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Report to the Chairman, Subcommittee on Oversight and Investigations, Committee on Commerce, House of Representatives

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FOOD AND DRUG ADMINISTRATION

Improvements Needed in the Foreign Drug Inspection Program

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GAO

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Health, Education, and
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The Honorable Joe Barton
Chairman, Subcommittee on Oversight and
Investigations
Committee on Commerce
House of Representatives

Dear Mr. Chairman:

In the late 1980s, at least 15 Americans reportedly suffered epileptic seizures, and 2 died, after taking a drug that allegedly contained a poor-quality ingredient that had been manufactured in a foreign country and imported by a U.S. pharmaceutical company. Reports of these tragic incidents and other problems raised concerns about the Food and Drug Administration's (FDA) ability to ensure the safety and quality of the increasing volume of foreign-produced drugs imported daily into the United States.

According to FDA, as much as 80 percent of the bulk pharmaceutical chemicals used by U.S. manufacturers to produce prescription drugs is imported. Moreover, the number of finished drug products manufactured abroad for the U.S. market is increasing. FDA inspects foreign manufacturers to help ensure that pharmaceutical products entering the United States are safe, pure, and high in quality.[1] However, a 1988 FDA internal review and a 1993 internal discussion paper identified serious problems with the agency's foreign inspection program.[2] Specifically, these internal evaluations found that FDA was not taking prompt action against foreign manufacturers because inspection reports were not being prepared in a timely manner. The 1993 discussion paper also noted that headquarters staff often disagreed with field investigators about the results of foreign inspections and whether FDA should reinspect problem manufacturers to verify that they had corrected serious deficiencies. Further, the evaluations found that FDA was not routinely inspecting foreign manufacturers to ensure that they complied with U.S. manufacturing standards. Finally, the evaluations found that FDA did not

[1]We use "pharmaceutical products" to refer to pharmaceuticals imported in finished dosage form as well as bulk drug substances (for example, active pharmaceutical ingredients or bulk pharmaceutical chemicals).

[2]Office of Regulatory Affairs, Program Evaluation Branch, "An Evaluation of FDA's Foreign Inspection Program," Rockville, Md., March 1988, and the internal FDA discussion paper entitled "Recommendations to Strengthen Surveillance and Enforcement Operations Associated with the Importation of Human Drugs," prepared by the Regional Director and senior staff, mid-Atlantic Region, 1993.

have a comprehensive data management system to monitor foreign manufacturers. The evaluations concluded that unless corrected, problems in FDA's foreign inspection program could lead to the importation of adulterated and low-quality drugs that could pose serious health risks to Americans.

This report responds to your request that we examine FDA's efforts to correct problems identified in the earlier evaluations. In subsequent discussions with your office, we agreed to examine FDA's efforts to

- prepare inspection reports and take enforcement actions against foreign pharmaceutical manufacturers in a timely manner,
- improve the consistency with which FDA evaluates the results of foreign inspections and conducts reinspections to verify that foreign pharmaceutical manufacturers have corrected serious deficiencies,
- conduct routine inspections of foreign pharmaceutical manufacturers to monitor their compliance with U.S. quality standards, and
- improve the management of data needed for planning inspections, monitoring inspection results, and taking enforcement actions.

To obtain information on FDA's foreign inspection program, we interviewed FDA officials and examined documents regarding FDA's requirements for inspecting, reporting, and taking enforcement actions against foreign pharmaceutical manufacturers. We also examined FDA's 1988, 1993, and 1997 internal evaluations of its foreign inspection program and discussed them with agency officials.[3]

To determine the timeliness of enforcement actions, the consistency of evaluations of foreign inspection results and enforcement actions, the frequency of routine inspections, and the management of data, we analyzed computerized data on the 287 foreign inspection reports FDA reviewed during fiscal year 1996 and the 257 it reviewed during fiscal year 1997. In addition, we reviewed inspection reports for 22 pharmaceutical manufacturers in China and 17 in India that were inspected between January 1, 1994, and May 15, 1996. We focused on China and India because they represent two developing countries that had large increases in pharmaceutical products exported to the United States. We interviewed the investigators who conducted the inspections and the FDA officials responsible for reviewing these inspection reports. We did not independently verify the accuracy of data provided by FDA. These are the

[3]Office of the Commissioner, U.S. Food and Drug Administration, "Summary Report of the Foreign Inspection Working Group," Rockville, Md., June 1997.

same data FDA uses to manage the foreign inspection program. Except for this, we performed our work from April 1996 to February 1998 in accordance with generally accepted government auditing standards.

Results in Brief

FDA has taken several actions to address problems with its foreign inspection program that were identified in two previous internal evaluations. Although FDA has improved the timeliness with which investigators submit inspection reports, in fiscal year 1996, almost 60 percent were still submitted later than called for by agency standards, including half the reports that identified the most serious deficiencies in manufacturing quality. Moreover, FDA is still experiencing delays in taking prompt enforcement action against foreign pharmaceutical manufacturers. During fiscal year 1996, FDA took, on average, almost four times longer than its required time to issue warning letters to foreign pharmaceutical manufacturers with serious manufacturing deficiencies. The extent of these delays can be significant. For example, in one case FDA allowed a manufacturer in India to continue exporting its pharmaceutical products to the United States despite its investigator's finding that the manufacturer could not adequately test for impurities in its product and water system. Nearly 2 years elapsed before FDA determined that enforcement action had not been taken against this manufacturer.

During fiscal years 1996 and 1997, headquarters review personnel continued to downgrade the classifications of inspections recommended by its field investigators who conducted the inspections. Most of the decisions to downgrade the classifications were based on foreign manufacturers' promises to implement corrective actions. As a result, FDA conducted fewer reinspections of these facilities to verify that foreign manufacturers had corrected serious manufacturing deficiencies. In one case, for example, FDA headquarters reviewers accepted a manufacturer's written explanation of the actions it was taking to correct deficiencies in its testing procedures, instead of issuing the manufacturer a warning letter. As a result, this facility was not reinspected even though agency documents raised questions about the manufacturer's trustworthiness. Our analysis showed that in fiscal year 1996, half of the inspections in which field investigators recommended agency enforcement action were downgraded by headquarters review staff, which meant that FDA conducted 50 percent fewer reinspections to verify that foreign manufacturers corrected the deficiencies observed during their initial inspections. The frequency of downgrades has increased significantly in the past year. In fiscal year 1997, FDA downgraded about two-thirds of the

inspections in which field investigators recommended agency enforcement action.

FDA conducts infrequent routine inspections of foreign manufacturers to ensure that they continue to comply with U.S. quality standards, although routine surveillance inspections constitute FDA's most comprehensive program for monitoring the quality of marketed pharmaceutical products. Most inspections of foreign pharmaceutical manufacturers are performed to approve the marketing of new products. Routine surveillance inspections of manufacturers producing approved pharmaceutical products already marketed in the United States accounted for only 20 percent of FDA's foreign inspections during fiscal year 1995. As a result, routine inspections of foreign pharmaceutical manufacturers occur with far less frequency than the 2-year interval required for domestic manufacturers. In China and India, for example, 4 to 5 years elapsed between FDA inspections of pharmaceutical manufacturers. Acknowledging that it needs to conduct more routine surveillance inspections, FDA has developed a four-tier strategy aimed at ensuring that high-risk foreign pharmaceutical products and manufacturers are inspected more frequently. While this strategy may improve the frequency of routine inspections for some facilities, FDA acknowledges that most foreign pharmaceutical manufacturers may never receive a routine surveillance inspection.

FDA has been striving to improve its management of data needed for planning inspections, monitoring inspection results, and taking enforcement actions. At present, FDA relies on 15 separate systems to identify foreign pharmaceutical manufacturers, plan foreign inspection travel, track inspection results, and monitor enforcement actions. As a result, essential foreign inspection data are not readily accessible to the different FDA units that are responsible for planning, conducting, and reviewing inspections and taking enforcement actions against foreign manufacturers. FDA is developing a comprehensive, agencywide automated system to provide better data for managing its foreign inspection program. The first phase of FDA's new Field Accomplishments and Compliance Tracking System (FACTS) is expected to be implemented during fiscal year 1998.

Our report contains several recommendations to the Commissioner of FDA to establish procedures to help ensure timely compliance with U.S. quality standards by foreign pharmaceutical manufacturers.

Background

FDA is responsible for the safety and quality of domestic and imported pharmaceutical products under the Federal Food, Drug, and Cosmetic Act. Specifically, FDA's Center for Drug Evaluation and Research (CDER) establishes standards for the safety, effectiveness, and manufacture of prescription pharmaceutical products and over-the-counter medications. CDER reviews the clinical tests and manufacture of new pharmaceutical products before they can be approved for the U.S. market, and it regulates the manufacture of pharmaceutical products already being sold to ensure that they comply with federal statutes and regulations, including current "good manufacturing practice" (GMP). GMP requirements are federal standards for ensuring that pharmaceutical products are high in quality and produced under sanitary conditions.[4] In addition, CDER enforces the act's prohibitions against the importation of adulterated, misbranded, and counterfeit pharmaceutical products.

CDER regulates the manufacture of pharmaceutical products by requesting that FDA's Office of Regulatory Affairs (ORA) inspect manufacturers both at home and abroad to ensure that pharmaceuticals are produced in conformance with GMPs. ORA manages investigators located in FDA's 21 district offices. Approximately 375 investigators and 75 microbiologists and chemists conduct inspections of foreign pharmaceutical manufacturers. ORA's investigators inspect manufacturers that produce pharmaceuticals in finished form as well as manufacturers that produce the active ingredients used in finished pharmaceutical products. Typically, ORA investigators travel abroad for about 3 weeks at a time during which they inspect approximately three manufacturers. Each inspection ranges from 2 to 5 days in length, depending on the number and types of products inspected.[5] In fiscal year 1996, FDA reviewed the results of 287 inspections of foreign pharmaceutical manufacturers conducted by its investigators in 35 countries (see figure 1). About 70 percent of these inspections were performed in manufacturing facilities that produce the active ingredients used in finished pharmaceutical products.

