REPORT TO THE CONGRESS

Problems In Obtaining And Enforcing Compliance With Good Manufacturing Practices For Drugs

B-164031(2)

Food and Drug Administration
Department of Health, Education,
and Welfare

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

MARCH 29, 1973

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON D C 20548

B-164031(2)

To the President of the Senate and the
Speaker of the House of Representatives

This is our report on problems in obtaining and enforcing compliance with good manufacturing practices for drugs, Food and Drug Administration, Department of Health, Education, and Welfare

Our review was made pursuant to the Budget and Accounting Act, 1921 (31 U.S.C. 53), and the Accounting and Auditing Act of 1950 (31 U S.C. 67).

Copies of this report are being sent to the Director, Office of Management and Budget, and to the Secretary of Health, Education, and Welfare

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Comptroller General
of the United States

Contents

ABBREVIATIONS

FDA	Food and Drug Administration
FD&C Act	Food, Drug, and Cosmetic Act
GAO	General Accounting Office
GMPs	good manufacturing practices
HEW	Department of Health, Education, and Welfare
OEI	official establishment inventory

COMPTROLLER GENERAL'S REPORT TO THE CONGRESS

PROBLEMS IN OBTAINING AND ENFORCING COMPLIANCE WITH GOOD MANUFACTURING PRACTICES FOR DRUGS Food and Drug Administration Department of Health, Education, and Welfare B-164031(2)

D I G E S T

WHY THE REVIEW WAS MADE

Drugs sold in the United States during recent years have been produced by about 6,400 firms Although each is accountable for the quality of its products, the Congress placed upon the Food and Drug Administration (FDA) the responsibility that drugs, shipped across State borders, be of satisfactory quality when sold to consumers

The Federal Food, Drug, and Cosmetic Act (FD&C Act) makes FDA responsible for insuring that adulterated drugs are prevented from reaching the market This law

--defines an adulterated drug as one, among other things, which has not been produced in conformity with good manufacturing practices and

--requires FDA to inspect drug manufacturers and repackers (referred to hereinafter as drug producers) at least once every 2 years

Good manufacturing practices include (1) maintaining formula and batch-production control records and procedures, (2) establishing test procedures to insure that drug components or the finished product conform to appropriate standards of identity, strength, quality, and purity, and (3) keeping distribution records of each batch of a drug to facilitate its recall from distribution, if necessary.

In this review the General Accounting Office (GAO) has evaluated FDA's program for inspecting drug producers and enforcing compliance with good manufacturing practices. GAO reviewed the inspection records of 73 drug producers inspected during the 2-year period ended March 31, 1971, and the inspection records of 98 drug producers which were not inspected during this period

Except for five large drug producers, firms were randomly selected for review The drug producers were in three FDA districts in which nearly 25 percent of the Nation's 6,400 drug producers were located.

FINDINGS AND CONCLUSIONS

Overall findings

Several factors have hindered FDA's obtaining and insuring compliance with good manufacturing practices by drug producers.

--FDA has not always enforced aggressively compliance with good manufacturing practices by many

of the drug producers it has inspected, even though deviations from these practices can lead to adulterated products

--Proper and timely written notification of needed corrections was not provided to drug producers' top management, and followup inspections were usually untimely, hampering, in many instances, FDA's efforts to obtain voluntary compliance with good manufacturing practices

--Some drug producers have not been inspected as often as required, although FDA considers its inspections to be an integral part of its defense against adulterated products reaching the consumer

--FDA did not have a complete and accurate list of drug producers required to be registered and inspected

FDA has taken some steps to overcome these problems More are needed

According to FDA, two factors have contributed to existing conditions (1) its limited resources and (2) its need to be concerned with good manufacturing practices for drugs posing the most significant potential health hazard

Limited enforcement

FDA inspections have shown a large number of producers to be deviating from good manufacturing practices Although such deviations can lead to adulterated drugs, FDA has not enforced compliance with good manufacturing practices by many of the drug producers it has inspected

During fiscal year 1971, FDA made 7,124 inspections of drug producers Of these, nearly 4,000 were followup inspections where deviations from good manufacturing practices had been reported previously Over half of the followup inspections, 2,174, showed that producers still were not complying with good manufacturing practices.

In reviewing inspection records of 73 drug producers, GAO found that 48 percent of the producers critically deviated from good manufacturing practices on successive inspections FDA identifies critical deviations as those having the greatest probability of creating adulterated products (See p 12)

FDA has taken relatively few legal actions to enforce compliance During fiscal years 1970 and 1971, FDA approved only 51 seizures, 2 injunctions, and 5 prosecutions for deviations from good manufacturing practices.

