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The Honorable John D. Dingell
Chairman, Committee on Energy and Commerce
House of Representatives

The Honorable Orrin G. Hatch
United States Senate

Because of changes over the last few years in the Food and Drug Administration's (FDA) monitoring of generic drug manufacturers,[1] you were concerned about possible inconsistencies in FDA oversight that could lead to inequitable treatment of manufacturers. Specifically, you requested that we examine whether policies and procedures exist to ensure that FDA is reasonable in selecting manufacturers to inspect, in assessing manufacturers' compliance with good manufacturing practices (GMP),[2] and in pursuing enforcement actions against manufacturers. In addition, you requested that we determine whether manufacturing firms know of FDA's standards for assessing compliance with GMPs.

To ensure that manufacturers produce safe and effective products, FDA personnel apply and enforce GMPs requiring interpretation of FDA's policies and procedures.

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[1]A generic drug is usually manufactured after an innovator or brand name drug's patent has expired and is generally a lower cost alternative to the brand name drug. Some manufacturers produce both types. FDA does not distinguish between manufacturers of generic drugs and innovator drugs in its inspection and enforcement actions.

[2]GMPs represent the minimum practices for methods, facilities, and controls to be used in manufacturing, processing, packing, or storing a drug. As an example, the "Production and Process Controls" GMP requires written procedures to assure that products have the identity, strength, quality, and purity that they are represented to possess, and that any deviation from the written procedures is recorded and justified.

Manufacturers should be able to expect fair treatment from FDA through consistent interpretations of its policies and procedures. Without such treatment, the possibility exists for manufacturers to be held to different standards or one manufacturer with facilities in more than one of FDA's districts to find the facilities' being held to varying standards for compliance.

In this correspondence, we present the results of our review. We reviewed FDA's policies and procedures for communicating its standards to FDA personnel and the manufacturing community. Specifically, we reviewed guidance for inspection, enforcement, quality assurance, and training. We also reviewed reports in each of these areas. We discussed the application of the guidance with FDA headquarters and district officials and officials of manufacturing firms and pharmaceutical trade organizations. We reviewed inspection findings from two districts and discussed them with FDA investigators and other officials. We also discussed the findings with officials of the manufacturers and trade organizations. We could not independently verify FDA's findings of noncompliance with GMPs because we did not participate in on-site inspections. (See enclosure I for additional information on our scope and methodology.)

In summary, we found that the general nature of the GMP guidance and FDA's decentralized management allow for the possibility of unfair treatment of manufacturers. FDA districts have a great deal of discretion in dealing with manufacturers and training their investigators. As a result, FDA lacks assurance that districts select and inspect manufacturers fairly and that districts forward recommendations for enforcement action to headquarters based on a common understanding of the types of violations that warrant a referral. To help ensure that investigators meet a basic level of training, experience, and competency, FDA is developing certification criteria for drug investigators.

Despite the possibility of inconsistent treatment of manufacturers, we did not find specific examples of inappropriate FDA inspection and enforcement actions. Manufacturers indicated that they are generally aware of the standards that FDA uses to determine GMP compliance. Although some of the manufacturers that we visited took exception to some of FDA's findings of noncompliance, they could not provide examples of negative impact on their firms.

BACKGROUND

FDA is responsible for ensuring the safety of the nation's foods, drugs, medical devices, radiological products, and cosmetics. The Federal Food, Drug and Cosmetic (FD&C) Act requires FDA to inspect each drug manufacturer at least every 2 years to ensure that the manufacturers are producing safe products.[3] FDA also inspects manufacturers for such reasons as (1) the manufacturer has submitted a drug application (preapproval inspection), (2) FDA is following up on prior GMP violations, or (3) FDA has received complaints about the manufacturer. During an inspection, FDA investigators examine facilities and processes, review records, collect product samples for testing, and hold discussions with officials and employees of the manufacturer. Upon an investigator's finding of noncompliance, district offices and headquarters may become involved in the enforcement process.