[4]The current good manufacturing practice regulations (21 C.F.R. parts 210 and 211) provide a framework for manufacturers to follow to ensure that they produce safe, pure, and high-quality pharmaceutical products. While FDA has an essential role in ensuring safe, pure, and high-quality pharmaceutical products, the individual manufacturers are ultimately responsible for the safety and quality of their products.

[5]FDA contends that foreign inspections now range from 2 to 7 days and may be performed by a single investigator or an inspection team.

Figure 1: The 287 FDA Inspections of Foreign Pharmaceutical Manufacturers in 35 Countries Reviewed During Fiscal Year 1996

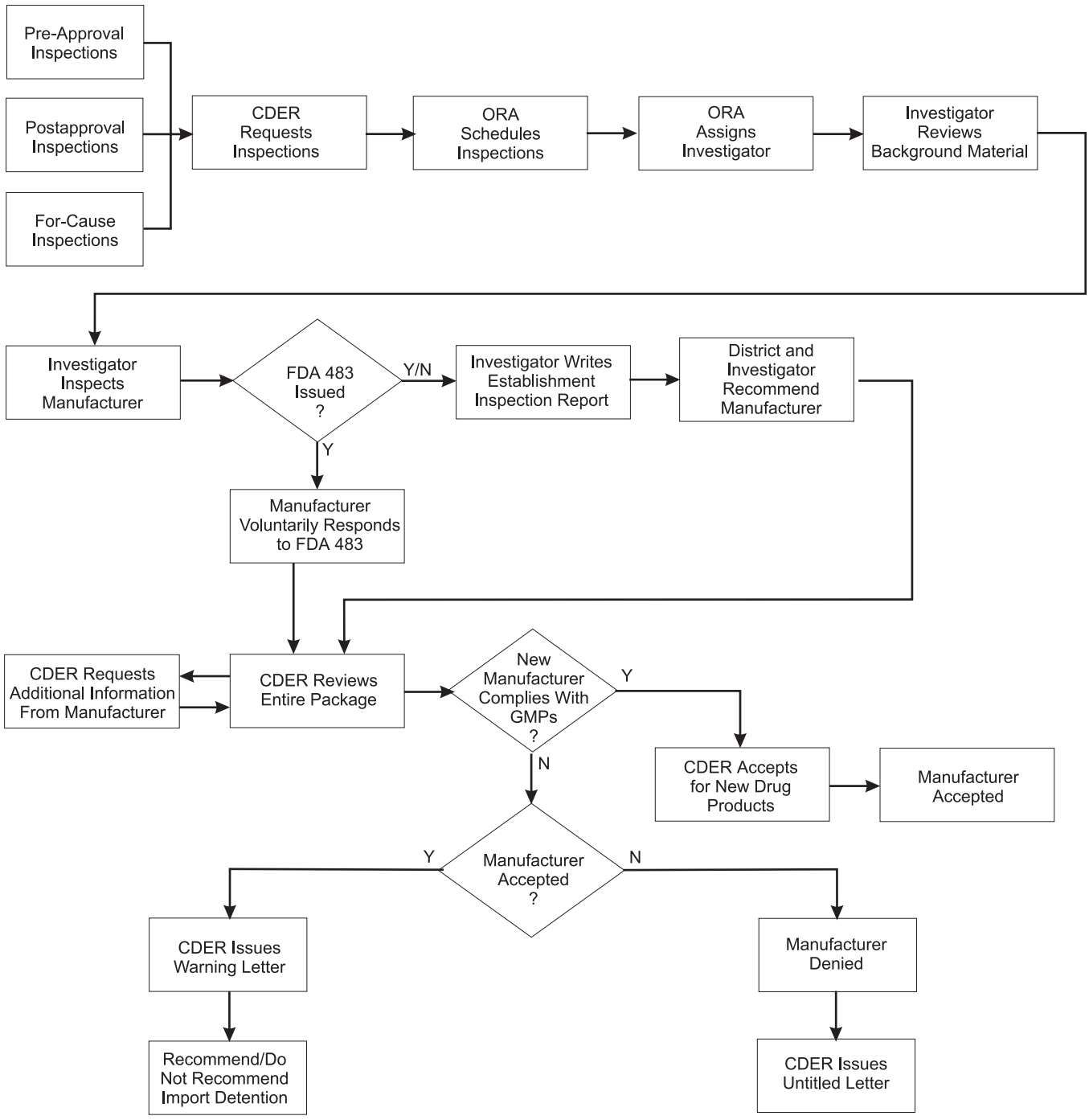

Norway–3
Sweden–9
Finland–4
Denmark–5
Netherlands–4
Belgium–6
United Kingdom–21
Germany–19
Czech Republic–1
Slovakia–1
Hungary–5
Bulgaria–1
Turkey–1
Ireland–8
France–18
Portugal–2
Spain–15
Switzerland–11
China
12
India
8
Republic of Korea–1
Japan–44
Macau–1
Taiwan–1
Slovenia–3
Israel–7
Italy–34
Niue–1
Australia
1
South Africa
3

CDER requests that ORA's investigators conduct inspections for three reasons. First, CDER requests pre-approval inspections to ensure that before a new drug application is approved, the manufacturer of the finished pharmaceutical product as well as each manufacturer supplying a bulk pharmaceutical chemical used in the finished pharmaceutical product comply with GMPs. Each step in the manufacture and processing of a new drug, from the sources of raw materials to final packaging must be approved by FDA. Second, CDER requests postapproval or routine surveillance inspections to periodically assess the quality of marketed pharmaceutical products. During these inspections, investigators verify that manufacturers of finished pharmaceutical products and bulk pharmaceutical chemicals comply with GMPs.[6] Third, CDER requests for-cause inspections when it receives information indicating problems in the manufacture of approved pharmaceutical products. In addition, CDER requests for-cause inspections of manufacturers that were not in compliance with GMPs during previous inspections. In for-cause inspections, FDA investigators determine whether the manufacturer has improved its production processes to comply with GMPs.

During an inspection, the ORA investigator examines the pharmaceutical manufacturer's production processes, product packaging and labeling processes, product contents, warehouse practices, quality control, laboratories, recordkeeping systems, and other manufacturing practices. The investigator reports observations of significant objectionable conditions and practices that do not conform to GMPs on the list-of-observations form, commonly referred to as FDA form 483. At the end of the inspection, the investigator gives a copy of the form 483 to the highest ranking management official present at the manufacturing facility. The investigator also discusses the observations on the form 483 with the firm's management to ensure that they are aware of any deviations from GMPs that were observed during the inspection and suggests that the manufacturer respond to FDA in writing concerning all actions taken as a result of the observations. Figure 2 shows FDA's process for managing foreign pharmaceutical inspections.

[6]FDA's surveillance of foreign pharmaceutical products also includes routine sampling of imports at the port of entry to the United States. In addition, FDA's postapproval surveillance system for human pharmaceutical products consists of inspections of manufacturing establishments, which we discuss in this report.

Figure 2: How FDA Manages Foreign Pharmaceutical Inspections



After returning to the district office, the investigator prepares an establishment inspection report that describes the manufacturing operations observed during the inspection and any conditions that may violate federal statutes and regulations. The investigator also recommends whether the manufacturer is acceptable to supply pharmaceutical products to the United States. The investigator's district office formally endorses the recommendation after reviewing the inspection report to determine if it supports the proposed recommendation. The district office forwards its endorsement along with the investigator's establishment inspection report and the form 483 to CDER. The foreign inspection team within CDER's Office of Compliance reviews the documentation and the manufacturer's written response to FDA about any corrective actions taken. CDER then decides whether the manufacturer complies with GMPs.

Inspections of pharmaceutical manufacturers are classified in one of three categories. As table 1 shows, during fiscal year 1996, 238 inspections (or 83 percent) revealed deviations from GMPs. Of these, CDER determined that 46 inspections revealed deviations from GMPs that ranked in the most serious (or "official action indicated") category.

Table 1: Distribution of Inspection Results of Foreign and Domestic Pharmaceutical Manufacturers, Fiscal Year 1996

		Foreign		Domestic	
Classification	**Explanation**	**Number**	**Percent**	**Number**	**Percent**
Official action indicated (OAI)	OAI classifications are considered the most serious and indicate deviations from GMPs that require some FDA intervention to ensure that corrections are made. OAI classifications require FDA to issue either a warning letter or an untitled letter, the manufacturer to correct problems and respond in writing to FDA about the corrections made, and FDA to reinspect the manufacturer to verify that it has improved its production processes to comply with GMPs.	46	16%	182	21%
Voluntary action indicated (VAI)	VAI classifications are considered less serious than OAI classifications and indicate deviations from GMPs that are amenable to corrective action by the manufacturer with no compromise to public safety. VAI classifications require the manufacturer to agree to voluntarily correct problems and FDA to verify that the manufacturer corrected all less-serious GMP deviations during the next routine surveillance inspection.	192	67	328	38
No action indicated (NAI)	NAI classifications indicate insignificant or no deviations from GMPs.	49	17	342	40
Total		**287**	**100%**	**852**	**99%[a]**

[a]FDA could not provide the inspection classification for 16 domestic inspections.

When CDER classifies a foreign pharmaceutical inspection as "official action indicated" (OAI), it sends the manufacturer an enforcement letter. CDER issues two types of enforcement letters: untitled letters and warning letters. CDER issues an untitled letter to a foreign manufacturer when the inspection was conducted as part of its review of a new drug application and the manufacturer has not previously been inspected and accepted to supply approved pharmaceutical products to the United States. The untitled letter notifies the manufacturer that its manufacturing process does not comply with federal statutes and regulations and that failure to take corrective action may result in the disapproval of any new drug application on which the manufacturer is listed.