GAO believes that producers chronically deviating from good manufacturing practices do not have sufficient incentive to correct their practices because FDA has not used available legal options

For example, FDA inspected one firm's manufacturing practices three times during the 32-month period ended December 15, 1971, concluding each time that the firm was not complying with good manufacturing practices such as formula and production control records not being maintained

The number of deviations increased from 6 in the first inspection, to 23 in the second, to 49 in the third inspection. Although 78 deviations were found, of which

39 were critical, legal action was not taken Instead, FDA relied primarily on oral and written communications with the firm and followup inspections to promote voluntary corrective actions

The shortcomings in FDA's enforcement are believed to stem primarily from a lack of instructions on when legal actions should be taken and the resultant confusion between district office personnel responsible for recommending legal action and FDA headquarters personnel responsible for approving it (See p. 19.)

A February 1972 policy change indicates FDA's intention to enforce good manufacturing practices more aggressively. GAO believes that the continuing lack of guidelines to the district offices will hamper the effectiveness of this change

Followup actions inadequate

Some drug producers have not corrected deviations from good manufacturing practices because FDA frequently did not take proper followup actions to insure that drug producers' top management was aware of inspection findings

GAO's examination of reports and other records relating to 150 inspections of 58 producers included in the sample showed that FDA issued a post inspection letter to top management in only 75 of 150 inspections made and that such letters were often untimely. (See p. 24)

FDA lacked guidelines for timely scheduling of followup inspections to determine whether producers take needed corrective action GAO reviewed 83 inspection cases involving deviations from good manufacturing practices for which followup inspections were scheduled to be made during a specific month prior to December 31, 1971 GAO found that only 25 were made when scheduled, 32 were made late, and 26 were not made by December 31, 1971 The timing of followup inspections is left to the discretion of each FDA district office (See p 26.)

The February 1972 policy change discontinued the use of post inspection letters as a means of notifying drug producers of inspection findings. Instead, warning letters will be used for minor deviations Action to seize products or cite firms for prosecution will be used for critical deviations. Subsequent to the completion of GAO's fieldwork FDA rescinded its policy statement of February 1972 and issued a new policy statement

However, the policy change does not provide guidelines to insure that drug producers' replies to warning letters or citations will be properly monitored and that timely followup inspections will be made when needed.

Warning letters--unlike post inspection letters and citations--do not specify a time limit in which a drug producer must notify FDA of corrective actions planned or taken

Inspection coverage

FDA lacks an effective means of insuring that all drug producers are inspected at least once every 2 years as required by law.

In the three FDA districts reviewed, at least 213 drug producers, or about 16 percent, had not been inspected during the 2-year period April 1969 through March 1971 Another 123 firms were listed as not inspected but records were not available to substantiate that the firms were in fact subject to inspection (See p 30.)

Records of 98 of the 213 firms not inspected showed that an average of 36 months had elapsed (as of March 31, 1971) since 74 of these firms were last inspected The remaining 24 firms had registered for the first time during the 2-year period and were not required to have been inspected by March 31, 1971 The 24 firms had been registered an average of 9 months--7 for over 12 months. (See pp. 31 and 32)

FDA had not established guidelines on how soon firms should be inspected after registration Since newly registered firms are permitted to produce and distribute drug products for consumer use, FDA should consider making an earlier initial inspection of such firms

The failure to inspect some producers when required can be attributed to weaknesses in the inspection scheduling process, the priority given to reinspecting other producers with a history of deviating from good management practices, diversion of manpower to crisis situations, and the lack of manpower

Although GAO found that noninspected firms generally were small producers of nonprescription drugs, the FD&C Act clearly requires that FDA inspect all drug producers regardless of size or product type (See p 32)

Inaccurate drug firm listings

FDA maintains two master firm listings for management and control purposes the drug firm registration listing and the official establishment inventory

The purpose of the registration listing is to identify all drug producers subject to the 2-year inspection requirement The official establishment inventory is FDA's official record of all firms producing products which fall into FDA's regulatory purview. The official establishment inventory is one tool headquarters uses to decide the annual allocation of each district's inspection manpower resources among various types of inspections.

