in the issuance of a warning letter.
- ▶ In "FDA Mammography Inspections: While Some Problems Need Attention, Facility Compliance is Growing" (GAO/HEHS-97-25, January 1997), GAO questioned the consistency of inspectors who used different criteria in citing mammography facilities. The GAO stated that FDA's monitoring and enforcement process did not ensure timely correction of deficiencies in these facilities. The GAO also noted that FDA district offices needed better information systems to manage inspections.

Based on GAO's concerns, we determined that this inspection was warranted.

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## METHODOLOGY

### On-site Warning Letter Tracking

We conducted on-site reviews at six district offices. We selected a stratified random sample of district offices to conduct the on-site fieldwork:

Number of warning letters issued during 1996	Number of district offices	Sample size
Fewer than 27	7	2
28 to 54	10	2
More than 54	4	2

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<sup>6</sup> FDA has recall authority only for infant formula, human tissue, and certain medical devices. Recalls of other products are voluntary. License suspensions and revocations are regulatory actions taken for biologicals.

At each district office, we reviewed warning letter and establishment files. We tracked the outcome of all warning letters issued by the district office during fiscal year 1996 to determine whether FDA conducted follow-up inspections where appropriate and whether the firm had sufficiently addressed the issues noted in the warning letter. We projected our findings to the universe of district offices to assess the overall effectiveness of warning letters.

## **Interviews with FDA and Regulated Firms**

We conducted either in-person or telephone interviews with each district office. We asked district office staff about their organizational structure, their experiences with warning letters, the factors that contributed to their increase or decrease in warning letters, and the responsiveness of the centers to their warning letter recommendations. We also interviewed staff from FDA headquarters, analyzed inspection and warning letter trends, and reviewed FDA's Regulatory Procedures Manual.

We selected a simple random sample of 40 firms that received warning letters during fiscal year 1996 and completed telephone interviews with 24 of them. The remaining firms did not return phone calls or had gone out of business. We asked firms about the violations that resulted in the warning letter and their experiences with FDA.

*This report is the one of two reports on the FDA warning letter process. In a companion report, "FDA Warning Letters: Trends and Perspectives" (OEI-09-97-00380), we found that changes in FDA policies and practices and better industry compliance have contributed to decreases in warning letters since 1994. Despite the existence of clear warning letter guidance, differences in district office attitudes, experience, and the types of firms in the district affect warning letter volume. Firms would like to better understand the warning letter process and suggested some minor changes. With some exceptions, firms were satisfied with FDA's customer service during the warning letter process.*

# FINDINGS

## Warning letters are an effective compliance tool

When FDA conducts follow-up activities, it finds that firms have either corrected the violations cited in warning letters or have made significant progress toward doing so. Firms take warning letters very seriously. Almost 90 percent of firms respond in writing to warning letters within 15 days of receiving them, detailing corrective actions that they intend to take. The following examples describe the effect that warning letters have on firm compliance with FDA laws and regulations:

- ▶ A district office issued a warning letter to a firm for inadequate procedures and product labeling. The firm responded within 15 working days and requested information about how to come into compliance. The FDA provided educational materials and training. Upon reinspecting the firm 5 months after the warning letter, FDA found no violations.
- ▶ A district office issued a warning letter to a firm that had failed to report several recalls and product withdrawals. The firm provided FDA with extensive documentation on the recalls and changed its policies to avoid repeating the same violation in the future. Upon reinspecting the firm, FDA found that, although most of the violations had been corrected, some remained and new ones appeared. The investigator issued a new *FDA-483*. Based on the firm's progress and cooperation, FDA determined that additional compliance action was not necessary pending the firm's next routine inspection.
- ▶ A district office issued a warning letter to a firm that had advertised a product as "FDA-approved." Within a few days of receiving the warning letter, the firm submitted a revised advertisement that did not include that phrase.

The threat of subsequent compliance actions or other remedies enhances the value of the warning letter. For example, FDA may refuse to take action on 510(k) or premarket approval applications or refuse to issue export certificates until firms correct warning letter violations. In addition, the publicity associated with a warning letter--and a firm's failure to correct the violations--can cause major harm to the firm's reputation and revenue.