CDER issues a warning letter to a foreign manufacturer when a subsequent inspection of its facility is classified as OAI. Warning letters are issued to manufacturers that are already supplying approved pharmaceutical products to the United States. Warning letters indicate that serious manufacturing deficiencies can and are affecting commercially marketed

products. The warning letter notifies the manufacturer of its violation of federal statutes and regulations and that failure to take corrective action may result in further FDA enforcement action. CDER issued 17 untitled letters and 19 warning letters to foreign pharmaceutical manufacturers in fiscal year 1996.

If CDER classifies an inspection as OAI and believes the manufacturer's product is adulterated because it was not produced in compliance with GMPs, CDER can instruct the district offices to cooperate with the U.S. Customs Service in detaining the manufacturer's product when it is offered for entry into the United States. In such a situation, the warning letter may also threaten to detain the manufacturer's products at U.S. entry points or notify the manufacturer that detention will occur. Customs, which controls the points where foreign shipments enter the United States, ensures that adulterated pharmaceutical products are either exported from the United States or destroyed. In fiscal year 1996, CDER determined that the pharmaceutical products made by two foreign manufacturers should be detained.

Timeliness of Inspection Reports Has Improved, but Delays in Taking Prompt Enforcement Actions Continue

FDA's 1988 internal evaluation found that delays in the submission of final inspection reports by investigators made it difficult for FDA to take prompt enforcement action against foreign manufacturers that did not comply with federal regulations that ensure the safety, purity, and quality of pharmaceutical products. Since then, FDA has taken several actions that have reduced the average time required by investigators to submit foreign inspection reports to headquarters. Despite this improvement, only about a quarter of the warning letters FDA issued in fiscal year 1996 to foreign pharmaceutical manufacturers found to have serious deficiencies met FDA's timeliness standards. The lack of prompt enforcement action may impair FDA's ability to prevent foreign manufacturers from exporting contaminated or adulterated pharmaceutical products to the United States.

FDA Has Acted to Improve the Timeliness of Enforcement Actions

FDA's 1988 internal evaluation of its foreign inspection program reported that the average length of time required from the completion of an inspection to CDER's receipt of a final report was slightly more than 3 months. Delays in submitting inspection reports may hinder CDER's ability to initiate timely enforcement actions to prevent contaminated or adulterated products from entering the United States. To reduce these

delays, the evaluation recommended that FDA explore new ways of processing inspection reports.

To strengthen its enforcement strategy, FDA revised its timeliness standards for new drug applications in October 1991 by requiring investigators and districts to submit all inspection reports classified as OAI or "voluntary action indicated" (VAI) to CDER within 30 work days of completing inspections.[7] FDA also revised its enforcement policy to require CDER to review OAI inspection reports containing recommendations for warning letters and issue the letters within 15 work days.

According to FDA officials, additional changes were made to help investigators submit more timely inspection reports on foreign manufacturers. In the early 1990s, FDA reduced the length of foreign inspection trips from about 6 to 3 weeks as well as the number of inspections an investigator conducted during the trip. The agency also revised inspection requirements for international travel to build time into foreign inspections for investigators to prepare their reports and provided investigators with notebook computers so that they could begin preparing their reports overseas.

Inspection Reports Are More Timely, but Many Miss FDA's Reporting Deadline

Although FDA has reduced the average time it takes to submit reports after inspections are completed from slightly more than 3 months to 2, over half of the reports in fiscal year 1996 did not meet FDA's timeliness standard. Our analysis of 287 foreign inspection reports CDER reviewed during fiscal year 1996 showed that about 42 percent (102) of the inspections that identified GMP deficiencies (either OAI or VAI) were submitted on time or within 30 work days of completing inspections. However, 58 percent (141) of the inspection reports were not timely (see table 2).[8]

[7]The same timeliness standards were extended to approved drug products in September 1994.

[8]Investigators classified an additional 44 inspections as not requiring any action by FDA or foreign manufacturers because insignificant or no deviations from U.S. GMPs had been observed.

Table 2: Work Days Between the Completion of Foreign Inspections and Submission of Inspection Reports to CDER, Fiscal Year 1996

	Inspection classifications recommended by investigators and districts			
Submitted to CDER (in work days)	Official action indicated	Voluntary action indicated	Total	Percent
30 days or less	41	61	102	42%
31- 60 days	37	79	116	48
61-90 days	4	14	18	7
91-120 days	0	3	3	1
121 days or more	0	4	4	2
Total	**82**	**161**	**243**	**100%**

About half of the inspections with the most serious deficiencies (classified as OAI or requiring official action) were submitted on time and half were not. Most of the OAI inspection reports that were submitted to CDER after the 30-day deadline were submitted within 60 work days. CDER received about one-third of the inspection reports with less serious deficiencies (classified as VAI, allowing foreign manufacturers to voluntarily make corrections) on time; two-thirds were late.

FDA reported more recently that its analysis of fiscal year 1997 data showed a modest improvement in the submission times for OAI and VAI inspection reports. FDA reported that in its analysis of 230 foreign inspection reports reviewed during fiscal year 1997, about 47 percent (75) of the inspections that identified GMP deficiencies (either OAI or VAI) were submitted on time. However, 53 percent (85) of the inspection reports were not timely.

Our review of inspection reports for China and India showed that regardless of the seriousness of the GMP deficiencies found, CDER did not receive the majority of the inspection reports within the 30-work day requirement. Specifically, 22 of the 36 OAI and VAI inspection reports (61 percent) we reviewed for China and India were not submitted on time.[9]

Although there was no one reason for the late submissions, CDER officials told us that an investigator may return to the United States 3 weeks after conducting his first inspection, making it impossible for him or her to submit an inspection report within 30 work days. Some investigators told us that the paperwork, which includes preparing numerous documents and exhibits to support the deficiencies observed, is time-consuming. In

[9]Three of the inspection reports we reviewed did not identify any deviations from U.S. GMPs.

addition, after returning to their district offices, some investigators stated that they are often confronted with competing demands on their time, such as responding to problems with domestic pharmaceutical manufacturers.

FDA Enforcement Actions Still Take Too Long

Although FDA established a 15-work-day standard for issuing warning letters, about one out of four warning letters issued by CDER during fiscal year 1996 was issued on time. The extent of these delays can be significant. For example, CDER took 4 months (80 work days) to issue a warning letter to one Chinese manufacturer inspected in September 1994. In the inspection report, received by CDER 2 months after the inspection, the investigator noted 20 significant deviations from U.S. GMPs and wrote that the manufacturer was incapable of producing the injectable pharmaceutical product for which it was seeking approval. The investigator wrote that "Virtually all of the processing equipment for the first phases of processing is filthy, in [an] extreme state of disrepair, and was removed during this inspection." Despite the severity of the inspection findings, it was not until March 1995 that CDER sent a warning letter to the manufacturer.

As shown in table 3, it took more than 15 work days to issue 23 of the 30 warning letters sent to foreign pharmaceutical manufacturers. After receiving the inspection reports from investigators, it took CDER between 21 and 148 work days to issue the 23 late warning letters, with an average of 57 work days. According to a CDER official, CDER experienced staffing shortages during the period we examined that delayed the review of incoming foreign inspection reports.

Table 3: Work Days Between CDER's Receipt of Inspection Reports and Issuance of Warning Letters, Fiscal Year 1996

Issued by CDER (in work days)	Number of warning letters issued	Percent
15 days or less	7	23%
16-30 days	6	20
31-45 days	5	17
46-60 days	2	7
61-75 days	3	10
76-90 days	3	10
91-105 days	2	7
106 or more days	2	7
Total	**30**	**101%[a]**

[a]Total does not add to 100 because of rounding.

More recently, FDA reported that its analysis of fiscal year 1997 data showed a substantial improvement in the time CDER spent in processing warning letters. FDA reported that 30 percent or 3, of the 10 warning letters issued to foreign pharmaceutical manufacturers during fiscal year 1997 were sent within 15 work days. On average, FDA issued the 10 warning letters in about 24 work days. However, compared with the number of warning letters issued during fiscal year 1996, FDA issued two-thirds fewer warning letters during fiscal year 1997.

Our analysis of inspections conducted in China and India between January 1, 1994, and May 15, 1996, showed that CDER did not issue any of the six warning letters within the agency's 15-work-day standard. The number of work days from CDER's receipt of inspection reports to the issuance of these warning letters ranged from 24 to 86 days, with an average of 40 days.

In one case, a February 1994 inspection of a plant in India making an antibacterial agent identified serious problems, including failure to ensure that the proper manufacturing process was followed and inadequate testing of impurities in the product and water used by the plant. The investigator also found that two deficiencies identified during a 1985 FDA inspection had not been fully corrected to meet U.S. quality standards.[10] Given the significance of the deficiencies found during the 1994 inspection, the investigator and his district office recommended that CDER

[10]During a 1994 inspection, FDA found that the manufacturer had not packaged stability samples of its product in simulated market containers as agreed and had implemented laboratory procedures for impurity testing that did not meet U.S. GMPs.

(1) not approve the new drug application, (2) advise FDA district offices to deny entry into the United States of any pharmaceutical products from this manufacturer, and (3) pursue additional enforcement actions against pharmaceutical products from the manufacturer that were already distributed in the United States. Notwithstanding the seriousness of the problems or the recommended enforcement action, it took 2 years for CDER officials to determine that they had not taken any enforcement action against this foreign manufacturer.

While CDER officials agreed with the district recommendation and planned to issue a warning letter, the letter was never sent to this foreign pharmaceutical manufacturer because CDER lost track of it during staffing changes. In March 1996, CDER officials determined that they had allowed this foreign manufacturer to continue shipping already approved bulk pharmaceutical products to the United States, even though the inspection had identified manufacturing problems such as unacceptable impurity testing procedures, no periodic review of the production process, and the failure to investigate product yields that were lower than the specified amount.[11]

In another case, it took CDER about 3 months to issue a warning letter to a foreign pharmaceutical manufacturer operating with 17 serious GMP deficiencies. FDA inspected this foreign manufacturer in April 1995, after receiving several new drug applications listing the manufacturer as a supplier of bulk pharmaceutical chemicals for use in U.S. finished drug products. The investigator found that the manufacturer did not have an appropriate impurity testing system and identified questionable results from impurity testing. The investigator believed that these questionable results represented a deliberate attempt to conceal instances in which the pharmaceutical products contained higher levels of impurities than permitted by U.S. standards. As a result, the investigator and his district office recommended that CDER not approve the new drug applications and that it issue a warning letter to the manufacturer.