GAO found that these two listings for calendar year 1971 were inaccurate and FDA had neither monitored nor enforced annual registration of drug producers as required by law In GAO's opinion, the usefulness of the listings has been significantly reduced as a basis for management decisionmaking and control (See p 37.)

RECOMMENDATIONS

The Secretary of Health, Education, and Welfare (HEW) should direct the Commissioner, FDA, to

--Establish more definitive guidelines to be followed by FDA headquarters and district offices, specifying (1) when products should be seized--especially those posing a questionable health

hazard, (2) the amount and type of documentation needed to adequately support the seizure action, and (3) when firms should be cited for prosecution

--Consider establishing a time limit for receipt of the written response requested in warning letters.

--Correct the inventory of drug producers subject to the 2-year inspection requirement so that FDA will have complete and accurate knowledge of the scope of its inspection responsibilities.

--Establish an inspection scheduling system monitored by FDA headquarters to insure that all drug producers are inspected at least every 2 years

--Establish guidelines to insure timely initial inspection of newly registered drug producers

--Properly enforce the annual drug producers' registration requirement and effectively monitor the accuracy and completeness of the registration listing to permit its use as a cross-check on the official establishment inventory listing

AGENCY ACTIONS AND UNRESOLVED ISSUES

HEW concurred in GAO's recommendations and advised that a number of corrective actions had been or would be taken. (See pp. 22, 29, 35, 36, and 41.)

MATTERS FOR CONSIDERATION BY THE CONGRESS

This report provides the Congress with information on FDA's drug firm inspection coverage and enforcement of good manufacturing practices

CHAPTER 1

INTRODUCTION

Protecting the consumer from unsafe and ineffective drugs is one of the primary responsibilities of the Food and Drug Administration (FDA). Drugs, one of mankind's most effective means of preventing and treating diseases and other ailments, are produced by about 6,400 drug producers in the United States Sales of drugs in 1970 amounted to about $12 5 billion. While each producer is responsible for the quality of its products, the Congress gave FDA the responsibility for insuring that only drugs of satisfactory quality are sold to the consumer

FDA derives its authority to regulate drugs from the Federal Food, Drug, and Cosmetic Act (FD&C Act), as amended (21 U.S C. 301). The FD&C Act defines drugs as articles intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in man and articles (other than food) intended to affect the structure or any function of the body of man (for example, articles intended for weight reduction). The FD&C Act prohibits the shipment of adulterated drugs in interstate commerce and defines an adulterated drug as, among other things, one which has not been produced in conformity with good manufacturing practices (GMPs).

FDA inspects drug producers to insure that drugs are produced in accordance with GMPs Because FDA's ability to protect the consumer depends to a large extent on effectiveness of its efforts to inspect drug producers and enforce compliance with GMPs, we examined FDA's inspection and enforcement program in three FDA districts in which nearly 25 percent of the 6,400 drug producers were located

To keep adulterated drugs from reaching the consumer, the FD&C Act authorizes FDA to inspect drug producers. Each domestic drug producer must register annually with FDA and be inspected at least biennially. FDA's inspections are to determine whether sound methods, facilities, and controls are used in all phases of drug manufacture and distribution, FDA inspections include equipment, finished and unfinished materials, containers, manufacturing records, and laboratory controls.

The 1962 drug amendments to the FD&C Act introduced the concept that drugs should be produced in accordance with GMPs. The drug industry and FDA jointly developed the GMPs after a careful review of the methods followed in producing drugs By following the jointly developed guidelines, it is presumed that the marketing of adulterated drugs will be minimized and that if marketed, they could be readily recalled.

The Secretary of Health, Education, and Welfare (HEW) issued regulations (21 CFR 133) for determining whether drugs have been manufactured, processed, packed, or held in accordance with GMPs Some examples of GMPs are

--Prepare and maintain for at least 2 years a separate batch-production control record for each batch of drugs produced. The record should include an accurate reproduction of the appropriate formula and a description of each step in the manufacturing, processing, packaging, labeling and controlling of the batch, including dates and specific identification of each batch of components used.

--Establish laboratory controls that include adequate specifications and test procedures to insure that components, drug preparations in the course of processing, and finished products conform to appropriate standards of identity, strength, quality, and purity.

--Maintain, for at least 2 years, complete records of the distribution of each batch of drug in a manner that will facilitate its recall if necessary.

The regulations also include GMPs covering such areas as buildings, equipment, personnel, components, production and control procedures, product containers, packaging and labeling, and complaint files. Appendix II contains more details on GMPs.