## The warning letter's effectiveness depends on conscientious follow-up

### The FDA completed appropriate follow-up in approximately 97 percent of cases

If investigators feel it is necessary, FDA may reinspect a firm to verify that the warning letter violations have been corrected. If more appropriate, districts may conduct other follow-up, such as soliciting documentation or meeting with industry officials to address compliance issues. In some cases, such as with tissue residue violations, FDA does not require any follow-up except to ensure that the firm responds to the warning letter.

In almost all of the cases that we reviewed, FDA conducted some type of follow-up activity to assess firm compliance. The following table illustrates the types of follow-up district offices conducted in 1996 and the result of that follow-up:

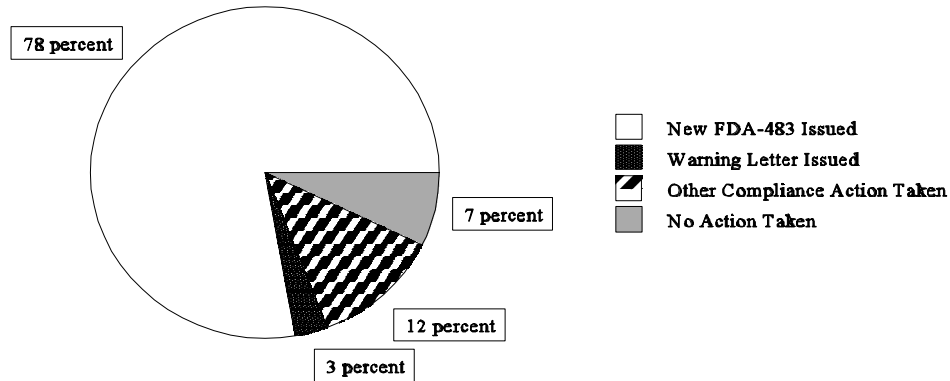
*FDA follow-up activities confirm firms' compliance*

Follow-up Method	Result	FDA Action	Percentage
Reinspection	Observations noted	New <i>FDA-483</i> issued	30 percent
Reinspection	Observations noted	New warning letter issued	1 percent
Reinspection	Observations noted	Other compliance action taken	5 percent
Reinspection	Observations noted	No action taken	3 percent
Reinspection	No observations noted	N/A	20 percent
Documentation of compliance submitted by firm	N/A	N/A	12 percent
No follow-up per FDA guidelines (other than to assure written response from firm)	N/A	N/A	23 percent
Other follow-up occurred (meetings, phone calls)	N/A	N/A	3 percent
No follow-up although it appears to be warranted	N/A	N/A	3 percent

Follow-up inspections frequently uncover other violations, but FDA rarely has to initiate compliance actions. As this table shows, FDA reinspected almost 60 percent of the firms that received warning letters. Of the firms that FDA reinspected, investigators found violations--repeat or new--in approximately two-thirds of the cases. Despite the discovery

of new violations, FDA rarely determined that another warning letter or a more serious compliance action was warranted. As the table shows, and the following chart illustrates, new violations are most frequently cited by using an *FDA-483*:

*New warning letters are the least common outcome of a follow-up inspection*



District office staff were not concerned that they found new or uncorrected violations during two-thirds of reinspections. In almost all of these cases, investigators were satisfied with the firm’s progress or correction of other warning letters violations. They did not believe that a more serious compliance action, such as a seizure, was necessary. According to district office staff, some warning letters cite numerous violations, and investigators often believe that issuing an additional warning letter or initiating a more serious compliance action would not help assure compliance. This is particularly true if a firm has responded to the warning letter and indicates that it is willing to correct all violations.

**Follow-up inspections generally occur long after the warning letter is issued**

When FDA conducts a follow-up inspection, it occurs 278 days after the warning letter is issued, on average. Almost one-quarter of follow-up inspections are delayed by more than a year. The timing of the follow-up inspection depends on multiple factors:

- ▶ *Workload:* District offices frequently must shift their priorities to meet agency demands and goals. Follow-up inspections sometimes are delayed in order to focus on other priorities.
- ▶ *Type of violation:* If the district office decides to conduct a follow-up inspection, the timing depends on whether the violations are easy to correct or require significant time to correct (e.g., developing new manufacturing guidelines).

- ▶ *Severity of violation:* If an inspection uncovers very severe violations, a district office might decide to conduct an immediate follow-up inspection. On the other hand, if the violations are less grievous, the district office may simply verify corrections during its next routine inspection of the firm.
- ▶ *Number of violations:* District offices sometimes allow a firm extra time to correct multiple violations prior to conducting a follow-up inspection.
- ▶ *Firm history:* District offices keep a close watch on firms with a history of violations. These firms are more likely to receive a follow-up inspection soon after the warning letter is issued.