Notwithstanding the serious nature of the investigator's findings, it took ORA about 2 months to submit the inspection report to CDER and another month for CDER to review the report. On August 1, 1995, slightly more than 3 months after the inspection, CDER issued a warning letter stating that it would not approve any applications listing this foreign pharmaceutical manufacturer as a supplier. During the time it took CDER to act on the

[11]According to FDA, a reinspection of this manufacturer found that it had implemented promised corrections and was in compliance with U.S. GMPs.

serious deficiencies and possible fraud identified by the investigator, a U.S. finished-drug manufacturer discovered that several containers labeled as a bulk pharmaceutical chemical product from the same foreign manufacturer contained an herbicide rather than a bulk chemical.

FDA Verifies Corrective Actions in Only About Half the Cases in Which Serious Deficiencies Are Identified

Members of the Congress and industry representatives have been concerned about the consistency of FDA inspections and subsequent enforcement actions taken against domestic and foreign pharmaceutical manufacturers. In FDA's 1993 internal evaluation, these concerns were attributed to differences in how field investigators and headquarters staff evaluated foreign inspection results and determined the appropriate follow-up activity. Moreover, the internal evaluation acknowledged that there was a perception that FDA relied on foreign facilities to correct manufacturing deficiencies because there were insufficient resources to conduct follow-up inspections to confirm that corrective actions had been implemented.

Our analysis of the foreign inspection reports reviewed during fiscal year 1996 showed that in about half the instances in which field staff concluded that the severity of inspection findings warranted a reinspection, headquarters disagreed. For domestic manufacturers with a history of serious GMP manufacturing problems, FDA typically conducts a reinspection to verify that promised corrective actions have been implemented. However, current FDA policy does not address the need for verifying the corrective actions of foreign pharmaceutical manufacturers in instances in which FDA headquarters downgrades the severity of inspection findings. As a result of downgrading, FDA conducted far fewer reinspections of foreign manufacturers than was recommended by its investigators. Without reinspections, FDA cannot adequately verify that foreign manufacturers have corrected serious deficiencies that could affect the safety, purity, and quality of their pharmaceutical products.

FDA's 1993 Internal Review Identified Differences in the Evaluation of Inspection Findings That Affected the Frequency of Reinspections

In the 1993 internal discussion paper, FDA managers found that agency headquarters' personnel downgraded the severity of the manufacturing deficiencies identified in foreign inspections and the need for reinspecting violative foreign manufacturers. However, they stated that FDA did not downgrade the severity of inspection findings for domestic manufacturers that had similar deficiencies. According to the review, this was caused by different FDA units being responsible for reviewing and evaluating inspection results and planning reinspections of foreign and domestic

pharmaceutical manufacturers to verify corrective actions. The discussion paper identified several instances in which approval of new drug applications was withheld, based on significant GMP deficiencies discovered during domestic inspections, whereas similar deficiencies found at foreign manufacturing facilities resulted in the approval of applications.

In the discussion paper, FDA managers stated that differences between the evaluations of foreign and domestic inspection results existed for two reasons. First, unlike for domestic inspections, decisions regarding the severity of the manufacturing deficiencies identified during foreign inspections are made by CDER staff rather than by the field investigators who actually conducted the inspections and their district office managers who endorse their recommendations. Second, they indicated that a perception existed that FDA has too few resources to conduct a reinspection of a foreign manufacturer to verify that corrections have been made. According to the review, this leads CDER staff to "trust" a foreign manufacturer to correct serious manufacturing deficiencies. The review described several instances in which significant GMP deficiencies at foreign facilities received little or no enforcement action, while similar deficiencies at domestic facilities resulted in product recalls or application denials.

To correct this problem, the discussion paper recommended that district offices, where the investigators are located, rather than CDER be responsible for evaluating the results of foreign inspections and determining the appropriate enforcement action, including the need for reinspecting the manufacturer. FDA officials disagreed with the assertion that its inspection and enforcement programs were applied disparately to domestic and foreign pharmaceutical manufacturers. Further, they argued that district offices already had this responsibility.

CDER Often Downgrades Investigators' Recommended Classifications of Inspection Findings

Our analysis of FDA computer data of foreign inspection reports reviewed during fiscal year 1996 showed that CDER and field investigators often disagree on the classification of inspection findings and the severity of the enforcement action that should be taken against foreign pharmaceutical manufacturers when GMP deficiencies are found. For 82 of the 287 foreign inspections reviewed during this period, field investigators concluded that the severity of the GMP deficiencies they observed warranted that CDER initiate official action against the manufacturers. The investigators' district offices also endorsed their classifications of these inspections and their

recommendations for enforcement action before these were forwarded along with the inspection reports and the form 483s to CDER. However, CDER officials downgraded the inspection classifications and recommendations for enforcement action in 41 of these inspections, based on foreign manufacturers' promises to implement corrective actions. CDER officials decided that rather than OAI, 40 of these inspections should be classified as VAI and 1 should be classified as "no action indicated" (NAI). Conversely, CDER officials upgraded the field investigators' classifications and recommendations for enforcement action in 11 foreign inspections and classified them OAI rather than VAI.

In instances in which inspections found serious GMP deficiencies but CDER downgraded the inspection classifications, FDA's procedures allow foreign manufacturers to continue exporting pharmaceutical products to the United States without reinspections to evaluate whether they comply with U.S. quality standards. The classification of an inspection determines to a large degree whether a reinspection is conducted. The OAI classification is the most serious and requires FDA to reinspect the manufacturer to verify that it has improved its production processes to comply with GMPs. When CDER does not accept the investigators' recommendations and classifies inspections as VAI rather than OAI, foreign manufacturers are allowed to voluntarily correct their deficiencies and respond in writing to FDA about the corrections made.[12] FDA officials have acknowledged that they sometimes base their downgrades of inspection classifications and approvals of new drug applications on foreign manufacturers' promises to implement corrective actions. They contend that during the next inspection, whenever it may be, FDA confirms that the corrections were made.

Our analysis of FDA computer data of foreign inspection reports reviewed during fiscal year 1997 showed that CDER and field investigators continue to disagree on the classification of inspection findings and the severity of the enforcement action that should be taken against foreign pharmaceutical manufacturers when GMP deficiencies are found. For 49 of the 230 foreign inspections reviewed during this period, field investigators concluded that the severity of the GMP deficiencies they observed warranted that CDER initiate official action against the manufacturers.

[12]FDA's field offices are responsible for determining the severity of inspection findings and enforcing facility compliance for U.S. pharmaceutical manufacturers. As a result, even in instances where CDER does not approve the enforcement actions recommended by the district offices, CDER does not downgrade the field offices' classifications of domestic inspections when violations are identified. Consequently, unlike foreign manufacturers, U.S. pharmaceutical manufacturers are subject to reinspections to verify that promised corrective actions have been implemented and manufacturing operations meet GMP requirements.

However, CDER officials downgraded the inspection classifications and recommendations for enforcement action in 32 of these inspections. CDER officials decided that rather than classify these inspections OAI, 32 of the 49 inspections (65 percent) should be classified VAI. CDER officials also upgraded the field investigators' classifications and recommendations for enforcement action for two foreign inspections and classified them OAI rather than VAI.

FDA officials believe that in some instances the agency can adequately verify that foreign manufacturers have corrected serious deficiencies without reinspecting them. They said that foreign pharmaceutical manufacturers nearly always respond in writing concerning corrective actions taken as a result of the observations listed on the FDA form 483. They said that these responses typically include copies of the manufacturer's documentation of the corrective actions taken, such as photographs, laboratory test results, and corrected manufacturing procedures. Consequently, FDA officials said they can evaluate a manufacturer's corrective actions to ensure the safety, purity, and quality of its pharmaceutical products without conducting a reinspection based on the deficiencies found, the documentation provided, and the manufacturer's history of implementing corrective action. While we recognize that there may be instances in which documentation could suffice to verify the correction of manufacturing deficiencies, inspections of facilities in China and India that we reviewed give instances in which such documentation may not have been sufficient.

A pre-approval inspection of a bulk drug manufacturer in India found several deficiencies in the procedures used to test impurity levels in the product being manufactured. Although ORA personnel recommended withholding approval of the new drug application until corrective actions had been implemented, CDER changed the final inspection classification based on its review of the manufacturer's written explanation of the actions it was taking to correct the deficiencies identified during the inspection. CDER did not request a reinspection to verify that the corrective actions had been taken, even though FDA documents raised questions about the trustworthiness of the manufacturer. According to these documents, FDA had been notified several years earlier that this manufacturer had informed the U.S. Department of Commerce that it was no longer making a particular pharmaceutical product, despite evidence that the manufacturer was still shipping the product to the United States.

In another case, FDA conducted a for-cause inspection of a bulk pharmaceutical manufacturer in India to investigate reports that the manufacturer was using chloroform in its manufacturing process (a substance that had been found at higher than acceptable levels in the bulk pharmaceutical chemical). While the investigators found that the manufacturer was no longer using chloroform, they identified other deficiencies in how the company was measuring the impurities present in other bulk drug products that an FDA chemist characterized as "incompetence bordering on fraud." The investigators recommended from these deficiencies that the manufacturer be considered an unacceptable source of bulk pharmaceutical chemicals. CDER disagreed with this recommendation after reviewing the manufacturer's response to the investigators' findings and accepted the manufacturer as a supplier of bulk pharmaceutical chemicals without verifying that it had corrected deficiencies in its impurity testing procedures.[13]

FDA Conducts Infrequent Routine Inspections of Foreign Pharmaceutical Manufacturers

FDA's 1988 and 1993 internal evaluations found that while FDA routinely conducted surveillance inspections of domestic pharmaceutical manufacturers, foreign manufacturers were typically inspected only when they were listed in new drug applications. The evaluations concluded that this practice, which FDA said was because of limited resources, was unreasonable and unfair to domestic manufacturers. In addition, FDA's 1993 evaluation concluded that in the absence of reinspections, FDA could not adequately verify that foreign manufacturers corrected deviations from GMPs that had been observed during prior FDA inspections. Both evaluations recommended that FDA increase the frequency of its inspections of foreign manufacturers that supply approved pharmaceutical products to the United States.