Six regional offices direct field enforcement programs and allocate resources to FDA's 21 district offices. FDA's approximately 1,000 investigators, each assigned to one of the district offices, provide inspection coverage to all FDA-regulated products, including drugs, foods, and medical devices, among others. FDA estimated that 30 percent of investigators' workload involved drug inspections in fiscal year 1993. The majority of investigators are trained as generalists, with certain ones later specializing in a specific product. Investigators specializing in inspecting drug manufacturers typically devote some part of their time to inspections of other regulated products.

FDA districts are responsible for planning, prioritizing, and conducting the inspections. FDA's guidance for conducting inspections is in the form of regulations, manuals, guidelines, and correspondence. FDA also has designed courses to train investigators in assessing manufacturers' compliance.

Inspections are typically unannounced to the manufacturer and can last from 1 day to several months depending, for example, on the size of the manufacturer and the complexity of the matters being investigated. Depending on its nature, an inspection may be done by one or several investigators or other FDA personnel, such as chemists. Among other things, investigators assess a firm's

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[3] 21 U.S.C. 360(h).

compliance with current GMPs. The FD&C Act[4] stipulates that the failure to comply with a GMP makes a drug product adulterated, and the product and the person responsible for the failure are subject to regulatory action. At the end of an inspection, FDA investigators provide a written report listing instances of GMP noncompliance to the manufacturer and to their district office.

When investigators find instances of noncompliance, district officials have several options. They may choose to accept a manufacturer's promise to correct the problem without taking additional enforcement action. Alternatively, district officials may issue a warning letter or, in more significant cases, forward a recommendation to FDA headquarters for other enforcement actions. These actions include seizing the manufacturer's products, prosecuting the manufacturer, or prohibiting, through an injunction, the manufacturer from continuing production. If FDA headquarters officials concur with a district's recommendation, the Department of Justice reviews the case, and if it concurs, files motions with the appropriate federal court to carry out the enforcement action.

Relatively few inspections result in a warning letter or other enforcement action. In fiscal year 1993, FDA conducted 3,846 inspections of drug manufacturers, including those producing generic drugs. During the year, FDA issued 501 warning letters and 59 seizures, prosecutions, or injunctions against manufacturers.[5]

DISTRICTS HAVE DISCRETION IN SELECTING MANUFACTURERS TO INSPECT

Districts have discretion in selecting firms and scheduling inspections based on the availability of district staff, findings of recent inspections at the same firm, complaints about a firm, and requests for inspections from headquarters. In our analysis of the Chicago and Newark District Offices' inspections, we saw no evidence that FDA selects drug manufacturers for inspections in an unreasonable manner. We collected data on 156 inspections performed on 22 Chicago and Newark manufacturers between October 1988 and July 1993. The inspections were for

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[4] 21 U.S.C. 351(a)(2)(B).

[5]Because of FDA's review process, some of the actions occurred as a result of inspections from prior years.

various purposes, such as preapproval inspections, responses to complaints, follow-up on violations found in prior inspections, and routine GMP inspections.

For these inspections, we analyzed the length of time FDA waited to reinspect each manufacturer and whether, during a prior inspection, the manufacturer had or had not been in compliance with GMPs. Because of the discretion that district offices have in selecting manufacturers to inspect, the potential exists for unwarranted choices. However, we did not see an inappropriate pattern in FDA's selection of manufacturers for inspection.

FDA'S GMP GUIDANCE IS GENERAL IN NATURE

FDA's guidance for GMP compliance inspections is general and consists of federal regulations, FDA manuals, and additional publications. The regulations for drug manufacturing (21 CFR 210 and 211) list 10 basic areas of GMPs. These regulations generally list objectives but do not specify how to achieve them. FDA manuals focus more on FDA investigation and enforcement procedures than on evaluating manufacturers' compliance with GMPs. FDA has published some additional guidance documents, and its Center for Drug Evaluation and Research (CDER) is working on others.