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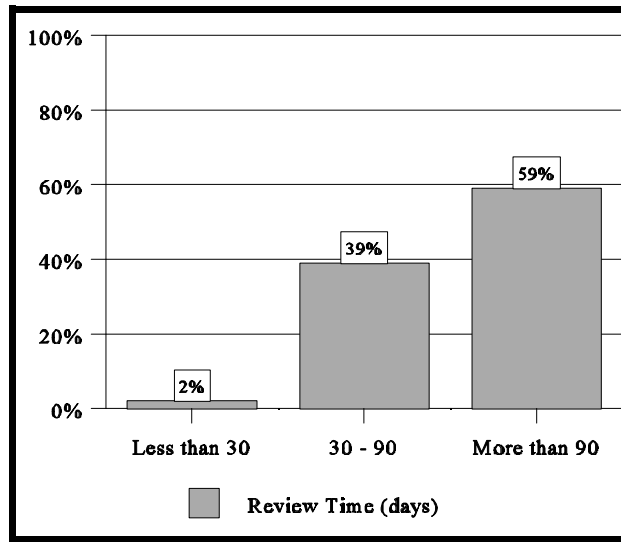
## **Warning letters are not always timely**

### **Headquarters rarely reviews and concurs with warning letter recommendations within FDA's 15-day guideline**

The FDA has a goal of 15 days for completion of headquarters warning letter review. However, less than 2 percent of letters that undergo headquarters review are completed within this time frame. In one case, review required well over one year, and, on average, review takes 121 days to complete. According to some district office staff, warning letters are a low priority in some of the centers. Districts believe that the centers have too much higher priority work to complete review within 15 days. One district office noted that all FDA time frames are difficult to meet, especially for the centers. The following table illustrates how long it took for the centers to complete their review of warning letters that were approved for issuance in 1996:



*Almost all center reviews of 1996 warning letters took more than 30 days*



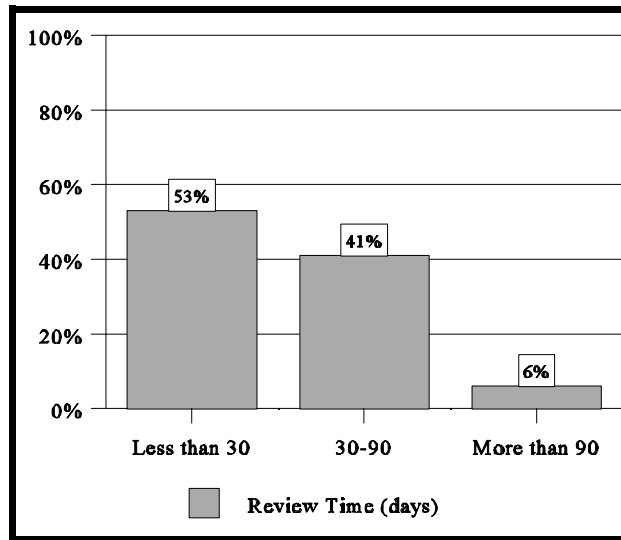
None of FDA’s district offices credited the centers with consistently meeting FDA’s guideline. District office staff understand the need for more time when the warning letter concerns a technical or complicated issue but described other instances where delays were unwarranted. District office staff stated that they frequently have to call the centers to determine the status of a warning letter recommendation.

The Center for Food Safety and Applied Nutrition received the most criticism for being “slowest,” and complicating the process with multiple layers of review. The other centers did not fare well either in our survey. Most district offices stated that none of the centers consistently met the 15-day guideline to approve warning letter recommendations or the 30-day guideline to justify nonconurrence.

**Even when headquarters does not review warning letters, it frequently takes district offices more than a month to issue a warning letter**

The Regulatory Procedures Manual states that district offices should submit warning letter recommendations to headquarters or issue warning letters to firms within 15 days of the end of an inspection. Excluding those cases where headquarters review was required, the average delay between the end of inspection and the date of the warning letter is 38 days, with about 6 percent requiring more than 90 days:

*Almost half of district offices warning letters took 30 days or more to issue*



**Firms reported that FDA was slow in issuing the warning letter after an inspection was completed but diligent in responding to their requests for information**

Approximately 40 percent of firms reported that FDA was not timely in issuing their warning letter. As a result, they were more likely to be surprised by receipt of the warning letter and less likely to believe that the warning letter was appropriate. Firms noted that they frequently have corrected all of the violations noted in the *FDA-483* weeks or months before receiving a warning letter. Consequently, they believe that they are being unduly and inappropriately punished.