FDA has authority to inspect foreign pharmaceutical manufacturers exporting their products to the United States under the Food, Drug, and Cosmetic Act. The purpose of the foreign inspection program is to ensure that internationally manufactured pharmaceutical products meet the same GMP standards for quality, safety, and efficacy that are required of domestic manufacturers. However, FDA is not required to inspect foreign pharmaceutical manufacturing facilities every 2 years as it is required by statute to do for domestic pharmaceutical manufacturers that must be registered with the agency. Enforcing GMP compliance through routine surveillance inspections is FDA's most comprehensive program for

[13]Again, according to FDA, more recent reinspections of these manufacturers found that they had implemented promised corrections and were in compliance with U.S. GMPs.

monitoring the quality of marketed pharmaceutical products. FDA also uses routine surveillance inspections to verify that manufacturers have corrected all less-serious GMP deficiencies that were observed in prior FDA inspections. Each year, FDA classifies about 65 percent of its foreign pharmaceutical inspections as VAI, which means that deviations from GMPs were found but they were not serious enough to warrant FDA intervention to ensure that corrections were made. In such instances, manufacturers agree to voluntarily correct any manufacturing procedures that do not comply with U.S. GMPs.

FDA's foreign inspection program has been predominantly a pre-approval inspection program—that is, most inspections of foreign manufacturers occur only when they are listed in new drug applications, with no routine follow-up thereafter. We found that the majority of FDA's foreign inspections of pharmaceutical manufacturers were conducted to ensure that before a new drug application was approved, each manufacturer listed as a supplier of a bulk pharmaceutical chemical used in the manufacture of the finished pharmaceutical product had been inspected within the previous 2 years and found to comply with GMPs. During fiscal year 1995, about 80 percent of FDA's foreign inspections were of pharmaceutical manufacturers listed in new drug applications. The remaining 20 percent consisted of routine surveillance inspections of accepted foreign pharmaceutical manufacturers. Consequently, FDA had few opportunities to verify that foreign pharmaceutical manufacturers had implemented prescribed corrective actions in response to prior inspections where less-serious GMP deviations were observed and were producing pharmaceutical products in compliance with GMPs.

FDA officials could not tell us how often accepted foreign manufacturers are inspected. FDA has inspected about 1,100 pharmaceutical manufacturers since the foreign inspection program began in 1955. For each fiscal year from 1990 through 1996, FDA conducted about 100 routine surveillance inspections of accepted foreign pharmaceutical manufacturers annually. At this rate, assuming that resources for the program remain constant, FDA will inspect each accepted foreign pharmaceutical manufacturer only once every 11 years, provided it is not listed on a new drug application.

Of the 39 inspections we reviewed for pharmaceutical manufacturers in China and India from January 1, 1994, through May 15, 1996, 11 (28 percent) were routine inspections of manufacturers producing approved pharmaceutical products rather than inspections conducted as

part of FDA's review of new drug applications. On average, we found that approximately 4 to 5 years elapsed between routine inspections of manufacturers in China and India producing approved pharmaceutical products for the U.S. market, more than twice FDA's 2-year inspection requirement for domestic pharmaceutical manufacturers.

FDA Plans to Conduct More Routine Inspections of Foreign Pharmaceutical Manufacturers

In June 1997, FDA's foreign inspection working group proposed a strategy for scheduling more routine surveillance inspections of accepted foreign pharmaceutical manufacturers. Led by the Deputy Commissioner of Operations, the group was asked to review the program and identify areas for improvement. The working group found that serious deviations from GMPs were identified more often in foreign pre-approval inspections (42 percent), compared with 18 percent at U.S. manufacturers. They concluded that by relying primarily on pre-approval inspections, FDA did not provide the necessary assurance that imported pharmaceutical products were manufactured in compliance with GMPs. The foreign inspection working group proposed that FDA's foreign inspection program include more routine surveillance inspections and fewer pre-approval inspections. To accomplish this, they suggested that FDA conduct fewer pre-approval inspections of accepted foreign manufacturers. Instead, they recommended that FDA use information from routine surveillance inspections in approving new drug applications in which accepted foreign manufacturers are listed.

Recognizing that FDA does not have sufficient resources for frequent inspections of all foreign manufacturers of pharmaceutical products imported into the United States, the working group proposed using risk-based criteria to prioritize the foreign manufacturers that FDA inspects. FDA's four-tier surveillance inspection strategy would vary the frequency of routine surveillance inspections depending on the public health risk associated with an accepted foreign manufacturer of an approved pharmaceutical product. Foreign pharmaceutical manufacturers whose prior inspections found serious deviations from GMPs would be placed in tier 1 and inspected annually. Routine surveillance inspections of all other foreign pharmaceutical manufacturers would vary from 3 to 6 years. Foreign manufacturers of pharmaceutical products that pose higher public health risks, such as sterile pharmaceutical products, would be placed in tier 2 and inspected every 3 years. Foreign manufacturers producing 10 or more pharmaceutical products for the U.S. market and those producing nonsterile bulk ingredients used in sterile finished pharmaceutical products would be placed in tier 3 and inspected every 5

years. All other foreign pharmaceutical manufacturers would be placed in tier 4 and inspected every 6 years (see table 4). The working group estimated that when the strategy is fully implemented, 60 percent of FDA's foreign inspections will be routine surveillance inspections. The remaining 40 percent will be inspections of foreign pharmaceutical manufacturers listed in new drug applications.

Table 4: FDA's Four-Tier Strategy for Scheduling Surveillance Inspections of Accepted Foreign Pharmaceutical Manufacturers

Tier	Type of manufacturer	Number of firms[a]	Frequency of inspection
1	Foreign pharmaceutical manufacturers whose prior inspections were classified OAI	35	Every year
2	Foreign manufacturers producing sterile bulk, finished, and aerosol pharmaceutical products	154	Every 3 years
3	Foreign manufacturers producing 10 or more nonsterile bulk or finished pharmaceutical products; also, foreign manufacturers supplying 10 or more U.S. pharmaceutical manufacturers and foreign manufacturers producing nonsterile bulk ingredients used in sterile finished pharmaceuticals	484	Every 5 years
4	Foreign manufacturers producing fewer than 10 nonsterile bulk or finished pharmaceutical products	427	Every 6 years

[a]Represents the 1,100 pharmaceutical manufacturers FDA has inspected since the foreign inspection program began in 1955.

FDA began implementing its four-tier surveillance inspection strategy in fiscal year 1997 by including routine surveillance inspections within its pre-approval inspections. FDA reported that 151 of the 230 foreign pharmaceutical inspections conducted during fiscal year 1997 (66 percent) were classified pre-approval and routine surveillance inspections. In addition, FDA planned to conduct routine surveillance inspections of about 150 accepted foreign pharmaceutical manufacturers placed in tiers 1 and 2. This group includes manufacturers that produce sterile pharmaceutical products and manufacturers that had prior inspections that revealed serious deviations from GMPs. FDA reported, however, that it conducted only 60 inspections of these manufacturers. As a result, although FDA conducted more routine surveillance inspections, most foreign pharmaceutical inspections still are limited predominantly to

manufacturers listed in new drug applications rather than those considered high risk.

In developing its new four-tier surveillance inspection strategy, however, FDA did not include all foreign pharmaceutical manufacturers that it should consider for a routine surveillance inspection. According to FDA data, about 3,200 foreign manufacturers have submitted information to FDA listing the pharmaceutical products that they intend to export to the United States. However, FDA prioritized for routine surveillance inspections only the 1,100 foreign pharmaceutical manufacturers that it had previously inspected. Consequently, FDA's scheduling strategy does not account for almost two-thirds of the foreign manufacturers that may be exporting pharmaceutical products to the United States. Moreover, according to the FDA official in charge of developing the surveillance inspection strategy, FDA may never inspect the majority of foreign manufacturers placed in tiers 3 and 4. However, while FDA has recognized that it does not have sufficient resources to routinely inspect all foreign manufacturers of pharmaceutical products imported into the United States, its strategy does not ensure that every foreign manufacturer exporting pharmaceutical products to the United States complies with U.S. quality standards.

Serious Problems Persist in Managing Foreign Inspection Data

Although both FDA's 1988 and 1993 internal evaluations identified serious problems in its foreign inspection data systems, the agency still lacks a comprehensive, automated system for managing its foreign inspection program. Instead, the information FDA needs to identify the foreign pharmaceutical manufacturers it is responsible for inspecting, manage its foreign inspection workload, and monitor inspection results and enforcement actions is contained in 15 different computer systems, very few of which are integrated. As a result, essential foreign inspection information is not readily accessible to the different FDA units that are responsible for planning, conducting, and reviewing inspections and taking enforcement actions against foreign manufacturers. While FDA's working group recently proposed several actions that FDA officials hope will correct these data system problems, they have not been implemented.

Lack of Comprehensive Automated Information System Inhibits Effective Management of Foreign Inspection Data

FDA's 1988 internal evaluation found that its automated field management information system did not contain complete information for 37 percent of the foreign inspections that FDA conducted during fiscal years 1982 through 1987. Specifically, the Program Oriented Data System (PODS) did not contain the results of 673 of the 1,813 foreign inspections that FDA investigators had conducted during this period. Moreover, the system did not contain any data for 251 of these inspections (14 percent). The evaluation attributed the missing inspection results to PODS not being updated after CDER's review and classification of the inspection reports. The evaluation recommended that FDA revise its procedures for entering foreign inspection data in PODS.