FDA and most drug manufacturer officials told us that there are benefits to having GMP guidance that is somewhat general. This allows for flexibility to incorporate technology changes to manufacturing processes and accommodate the wide variation in processes required for different products. Some FDA and manufacturing officials told us that more specific and updated guidance could help in reducing the amount of individual investigators' interpretation of GMPs. However, they also stated that explicit guidance would result in FDA's dictating procedures to firms, locking in current technology, and inhibiting innovation.

Because of the general nature of GMP guidance, investigators sometimes base their findings on their interpretation of the guidance while other findings require little or no interpretation. We reviewed the inspection reports for seven manufacturers relating to inspections occurring between 1991 and 1993. They contained 131 findings of noncompliance with GMPs. We determined the extent to which findings were based on an investigator's interpretation of FDA guidance. We classified findings

into two groups--those requiring the investigator to interpret existing FDA guidance and those requiring minimal, if any, interpretation. Examples of findings requiring minimal interpretation of the federal regulations are instances in which a manufacturer has not (1) followed the procedures contained in its approved drug application; (2) maintained written procedures and performed tests to ensure, among other things, stability and safety of the drug; and (3) adhered to standards of the U.S. Pharmacopeia.[6]

At the Newark District Office, the investigators had based 33 of 99 findings on their interpretation of guidance. At the Chicago District Office, 9 of 32 findings for one manufacturer involved interpretation of the guidance. The remaining findings in both districts required little or no interpretation of guidance, according to our analysis. We discussed the inspection findings with officials from five of the seven manufacturers. Some of the manufacturers told us they questioned some of FDA's findings of noncompliance or the seriousness of the findings. However, they generally agreed that FDA had a basis for the findings, and they could not provide examples of adverse impact on their firms from the inspections and related findings.

Officials of most of the nine manufacturers we visited indicated that they are generally aware of the standards that FDA uses to determine GMP compliance. Drug manufacturers have access to FDA regulations, guidance, and manuals. In addition, they can keep abreast of current GMPs through (1) industry publications, (2) FDA and industry conferences, and (3) publicly available inspection reports on other manufacturers. In discussions with trade associations about FDA's consistency and adverse impacts on firms, we became aware of only one problem, which dealt with an allegation of an inadequately trained investigator.[7]

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[6]The U.S. Pharmacopeial Convention, Inc. publishes drug standards in the U.S. Pharmacopeia (USP). The FD&C Act designates the USP as the official source of the standards for, among other things, strength, quality, and purity of those drug products listed in the USP (21 U.S.C. 351(b)).

[7]While inadequate training can lead to inconsistent actions, we could not obtain more details on this incident or its resolution because we received it from a trade association, which did not identify the firm.

DECENTRALIZED TRAINING DOES NOT ENSURE CONSISTENCY IN INSPECTIONS

One way to help ensure that investigators have a basic knowledge of inspection and enforcement policies and practices is through training. Districts are responsible for developing and providing most of the training that their investigators receive. Differences in training between districts could lead to differences among investigators in finding and reporting possible GMP violations. To help ensure the consistency of investigators' work, FDA is developing certification criteria for drug investigators.

FDA headquarters has set broad policies but has left most decisions about training to the districts. Newly hired investigators take an orientation training of up to 6 months, of which about half is in a classroom setting and, for the remainder, they accompany experienced investigators on inspections. Investigators specializing in drug inspections take two headquarters-managed courses on food and drug law and drug manufacturing and quality control. While several optional headquarters-managed courses exist, they are offered infrequently. Beyond initial training for new investigators, district offices have the responsibility to develop and present most of the advanced training courses for their investigators and to select which investigators enroll in them.

FDA headquarters does not track investigators' training or otherwise ensure that investigators receive training. FDA officials acknowledge that some districts are more active in developing drug inspection training for their investigators than others. Some FDA officials and manufacturers told us that the policy of district office discretion leads to differences in the level of training of investigators, both among district offices and within a single district. Such differences could lead to inconsistencies in inspection findings and subsequent enforcement actions.