Firms were pleased by their district office’s responsiveness to inquiries, however. Approximately three-quarters of the firms reported that FDA was timely in responding to their inquiries and following up with them.

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**Discrepancies between headquarters and district office data on warning letters are extensive**

We found significant differences between the headquarters warning letter database and the files we reviewed in the district offices. Almost 20 percent of the warning letters that we reviewed in the district offices were not accounted for in the headquarters database. These warning letters did not appear in the 1995 or 1997 warning letter databases either.

In addition, district offices were unable to provide us with all of the warning letters that appeared in the 1996 headquarters database. Approximately 16 percent of the warning letters in the headquarters database did not appear in the district offices' files.

To corroborate our on-site findings, we asked the 15 other district offices to provide us with the number of warning letters that they issued from 1994 to 1997 and compared their responses to the headquarters database. The numbers matched less than 10 percent of the time.

## RECOMMENDATION

Despite questions about annual decreases in warning letters, discrepancies in district office warning letter volume, and the overall effectiveness of warning letters, the findings in both of our reports indicate that the warning letter is one of several effective tools that district offices use to achieve compliance with Federal laws and regulations. In our companion report, we recommend that FDA continue to improve relations and communication with industry and consider issuing guidance that would authorize district offices to use *FDA-483s* and meetings to achieve compliance in lieu of warning letters. Based on the findings in this report, FDA should increase its effectiveness by:

- ▶ *improving the timeliness of the warning letter process and follow-up activities and*
- ▶ *revamping its warning letter data collection system to ensure accuracy.*

The delay between completing a firm's inspection and issuing a warning letter--which can be months or more than a year--lessens the effectiveness of the warning letter. The inaccuracy of FDA's warning letter database may contribute to poor communication between the centers and districts, or it could be a sign that communication is already a problem. Also, since FDA is required to make warning letters available through the Freedom of Information Act and posts them on the Internet, correct warning letter data is of primary concern.

We received comments on the draft report from FDA in which the agency concurred with our recommendation. Where appropriate, we have made revisions in the report in response to these comments. We also have responded to several of FDA's comments in the appendix.

# APPENDIX A

## AGENCY COMMENTS



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration

### Memorandum

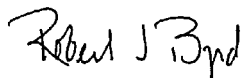
Date: NOV 30 1998

From: Deputy Commissioner for Management and Systems, FDA

Subject: OIG Draft Reports: "FDA Warning Letters: Trends and Perspectives," OEI-09-97-00380 and  
"FDA Warning Letters: Timeliness and Effectiveness," OEI-09-97-00381

To: June Gibbs Brown  
Inspector General

Thank you for the opportunity to review and comment on the two draft OIG reports, "FDA Warning Letters: Trends and Perspectives," and "FDA Warning Letters: Timeliness and Effectiveness." In general, FDA concurs with the reports and the recommendations. Our comments on both reports are attached for your consideration.

  
Robert J. Byrd

Attachment

**AGENCY COMMENTS TO THE OFFICE OF INSPECTOR GENERAL DRAFT  
REPORTS, "FDA WARNING LETTERS: TRENDS AND PERSPECTIVES," AND "FDA  
WARNING LETTERS: TIMELINESS AND EFFECTIVENESS"**

GENERAL COMMENTS

We are pleased to note, that both Warning Letter reports validate that the warning letter process works. It is highly effective in bringing firms into compliance with a moderate amount of human and resource expenditures. The process is understood by most of the regulated industry and adheres to FDA's long-standing policy of "prior warning."

It should be noted that the number of regional and district offices cited in both reports should be corrected. There are 5 Regional and 20 District Offices.

It should also be noted that the statistics provided regarding length of time between issuance of a warning letter and reinspection may be skewed somewhat, giving the appearance of untimely follow-up reinspection. For example, a significant part of NOL-DO's warning letters are addressed to the seafood industry. Much of this industry is seasonal, and that may preclude making a follow-up inspection until the firm begins processing on a regular basis the following year. Other districts may also have industry segments in the same situation.