FDA's 1993 internal evaluation found that essential data on foreign pharmaceutical manufacturers were not readily accessible to agency personnel. The evaluation indicated that comprehensive data for a foreign pharmaceutical manufacturer should include (1) its inspection history, (2) the results of its last FDA inspection, (3) the identification of responsible company personnel, (4) its U.S. agent or representative, (5) the products that it supplied to the United States, and (6) the domestic manufacturers and distributors that it supplied. The evaluation found that comprehensive foreign inspection information could be obtained only by searching multiple computerized databases and FDA headquarters' files. For example, the evaluation noted several instances in which ORA investigators conducting domestic inspections suspected that U.S. manufacturers had received adulterated bulk pharmaceutical chemicals from foreign manufacturers. However, the investigators' efforts to substantiate these suppositions were hampered because they could not readily gain access to comprehensive data for foreign pharmaceutical manufacturers. The evaluation recommended that FDA use its field management information system to provide agencywide access to complete data for all foreign manufacturers shipping pharmaceutical products to the United States.

In 1994, FDA began using a new information system to support the foreign inspection program. The Travel and Inspection Planning System (TRIPS) was specifically developed to assist FDA's foreign inspection planning staff in managing foreign inspection assignments and the program's budget. TRIPS is also used to monitor whether the inspection report has been completed as well as the results of the inspection. However, TRIPS is accessible to only ORA headquarters staff. As a result, foreign inspection data are not readily accessible to the different FDA units responsible for conducting foreign inspections and reviewing inspection results. FDA plans

to make data from TRIPS more broadly available within the agency when it upgrades its field management information system in fiscal year 1998.

TRIPS and PODS have not significantly improved the quality of FDA's foreign inspection data. Our analysis of data recorded in TRIPS and PODS disclosed that these systems did not contain the results of 111 of the 759 inspections (15 percent) FDA conducted of foreign pharmaceutical manufacturers between January 1, 1994, and May 15, 1996. For 68 of the 111 inspections, the database did not identify the foreign manufacturer that was inspected. TRIPS and PODS also did not include the correct inspection results for 10 of the 39 pharmaceutical manufacturers FDA inspected in China and India during this period. Specifically, the inspection results were missing for two of these manufacturers and were incorrect for eight others. The database errors in recording the results of inspections conducted in China and India occurred because the systems were not updated after CDER staff reviewed and classified the inspection reports. Without complete and accurate data, FDA cannot ensure that all "high-risk" foreign pharmaceutical manufacturers are targeted for more frequent routine surveillance inspections.

We also found that essential foreign inspection data are not readily accessible to the different FDA units responsible for planning and conducting domestic and foreign inspections, and conducting import operations. The information that FDA needs for identifying foreign pharmaceutical manufacturers, verifying their compliance with federal laws and regulations, and screening foreign-produced pharmaceutical products for importation is dispersed among 15 automated databases, most of which do not interface.

FDA's multiple and unlinked databases inhibit the effective management of the foreign inspection program by impeding the flow of foreign inspection data to agency personnel for use in screening foreign pharmaceutical products offered for entry into the United States. For example, table 5 illustrates how the lack of linkage between 8 of FDA's 15 databases not being linked impedes the flow of essential foreign inspection data. The first four databases described in the table are used by FDA's district offices to support import operations. The four other databases described in the table are used by FDA headquarters staff for monitoring foreign pharmaceutical manufacturers' compliance with federal statutes and regulations. However, because these systems do not interface, comprehensive data about foreign manufacturers are not readily available to FDA district personnel screening imported pharmaceutical products.

Consequently, much of the same data must be retrieved from one automated system to be manually entered into others. Moreover, staff must search multiple data systems to obtain a comprehensive profile of a foreign pharmaceutical manufacturer. FDA also cannot easily match foreign manufacturers that have listed with the agency with their compliance status and the pharmaceutical products that are imported into the United States.

Table 5: Limitations of Selected FDA Information Systems for Managing Foreign Manufacturers and Imported Pharmaceutical Products

System	Description	Limitation	Link to FACTS[a]
Compliance Status Information System (COMSTAT)	Provides the compliance status (acceptable or unacceptable) of foreign drug manufacturers based on the results of GMP inspections. These data are shared with other federal and state agencies and foreign countries to ensure that pharmaceutical products purchased or cleared for import meet applicable quality standards.	Does not interface with OASIS to automatically assist import officers in evaluating the compliance status of foreign manufacturers offering pharmaceutical products for import into the United States.	Replace
Electronic Entry Processing System (EEPS)/Operational and Administrative System for Import Support (OASIS)	Automates screening and identification of imported products and facilitates sampling and testing of foreign-produced pharmaceutical products by interfacing with the U.S. Customs Service automated data system to retrieve information.	FDA cannot automatically screen and identify imported pharmaceutical products because many pharmaceutical products are identified by a miscellaneous code in EEPS/OASIS. Also, EEPS/OASIS does not include the unique identification number FDA assigns to each foreign pharmaceutical manufacturer; consequently, there is no direct cross-reference between identifiers in EEPS/OASIS and any center systems.	Integrate
Import Detention System (IDS)	Provides information about the detention of imported products, permitting FDA to identify significant problem areas requiring FDA action.	IDS does not include the unique identification number FDA assigns to each foreign pharmaceutical manufacturer; consequently, FDA cannot easily identify foreign manufacturers and their pharmaceutical products.	IDS will be replaced by OASIS.
Program Oriented Data System (PODS)	Supports the management of the domestic pharmaceutical inspection program and contains limited information on foreign inspections, such as the resources expended by FDA's district offices to conduct foreign inspections.	Does not interface with OCFITS; accordingly, compliance status must be entered into both systems. Sometimes contains incorrect inspection classification because final data are forwarded from CDER for input.	Replace

(continued)

System	Description	Limitation	Link to FACTS[a]
Drug Registration and Listing System (DRLS)	Provides information on foreign pharmaceutical manufacturers based on the statutory requirement that they list the drug products they ship to the United States.	Does not interface with COMSTAT to ensure that foreign manufacturers listing their pharmaceutical products with FDA have been inspected and comply with GMPs. Because the system does not include the identification number FDA assigns to each manufacturer, FDA cannot easily match foreign manufacturers that have listed their pharmaceutical products with their compliance status. Does not interface with OASIS to assist import officers by automatically comparing foreign manufacturers and pharmaceutical products listed to products offered for importation.	Interface
Establishment Evaluation System (EES)	Tracks requests for and monitors the status of GMP inspections of pharmaceutical manufacturers named in new, abbreviated, and supplemental drug applications. Supports CDER's pre-approval inspection process by permitting electronic communication with field offices.	EES-entered information is not captured by COMSTAT.	Interface
Office of Compliance Foreign Inspection Tracking System (OCFITS)	Tracks the results of CDER's Office of Compliance reviews of foreign inspection reports and recommendations for FDA enforcement action.	Does not interface with COMSTAT, PODS, or TRIPS; consequently, some of the same information must be entered into all four systems.	None
Travel and Inspection Planning System (TRIPS)	Provides data on inspections of foreign pharmaceutical inspections, including the manufacturer, the drug products covered, time expended, and inspection results. Facilitates the scheduling of foreign travel and managing the foreign inspection travel budget.	Does not interface with COMSTAT, OCFITS, or PODS, thereby requiring much of the same data to be entered into each system.	Replace foreign firms/ inspection functions

[a]FACTS will completely or partially replace many functions now provided by FDA's field information system and other independent systems used by ORA headquarters and personnel in the field. Also, FACTS will support automated interfaces with several existing FDA systems. Some of these systems will receive information from FACTS, others will pass information to FACTS, and a few will do both. OASIS will be integrated with FACTS. Although OASIS and FACTS will be separate applications, they will share parts of the same database to manage information about manufacturers of FDA-regulated products and authorize user access to the system.

FDA's foreign inspection working group concluded in June 1997 that the agency continues to be plagued by having too many databases that do not automatically interface. FDA is relying on a new automated field management information system to provide agencywide accessibility to comprehensive foreign inspection data. The Field Accomplishments and Compliance Tracking System is expected to replace approximately 22 computerized databases and support automated interfaces with several

existing databases. The first installment of FACTS, which is to include an inventory of foreign and domestic pharmaceutical manufacturers, is scheduled to go on line during fiscal year 1998. FDA also plans to develop additional FACTS components to assist the agency in managing its foreign inspection workload and compliance activities. These components will be included in the second installment of FACTS, which is scheduled for fiscal year 1999.

Incomplete List of Foreign Manufacturers Shipping Drugs to the United States Hinders Inspection Planning

FDA's 1988 internal evaluation found that the agency did not maintain an inventory of all foreign pharmaceutical manufacturers that were subject to FDA regulation. At that time, the only computerized file of foreign manufacturers shipping pharmaceutical products to the United States was maintained on a personal computer that could be accessed only from within one FDA unit. The file listed the foreign pharmaceutical manufacturers that FDA had inspected and the results of the last inspection. The internal evaluation concluded that this file was inadequate because it did not contain an inspection history for each foreign pharmaceutical manufacturer that had advised FDA that it intended to ship pharmaceutical products to the United States. As a result, FDA could not ensure that it was aware of, and therefore inspecting, all foreign pharmaceutical manufacturers that were under its jurisdiction.

FDA's 1988 evaluation recommended that the agency develop a comprehensive inventory of all foreign manufacturers shipping pharmaceutical products to the United States that could be used to improve long-range inspection planning and scheduling. To use resources better and increase knowledge agencywide, the evaluation also recommended that this inventory be available on FDA's automated field information system.

FDA's 1993 internal evaluation found the same problem. According to the evaluation, the lack of an inventory of the foreign manufacturers that were shipping pharmaceutical products to the United States made it virtually impossible for FDA to inspect foreign manufacturers as frequently as domestic pharmaceutical manufacturers. The evaluation detailed several instances in which a database with a comprehensive history of each establishment's previous inspections would have assisted in identifying problems in foreign pharmaceutical manufacturers. FDA's 1993 evaluation recommended that the agency use its automated field information system to develop an accurate and comprehensive inventory of all foreign manufacturers shipping pharmaceutical products to the United States.