FDA officials told us that they are developing certification criteria for investigators to ensure that investigators meet at least a basic level of training, experience, and competency. They said that FDA will first certify investigators to perform medical device inspections. FDA officials told us that they also plan to certify investigators to perform drug inspections and that they may be able to implement it by early 1996. FDA

expects that districts would have discretion in determining how investigators would meet the criteria.

FDA LACKS ASSURANCE THAT SIGNIFICANT VIOLATIONS ARE REFERRED TO HEADQUARTERS

FDA lacks assurance that districts forward recommendations for enforcement action to headquarters based on a common understanding of the types of violations that warrant a referral. Investigators must decide whether a situation that they observe at a manufacturer's facility warrants recording in their report. District managers review the reports and decide whether they warrant being sent to headquarters with a recommendation for enforcement action. Under the policy of decentralized oversight, FDA headquarters does not know if all cases that warrant a recommendation are, in fact, referred to headquarters. Once headquarters receives a recommendation, FDA officials told us that their review process contributes to consistency in legal enforcement.

In most instances, FDA's guidance addressing enforcement issues does not provide specific criteria, such as the type and severity of violations, for assessing whether a recommendation for an enforcement action should be made. Rather, the guidance is designed to assist field and headquarters staff in meeting the procedural requirements for processing cases with a recommendation for legal enforcement action. FDA officials said that they cannot write a detailed decision-making guide by which districts can measure whether a case warrants an enforcement action. They believe that such guidance would not cover the variety of situations observed nor substitute for the experience and professional judgment that their staff must apply to cases. Moreover, FDA officials said that through experience, training, the enforcement action review process, and other communication methods, compliance officers in both the field and headquarters currently know what circumstances warrant an enforcement action.

FDA officials told us that their enforcement action review process contributes to consistency in legal enforcement. Supervisory investigators in the districts determine whether the inspection findings constitute significant violations. If a supervisory investigator recommends an enforcement action, several FDA personnel review the recommendation. In the district office, reviewers include a compliance officer, the investigations branch and compliance branch directors, and the district director. If the district office recommends enforcement action beyond a

warning letter, various headquarters units also review the case, including CDER, the Office of Enforcement (except for injunctions), the Department of Health and Human Services' Office of General Counsel, and the Department of Justice.

FDA officials told us that one of headquarters' primary methods for communicating enforcement criteria to districts is through memos, copies of which go to the districts, explaining the reasons why headquarters is accepting or rejecting an enforcement action recommendation. We reviewed 42 of these memos written by two CDER branches between January 1993 and January 1994. Seventeen of FDA's 21 district offices received at least one memo. Each memo was case-specific and sent to the district that had submitted the recommendation, as well as to the headquarters unit that would further review an approved recommendation. Although a memo provides useful information to a district, the memos do not provide widely applicable and broadly disseminated enforcement information to the field.

The other methods of communications include meetings and phone conversations. FDA convenes a series of separate annual meetings for each of the following personnel: District Directors, Investigation Branch Directors, and Compliance Branch Directors. The meetings bring together the field officials in each position and certain headquarters officials to discuss FDA initiatives and problems. Enforcement criteria may be discussed. This may also occur at periodic meetings of the Field Drug Advisory Committee, involving selected Regional and District Directors and headquarters officials. The Mid-Atlantic regional director has a monthly phone conversation with the district and branch directors within the region about problems and new agency policy, including enforcement criteria. Districts also may call headquarters units, including CDER and the Office of Enforcement, directly to ask questions about criteria and receive advice during the writing of inspection reports or recommendations.

FDA headquarters officials told us that they have not formally assessed the effectiveness of the various forms of communicating enforcement criteria to the field, in keeping with FDA's policy of decentralized quality assurance. Existing quality assurance reviews are conducted at the district level by various field staff and focus on procedures, not on assuring consistency of enforcement recommendations. FDA headquarters does not routinely receive reports of these reviews. As a result, headquarters does not learn of any cited district problems

with applying the enforcement guidance or participate in resolving such problems.