Both reports identify the three highest and three lowest warning letter producing Districts. While the report does not directly say it, it implies that high warning letter production is good and low warning letter production is bad.

The reports do not explain:

1. The nature and complexity of the inspections conducted have increased, thus the total number of inspections conducted has dropped. One would expect to see a corresponding drop in warning letter production with fewer inspections being conducted.
2. Warning letters are issued to importers for failure to hold product for FDA examination. In a big Import District, this will drive up the number of warning letters issued. A District with a low volume import operation would correspondingly expect to issue fewer warning letters. While this can account for large differences in warning letter production between Districts, it was not mentioned in the reports.

Both reports state that FDA believes that documentation of notice (warning) strengthens later regulatory actions. The reports should also highlight that FDA also believes that most firms, when given the chance, will choose to correct violations voluntarily.

The reports note the significant decrease in the number of warning letters issued and attributes it

to changes in FDA policies and better industry compliance. The primary reason for the decrease would be the changes in FDA policy as opposed to better industry compliance. It is not clear on what basis the statement is made that industry compliance has significantly increased.

The reports state that overall the warning letter is an effective tool, but then discusses issuing new guidance for more district discretion that would reduce the number of letters issued. We should not reduce the number of letters further if the review has demonstrated that the warning letter is an effective tool.

We believe that the Trends and Perspectives report should point out that the Agency is going to undertake a medical device Warning Letter Pilot.

#### TECHNICAL COMMENTS

##### *FDA Warning Letters: Trends and Perspectives*

Page 6, third paragraph - the form FDA-483 should include all significant objectionable observations that are linked to violations of the FD&C Act or deviations from related regulations not potential problems with the firm as the sentence states and implies.

Page 7, third paragraph - Not all headquarters units' issue warning letters for advertising. For example, CFSAN does not issue such letters, and rarely issues warning letters of any sort directly from the center. The report should be specific as to the headquarters unit in question.

Page 8, second paragraph - The second sentence implies that districts are solely responsible for determining whether a firm's response is adequate. This is not correct. The district, in coordination with the appropriate center, determines whether the firm's response is adequate.

Page 10, last paragraph - It is recognized that the medical device industry initiatives are being considered by FDA for broader implementation. Currently the draft Federal Register Notice is being reviewed in the agency.

##### *FDA Warning Letters: Timeliness and Effectiveness*

Page 2, second paragraph - FDA does not verify corrections by "offering meetings."

Page 2, fifth paragraph - the warning letter is not a tool for "assuring firms achieve compliance. . .," but is a tool for providing firms an opportunity to voluntarily make appropriate corrections without enforcement actions.

Page 5, third paragraph - the form FDA-483 should include all significant objectionable observations that are linked to violations of the FD&C Act or deviations from related regulations not potential problems with the firm as the sentence states and implies.

Page 6, third paragraph - Not all headquarters units issue warning letters for advertising. For

example, CFSAN does not issue such letters, and rarely issues warning letters of any sort directly from the center. The report should be specific as to the headquarters unit in question.

Page 7, second paragraph - The second sentence implies that districts are solely responsible for determining whether a firm's response is adequate. This is not correct. The district, in coordination with the appropriate center, determines whether the firm's response is adequate.

Page 7, fourth paragraph - FDA does not verify a firm's corrective actions by initiating meetings, conference calls, or administrative or regulatory actions. A firm's statement of corrective actions or promise to make appropriate corrective action is verified during a follow-up inspection.

Page 7, fifth paragraph - This paragraph implies that FDA has recall authority. FDA recalls are primarily voluntary. Except for infant formula, certain medical devices, and human tissue, FDA has no recall authority.

Page 7, fifth paragraph - Please note that license suspensions and revocations are regulatory actions for biological products taken under the provisions of section 351 of the Public Health Service Act (PHSA).

Page 11, first paragraph - FDA does not verify compliance by "soliciting documentation" and "offering meetings." There is no requirement that FDA district offices follow-up to ensure a firm responds to the warning letter as the sentence implies.

Page 11, Table - Please change "violations" under column 2 to "observations."

Page 11, last paragraph after table - The paragraph states that for firms reinspected, investigators found repeat violations or new violations in 2/3 of the cases. It is hard to see how the conclusion is drawn that the warning letter achieved compliance in such cases.

Page 13, first paragraph - "Severity of violations," the second statement implies that the agency sends warning letters for relatively minor violations.