It remains difficult for FDA to determine the number of foreign manufacturers shipping pharmaceutical products to the United States that should be considered for periodic inspections. Recently, an FDA official told us that the agency had to search four data systems just to determine the number of foreign manufacturers that should be considered for routine postapproval surveillance inspections.[14] They found that the systems did not include a common data element to permit them to easily identify a foreign manufacturer from system to system. Because the names and addresses of foreign manufacturers are sometimes incomplete or inaccurate, FDA officials found that matching data among the systems was an arduous, manual, and inconclusive effort.

The June 1997 report by FDA's foreign inspection working group acknowledged that the agency still lacked a complete list of foreign manufacturers that were shipping pharmaceutical products to the United States. According to the report, about 3,200 foreign pharmaceutical firms were listed with FDA as indicating their intent to ship products to the United States. However, FDA internal databases indicated that only about 1,100 pharmaceutical firms had been inspected by the agency. FDA officials could not explain why the remaining 2,100 firms had not been inspected.

The foreign inspection working group proposed two options for developing an official inventory of all foreign manufacturers that ship pharmaceutical products to the United States. One option would be for FDA to seek authority to require foreign pharmaceutical manufacturers to register and update their registration information annually. The other would use data from existing information systems to develop an official establishment inventory of foreign pharmaceutical manufacturers.

FDA's efforts to reconcile data from several of its databases to more accurately estimate the number of manufacturers that it should consider for inspection under its four-tier inspection strategy should identify all foreign manufacturers that are shipping pharmaceutical products to the United States. When completed by April 1998, FDA should have a comprehensive inventory of all foreign manufacturers shipping pharmaceutical products to the United States. This information could then be used to improve FDA's planning and scheduling of foreign pharmaceutical inspections.

[14]The systems were the Compliance Status Information System, the Drug Registration and Listing System, and the Travel and Inspection Planning System. (These systems and their functions are described in table 5.) The fourth system was the Drug Master File Information System that is used to track the receipt of submissions to the agency and may include foreign drug manufacturing processes.

Conclusions

Since 1955, FDA has inspected foreign pharmaceutical manufacturing facilities to ensure that drug products exported to the United States meet the same standards of safety, purity, and quality required of domestic manufacturers. However, two internal FDA evaluations in the past 10 years identified serious problems with the foreign inspection program that raised questions about FDA's ability to ensure that American consumers are protected from contaminated or adulterated drug products. FDA has taken some action to address these problems. However, we found indications that certain aspects of the foreign inspection program still need improvement.

FDA continues to experience problems in ensuring that inspection reports are submitted in a timely manner and that necessary enforcement actions are promptly initiated to prevent contaminated and adulterated pharmaceutical products from entering the United States. In addition, when FDA headquarters downgrades the severity of the inspection classifications recommended by field investigators, FDA is not verifying corrective actions that foreign manufacturers have promised to take to resolve serious manufacturing deficiencies. This impairs FDA's ability to ensure that American consumers are protected from potentially serious health risks posed by adulterated drug products.

FDA's risk-based inspection strategy recognizes that the agency does not have sufficient resources to routinely inspect all foreign manufacturers of pharmaceutical products imported into the United States. However, even though the strategy is intended to direct inspection resources according to risk, FDA's foreign inspection program continues to be driven by new drug applications and the agency acknowledges that it may never inspect most foreign manufacturers exporting pharmaceutical products to the United States.

Recommendations to the Commissioner of the Food and Drug Administration

To improve the effectiveness of FDA's foreign inspection program to ensure that only safe, pure, and high quality drugs are imported into the United States, we recommend that the Commissioner of FDA

- ensure that serious manufacturing deficiencies are promptly identified and enforcement actions are initiated by requiring investigators to prepare inspection reports and CDER to issue warning letters within established time periods and
- reexamine and revise FDA's foreign inspection strategy to provide adequate assurance that all foreign manufacturers exporting approved

pharmaceutical products to the United States comply with U.S. standards. At a minimum, the strategy should include (1) timely follow-up inspections of all foreign manufacturers that have been identified as having serious manufacturing deficiencies and that promised to take corrective action and (2) periodic surveillance inspections of all foreign pharmaceutical manufacturers, not just high-risk manufacturers.

Agency Comments and Our Response

In commenting on a draft of this report, FDA took issue with a number of our findings and recommendations. As discussed earlier, FDA believes it has made substantial improvement in the timeliness of inspection reports and enforcement actions. While we recognize FDA's progress, we note that the agency is still falling short of its standards for timeliness. As a result, we believe that FDA needs to monitor its investigators and CDER to ensure that they comply with established time periods in preparing inspection reports and issuing warning letters.

FDA was critical of our draft on several counts. FDA said we had accepted the recommendations in the 1993 discussion paper without verifying their validity or feasibility. FDA claimed that the findings and recommendations in the 1993 discussion paper were flawed in significant ways that limited its usefulness to the agency. We note, however, that subsequent to the discussion paper, in a 1995 memorandum to the agency's Assistant Inspector General, FDA officials reported that they had thoroughly reviewed the discussion paper, investigated the issues raised, verified program weaknesses, and had either begun or agreed to implement 10 of the 13 recommendations contained in the discussion paper.[15]

FDA also took issue with how our report described the processes followed by its district and headquarters for classifying domestic and foreign inspection reports. Specifically, FDA stated that the review performed by the supervisor or team leader in the district office is not considered to be a district endorsement of the investigator's recommendation. However, our review of FDA documents that describe the process for classifying domestic and foreign inspection reports supports our characterization. FDA issued guidance to its district offices in September 1996 indicating that beginning in fiscal year 1997, before inspection reports are forwarded to CDER, they "will be reviewed and endorsed by district management consistent with local procedures and timeframes for domestic reports." Also, in its memorandum to the Assistant Inspector General, FDA officials

[15]Memorandum from Associate Commissioner for Management, FDA, to Assistant Inspector General for Public Health Service Audits, Office of the Inspector General, Department of Health and Human Services, April 20, 1995.

reported that district offices had began endorsing foreign drug inspection reports before the 1993 discussion paper was issued.

FDA did not concur with our recommendation for conducting more frequent inspections of all foreign manufacturers that have been identified as having serious manufacturing deficiencies and have promised to take corrective action. FDA incorrectly suggests that our recommendation was based on the premise that a final classification that is lower than the recommended classification is always wrong if it results in a less-serious classification. Rather, our report questions FDA's ability to verify the adequacy of some corrective actions that foreign manufacturers promised to take to resolve serious manufacturing deficiencies without reinspecting them.

FDA also did not concur with our recommendation regarding the implementation of its routine surveillance inspection strategy. Given further clarification of the strategy, we have modified our recommendation.

FDA's written comments on a draft of this report are reproduced in appendix I. FDA also provided technical comments, which we considered and incorporated where appropriate.

As we arranged with your office, unless you publicly announce the report's contents earlier, we plan no further distribution until 30 days after its issue date. We will then send copies of this report to the Secretary of Health and Human Services, the Commissioner of the Food and Drug Administration, the Director of the Office of Management and Budget, and others who are interested. We will also make the report available to others upon request.

Please contact me on (202) 512-7119 or John Hansen, Assistant Director, on (202) 512-7105, if you or your staff have any questions. Others who contributed to this report are Gloria E. Taylor, Brenda R. James, and David Bieritz.

Sincerely yours,

Bernice Steinhardt
Director, Health Services Quality
and Public Health Issues

Contents

Abbreviations

CDER	Center for Drug Evaluation and Research
FACTS	Field Accomplishments and Compliance Tracking System
FDA	Food and Drug Administration
GMP	good manufacturing practice
NAI	no action indicated
OAI	official action indicated
ORA	Office of Regulatory Affairs
PODS	Program Oriented Data System
TRIPS	Travel and Inspection Planning System
VAI	voluntary action indicated

Comments From the Food and Drug Administration

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NOV 14 1997

Ms. Bernice Steinhardt
Director, HEHS
U.S. General Accounting Office
Room 5A26
441 G Street, N.W.
Washington, D.C. 20548

Dear Ms. Steinhardt:

Enclosed are the Food and Drug Administration's comments on the GAO Draft Report entitled "Food and Drug Administration: Improvements Needed In the Foreign Drug Inspection Program," GAO/HEHS-98-21, October 1997.

Sincerely,

for Diane E. Thompson
Associate Commissioner
for Legislative Affairs

Enclosure

COMMENTS OF THE FOOD AND DRUG ADMINISTRATION ON THE GENERAL ACCOUNTING OFFICE DRAFT REPORT ENTITLED, FOOD AND DRUG ADMINISTRATION: Improvements Needed In The Foreign Drug Inspection Program GAO/HEHS-98-21

GENERAL

We appreciate the opportunity to review the draft report and offer the Food and Drug Administration's (FDA or the Agency) comments. We recognize that both the General Accounting Office (GAO) and FDA have put a great deal of effort into this study, and we are happy to assist the GAO evaluators to ensure that the final report is accurate. In our review of the draft report, we found a number of areas where there are apparently misconceptions and some errors of fact that need to be corrected.

Over the last few years, as more drugs, particularly bulk drugs, are being imported from many different countries, FDA has made significant changes to the foreign inspection program by increasing the number of foreign drug inspections, increasing the length of time spent on the inspections, and by expanding the inspections to include more aspects of the Current Good Manufacturing Practices (CGMP) than was done before.

In addition, approximately two years ago, FDA's Deputy Commissioner for Operations established a working group to analyze the current foreign inspection and import programs, describe their current operations, and make recommendations for improving the programs within existing resources. The working group consisted of representatives of each of FDA's five Centers and the Office of the Commissioner. In May of 1997, the working group submitted a risk-based plan to the Deputy Commissioner that, if implemented, would provide a solid basis for making decisions about the approvability of new products as well as the admissibility of products presented at U. S. ports for entry. The plan also calls for focusing Agency resources on the high-risk product manufacturers to ensure that they either comply with CGMPs or are cease marketing products in the U. S. The plan was adopted by the Agency, and currently is being implemented to allow FDA to leverage its scarce resources to assure that the nation's drug supply is safe.