DESPITE THE POTENTIAL FOR INCONSISTENCY, WE DID NOT FIND A NEGATIVE IMPACT ON MANUFACTURERS

While unfair treatment of manufacturers could occur, no specific cases were brought to our attention during our review. FDA's selection of manufacturers for inspection did not appear to be without basis. Some of the manufacturers that we visited took exception to some of FDA's findings of noncompliance. However, they could not provide examples of negative impact on their firms because of FDA's inspection practices. In general terms, trade associations described some problems regarding FDA's consistency and adverse impacts on firms; however, the associations did not provide us with attributable cases on which we could conduct follow-up analysis.

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We obtained comments from FDA on a draft of this correspondence. FDA generally agreed with our findings and provided technical comments, which we incorporated as appropriate.

We will send copies of this correspondence to the Commissioner of the Food and Drug Administration and make copies available to others upon request.

If you or your staff have any questions concerning this information, please call me at (202) 512-7119 or Bruce D. Layton, Assistant Director, at (202) 512-6837.

Mark V. Nadel

Mark V. Nadel
Associate Director
National and Public Health Issues

Enclosure

SCOPE AND METHODOLOGY

We reviewed the Food and Drug Administration's inspection and enforcement policies, procedures, and controls related to good manufacturing practices. Specifically, we reviewed FDA's guidance for inspection and enforcement actions and training materials and discussed the extent to which the guidance was available and commonly understood throughout the agency and the manufacturing community. We held such discussions with FDA headquarters officials in the Office of Regulatory Affairs (ORA) and Center for Drug Evaluation and Research, FDA officials in the Chicago and Newark District Offices, FDA's Mid-Atlantic and Mid-West regional directors, nine drug manufacturers, and officials of five pharmaceutical trade organizations.

At the two FDA district offices that we visited, we reviewed documents and interviewed officials, including district office directors, directors of the investigations and compliance branches, compliance officers, supervisory investigators and investigators. With these officials we discussed (1) the availability and clarity of the guidance the districts receive from FDA Headquarters, (2) the districts' procedures for selecting manufacturers they inspect, and (3) the review process after an investigator completes an inspection. We reviewed FDA inspection reports to determine the degree to which inspection findings are based on an investigator's interpretation of FDA guidance. We spoke with the Mid-Atlantic and Mid-West regional directors about regional office involvement in the process.

Our review of inspections was limited to examining FDA's written records and discussing the findings and supporting documentation with investigators who performed the inspections, other FDA officials, and representatives of the affected manufacturers. We did not independently verify FDA's findings of noncompliance with GMPs.

We discussed FDA's training program with officials from ORA and CDER, regional directors, and district officials, focusing on the availability of training in the drug area and the selection of investigators for training. We reviewed FDA's National Training Course Catalog and other training documents provided to us. With ORA officials, we also discussed oversight of the training program.

To review FDA oversight and quality assessment procedures, we interviewed CDER and ORA investigations and enforcement officials and the Mid-Atlantic and Mid-West Regional Directors about the procedures that FDA Headquarters follows for monitoring inspections performed by the districts and any ensuing enforcement actions. We requested all of the memoranda to the districts explaining CDER's decision to approve further headquarters processing or to reject an enforcement action recommendation between January 1993 and January 1994. FDA provided 42 memoranda to us, all of which we reviewed.

We also reviewed ORA documents on quality assurance, including reports of internal reviews of the Field Compliance and Investigations Programs, the quality assurance program of the Atlanta District Office and that district's quality assessment activities in fiscal year 1991 (the most recent year for which the Atlanta District has written a report), and reports of quality assessments conducted of the Atlanta District Office by officials from other districts in FDA's Southeast Region.

We interviewed officials of nine drug manufacturing firms and five trade organizations on how manufacturers know what criteria FDA investigators will use to evaluate them. We discussed the extent to which manufacturers agreed with specific inspection findings. We also discussed their views on FDA's inspection and enforcement process.

We conducted our review from February 1993 through April 1994 in accordance with generally accepted government auditing standards.

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