Page 13, third paragraph - "Type of Firm," the report should explain how the size of a firm influences the time required for it to implement corrections.

Page 13, last paragraph - A statement is made "that the centers simply have too much work to complete review within 15 days." Is this statement based on established facts or someone's opinion? The report should clarify.

Page 17, Recommendations, last paragraph - The DCMO warning letter database is not intended to be the official record for filling FOI requests and posting on the Internet.



## RECOMMENDATIONS

### OIG Recommendation - "FDA Warning Letters: Trends and Perspectives"

The FDA should (1) continue to improve relations and communication with industry and (2) consider issuing guidance that would authorize district offices to use FDA-483s and meetings to achieve compliance in lieu of warning letters.

#### FDA Response

FDA concurs with this recommendation.

FDA has fostered a more cooperative relationship with industry and will continue to improve upon those relationships through use of a variety of mechanisms of communications, such as, public workshops, web sites, guidance documents, outreach programs, teleconferences or meetings, and letters to manufacturers.

FDA further believes that guidance that would authorize district offices to use FDA-483s and meetings to achieve compliance in lieu of warning letters is already in effect. The agency has guidance which provides that FDA-483s, meetings and other types of correspondence are appropriate in certain circumstances to achieve correction.

### OIG Recommendation - "FDA Warning Letters: Timeliness and Effectiveness"

The warning letter is an effective tool for assuring that firms achieve compliance with Federal laws and regulations. To increase its effectiveness, FDA should (1) improve the timeliness of the warning letter process and follow-up activities and (2) revamp its warning letter data collection system to ensure accuracy.

#### FDA Response

FDA concurs with the recommendation.

FDA will continue to work at ensuring that inspectional findings are reviewed and appropriate corrective actions are pursued. It is our intention to improve upon our record of a decrease in time between receipt of a recommendation and response, as resources permit.

FDA has contracted with Booz-Allen and Hamilton to develop an Agency-wide system, the Field Accomplishment and Compliance Tracking Systems (FACTS) that will help to ensure accuracy.

# APPENDIX B

## OIG RESPONSE TO AGENCY COMMENTS

We offer the following additional analysis based on FDA's comments.

At the time that this inspection began, there were six regional offices and 21 district offices as we stated in the draft report. The Mid-Atlantic and Midwest regional offices have since merged into the Central regional office, and the Buffalo district office has merged with the Brooklyn district office.

The seafood industry was the only industry in our sample that has a seasonal component. Analysis of the firms in our sample that market seafood shows that either there was no follow-up inspection conducted (most often because it was a "failure-to-hold" violation) or that reinspection was actually more timely than the average. Hence, reinspection delays resulting from the seasonal nature of the industry had either no effect or a diminishing effect on the 278-day average that we reported.

We did not intend to place any value judgments on the number of warning letters produced by a district. Our purpose in identifying these extremes is merely to indicate the wide variation in warning letter production that exists among the districts.

Analysis of FDA data indicates that while both the numbers of inspections and warning letters decreased from 1994 to 1997 (the range used for our statements in the reports), inspections decreased by 3.6 percent while warning letters fell 39 percent. In other terms, in 1994, about 9.1 inspections conducted yielded 1 warning letter. In 1997, the rate was 12.2 inspections per warning letter.

We agree that the prevalence of importers in a district could contribute to the variation in number of warning letters issued and have clarified their importance in the companion report entitled *FDA Warning Letters: Trends and Perspectives*.

The FDA's opinion that firms will voluntarily correct violations is highlighted in the background section of this report.

Several districts indicated that increased familiarity with FDA regulations leads to better industry compliance. We have clarified this point in the companion report.

Our recommendation was not intended to discourage the use of warning letters, but rather to encourage FDA to issue guidance which would allow a district office to select the tools it feels are most effective in achieving compliance in a given situation.

The medical device Warning Letter Pilot will allow FDA to use a firm's response to an FDA-483 or an untitled letter to preempt a warning letter for certain segments of the device industry. More information can be found on FDA's website or in the Federal Register for August 27, 1998.

With respect to FDA's comment on "Page 11, last paragraph after table" of the draft report (the table and paragraph now appear on page 12), we note that the paragraph below the pie chart on page 13 shows that despite the discovery of repeat or new violations on reinspection, the warning letter was still effective. As stated there, investigators believed that the violations found on reinspection were minor and that firms had made satisfactory progress towards compliance.