1993 DISCUSSION PAPER

The draft report reflects a misunderstanding of the 1993 "internal review" of the foreign drug inspection program. As we stated in the exit conference on November 5, the 1993 document is, in fact, an internal discussion paper entitled, "Recommendations to Strengthen Surveillance and Enforcement Operations Associated with the Importation of Human Drugs" which was written by a Regional Food and Drug Director. The recommendations were formulated on the basis of data from one Region only, and did not include Office of Regulatory Affairs (ORA) headquarters or CDER input. While the 1993 discussion paper was thoroughly reviewed, the issues investigated,

and the verified program weaknesses addressed, it should not be weighted equally with the Agency evaluations done in 1988 and 1997. This is especially important as the 1993 discussion paper served as the springboard for the current GAO evaluation; and the evaluators accepted the recommendations in the discussion paper without independently verifying their validity/feasibility. FDA's review of the 1993 discussion paper found it to be flawed in significant ways that limited its usefulness to the Agency. The evaluators were given a copy of FDA's memorandum to the Assistant Inspector General for Public Health Service Audits, OIG, in which many of the findings in the 1993 discussion paper were rebutted by FDA. Therefore, many of its recommendations have not been implemented, nor are there plans to do so. Those recommendations found to be valid and feasible were adopted.

CLASSIFICATION AND PROCESS

The draft report implies that there may be a significant difference between the processes followed by FDA's districts and headquarters for classifying domestic and foreign Establishment Inspection Reports (EIR). The draft report also frequently uses the terms "disagreed with" and "downgraded" to describe an apparent difference between domestic and foreign drug inspection processes (pages 25-31 and Footnote 8). In fact, the processes followed by both the Office of Regulatory Affairs (ORA) and the Center for Drug Evaluation and Research (CDER) are very similar. In both cases, an investigator recommends, on the basis of his/her knowledge about the manufacturer's operations as of the time of the inspection, an Official Action Indicated (OAI), Voluntary Action Indicated (VAI), or a No Action Indicated (NAI) classification of an inspection report. For a domestic OAI classification, the investigator recommends a classification and forwards the EIR package to the Investigations Branch Supervisor or Team Leader, who either agrees with the recommended classification or disagrees and adjusts the classification accordingly. Domestic EIRs and supporting documentation are then forwarded to the District Compliance Branch which may agree with the classification (endorse it), or disagree with the classification and change it to a different classification.

For most foreign inspections, an investigator prepares the EIR and recommended classification (OAI, VAI, NAI) just as for domestic inspections. The EIR may be reviewed by the Supervisor or Team Leader. This review is not considered to be a District endorsement of the inspector's recommendation. There is no further District involvement from this point. The EIR is forwarded to CDER, Office of Compliance, Foreign Inspection Team (FIT), for evaluation and classification. Final classifications by CDER are based upon the inspection report as well as FIT's knowledge of current policies, regulations, practices and the public health significance of any violations.

The EIR classification is the point at which the inspections and compliance are merged to evaluate and determine the compliance status of a firm. The compliance function supports the inspection functions and complements it with expertise regarding the Federal Food, Drug, and Cosmetic Act (FFDCA), FDA policies and procedures, the documentation supplied by the manufacturer in

response to the 483, their compliance history, and any further processing the imported drug may undergo, similar situations at other firms and how they were classified, how similar cases have been adjudicated, and the public health significance of the violations. This process is transparent and rapid in the districts. The purpose of the classification is to help the Agency determine what, if any, regulatory action should be initiated to correct a violation. While not all violative conditions require an immediate reinspection of the manufacturer, during the next inspection, whenever it may be, FDA always confirms that the corrections were made. This procedure helps direct the use of FDA's limited resources to those cases where it is important to assure correction of the most serious deficiencies by an immediate reinspection and where a routine inspection will suffice to protect the public.

In addition, the draft report indicates that CDER and the field investigators often disagree on the classification of inspection findings and the severity of the enforcement action. There is no evidence that inspectors disagree with final CDER classification once it has been made. The only thing established is that CDER did not accept the recommendation. The report does not attempt to assess the validity of CDER action, which is based on all the facts, or whether the inspector would agree if he/she had all the facts avaliable to CDER. In both foreign and domestic inspections, final classification represents the most well-thought-out decision based on the current inspection, past history of the establishment, and the significance of the drug. It is not valid or prudent to assume that the assignment of a final classification by CDER that is lower than the initial recommended classification will result in violative products entering the U.S.

Finally, the report states that, "FDA officials have acknowledged that because of resource limitations, they sometimes downgrade inspection classifications and approve new drug applications based on foreign manufacturers promises to implement corrective actions." As FDA explained during the exit conference, changing inspection classifications is not done to conserve resources. Rather, any change in classification by CDER is based solidly on the information contained in the EIR and other relevant other information that bears on the actions FDA would initiate to correct a violative condition.

GAO RECOMMENDATION

"To improve the effectiveness of FDA's foreign inspection program to ensure that only safe, pure and high quality drugs are imported into the United States, we recommend that the Commissioner of FDA:

-- ensure that serious manufacturing deficiencies are identified and enforcement actions are initiated, by requiring investigators and CDER to prepare inspection reports and issue warning letters within established time frames;"

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FDA COMMENT

FDA acknowledges that there are unique difficulties in completing foreign inspection reports on a timely basis. FDA has made changes in the length of scheduled foreign inspection trips, provided for report writing days during the foreign trip, and emphasized to district management that foreign travelers must be able to complete foreign inspection reports before being assigned other duties. Field Management Directive #86, Revised 7/31/96, identifies time frames for completion of foreign drug EIRs. Additionally, this topic was included in the most recent foreign inspection manual and the introduction to the foreign inspection training course held in May, 1997. Also, foreign inspection reports are now sent directly to CDER, Foreign Inspection Team, upon completion to eliminate a previous ORA step in the process.

FDA believes that the changes made and regular emphasis by FDA management is improving the timeliness of EIRs and decision-making. Table D shows the EIR submission data for FY-97 and Table E shows the processing times for Warning Letters issued. The results shown in both tables are based on CDER's review of 257 inspection reports as of November 7, 1997 of which 230 involved inspections of manufacturers.

TABLE D

Number of Work Days from Completion of FY-97 Foreign Inspections to Submission of Inspection Reports to CDER's Office of Compliance (Based on Initial EIR Classifications by Districts)

Submitted to CDER (in work days)	Official Action Indicated	Voluntary Action Indicated	Total Number of Inspection EIRs Reviewed Within Specified Time Frame	Percent
30 Days or Less	28	47	75	46.9
31 - 60 Days	17	44	61	38.1
61 - 90 Days	4	17	21	13.1
91 - 120 Days	0	2	2	1.3
121 Days or More	0	1	1	0.6
Total	49	111	160	100

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Table D shows that 47% of FY97 OAI/VAI EIRs were submitted to CDER in 30 days or less and 38% were submitted in 31-60 days. The average time for submission of OAI and VAI reports for FY-97 is 34 days and 41 days, respectively.

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TABLE E

Number of Work Days from Receipt of FY-97 Foreign Inspection EIRs to Issuance of Warning Letters

Time Frame (In Work Days)	Number of Warning Letters Issued	Percent
15 Days or less	3	30
16 - 30 days	4	40
31 - 45 days	2	20
46 - 60 days	1	10
61 - 75 days	0	0
76 - 90 days	0	0
91 - 105 days	0	0
106 or more days	0	0
Total	10	100

Table E shows that 30% of FY-97 Warning Letters were issued in 15 days or less after CDER received the EIRs, and another 60% were issued within 45 days. The average time for processing FY-97 Warning Letters is 24 days. For FY-96, CDER data showed that 26% of the Warning Letters issued in 15 days or less, and another 53% issued within 45 days after receipt of the EIR. The average time for processing FY-96 Warning Letters was 41 days.

To conclude, CDER analysis of FY-97 data shows a modest improvement in the submission times for OAI/VAI inspection reports, and a substantial improvement in the time expended by CDER in processing Warning Letters. The average processing time has been reduced from 41 days to 24 days; or a reduction of 42%.

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GAO RECOMMENDATION

-- "revise the risk-based inspection strategy to conduct more frequent inspections of all foreign manufacturers that have been identified as having serious manufacturing deficiencies; and"

FDA COMMENT

We do not concur. GAO may be basing this recommendation on the assumption that where inspection reports receiving a final classification of VAI after an initial recommendation of OAI, the OAI classification was, in fact, the correct assessment. In the absence of a re-review of final classifications, which GAO did not conduct, this would be an incorrect assumption. The Center-based compliance function is a separate, albeit complementary, function to the field-based inspection function. It cannot be assumed that a final classification which differs from the recommended classification is always wrong if it results in a less serious classification.

GAO RECOMMENDATION

-- "reevaluate plans for increasing the frequency of routine surveillance inspections of foreign pharmaceutical manufacturers to ensure that adequate resources are available to implement this strategy without diminishing FDA's ability to conduct pre-approval inspections."

FDA COMMENT

We do not concur. Rather than re-evaluating the plan at this time, FDA believes that it is more important to continue implementation of the plan and re-evaluate it in the future. FDA is committed to maximizing the use of routine surveillance inspections within existing resources. The FY97 results shown in Tables D and E, above, which are based on a review of 230 inspections of manufacturers show that 60 (26%) of the foreign drug inspections done during FY97 were classified as "post-approval" or surveillance inspections and 151 (65.7%) were classified as "pre-approval/CGMP" inspections. The strategy of including CGMP inspections as a part of pre-approval inspections is moving the program toward more uniform and balanced inspection coverage.

FDA also will analyze data from its newly installed OASIS program for processing import entries to determine which foreign drug manufacturers actually have products come into the U.S. Any foreign manufacturers that have not been inspected will be added to FDA's official inventory and scheduled for inspection based upon criteria in the new strategy.

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