To prevent adulterated drugs from reaching the consumer, FDA can initiate one or more of the following legal actions through the Department of Justice.

--Prosecute an individual who violates provisions of of the FD&C Act.

--Enjoin a producer or individual from violating the FD&C Act and FDA regulations.

--Seize any drug product that is adulterated or misbranded when introduced into, or while in, interstate commerce.

Although recall is not provided for under the FD&C Act, FDA permits producers to voluntarily recall drugs that are alleged to violate the FD&C Act. During fiscal years 1970 and 1971, respectively, 889 and 1,421 voluntary recalls of drugs were instituted. FDA officials stated in an August 1968 inspection instruction that most recalls stem from deviations from GMPs. Appendix III contains comments on FDA's enforcement alternatives.

A Commissioner, under the direction of the Assistant Secretary for Health, HEW, administers FDA. The drug firm inspection program, under the overall administration of FDA headquarters in Rockville, Maryland, is carried out by 19 district offices located throughout the United States and in Puerto Rico. FDA's appropriation for fiscal year 1972 was about $110 million.

For fiscal year 1972 FDA devoted about $5 million, including 275 man-years, to the inspection of drug producers.

We directed our review primarily at FDA's inspection program for drug producers to insure that quality drugs are produced and that actions are taken to have producers correct deviations from current GMPs. We also tested the accuracy and reliability of data generated by FDA's management information system.

We reviewed inspection records for 171 drug producers, of which all except 5 were randomly selected.

We interviewed FDA officials and reviewed applicable legislative history and FDA's regulations, policies, and practices for inspecting drug producers and initiating corrective actions. We also reviewed FDA records and files for fiscal years 1969-71 pertaining to the inspection of firms and the sampling of drug products.

We made our review at FDA headquarters in Rockville, Maryland, and at FDA district offices in Atlanta, Georgia, Detroit, Michigan, and Philadelphia, Pennsylvania.

CHAPTER 2

LIMITED ENFORCEMENT OF COMPLIANCE WITH GOOD MANUFACTURING PRACTICES

Although deviations from GMPs can lead to adulterated drugs, FDA has not enforced compliance with GMPs by many of the drug producers it has inspected. Of the 7,124 inspections during fiscal year 1971, nearly 4,000 were followup inspections where deviations from GMPs had been previously encountered. Over half--2,174--of the followup inspections showed that producers were still not complying with the FD&C Act.

The FD&C Act provides FDA with legal sanctions to enforce drug producer compliance with GMPs:

--Authority under section 301 to prohibit the introduction or delivery for introduction into interstate commerce of any drug that is adulterated.

--Authority under section 302 to initiate injunction proceedings--civil court actions--to restrain violations of section 301.

--Authority under section 303 to impose penalties for conviction of any person who violates a provision of section 301.

--Authority under section 304 to seize any drug that is adulterated or misbranded when introduced into or while in interstate commerce.

FDA's guidelines for using this authority provide that prosecution, injunction, or seizure may be considered on the basis of inspectional evidence only, i.e., a product need not be sampled and analyzed to show that it is adulterated The guidelines also provide that.

--Support for seizure actions should include documentation of the deviations from GMPs that demonstrate inadequate assurance of identity, strength, quality, or purity of the drug.

--Injunction action may be considered when a producer has generally ignored the principles of GMPs in the past and sufficient evidence is available to establish that continued violations are likely to occur.

--Prosecution may also be considered when a producer has generally ignored the principles of GMPs. A record of faulty past performance may be necessary to warrant prosecution when inspectional evidence is not accompanied by sample analysis showing adulterated drugs.

To evaluate FDA's effort to enforce compliance with GMPs, we reviewed the inspection records of 73 drug producers. Sixty-eight of these were randomly selected from 857 drug producers that had been inspected during the 2-year period ended March 1971 in the 3 FDA districts included in our review. We also reviewed the inspection records of 5 major prescription drug producers that received a more intensified FDA inspection of GMPs as part of a special program According to FDA, this indepth inspection program of the major prescription drug manufacturers resulted in massive improvements in manufacturing practices but was discontinued because it consumed tremendous resources.

LIMITED USE OF LEGAL SANCTIONS TO ENFORCE GMP COMPLIANCE

FDA has not always aggressively used its legal sanctions to enforce compliance with GMPs. Our examination of the inspection records for the 73 drug producers showed that

--58 of the 73 producers had a total of 1,015 GMP deviations of which 382 according to FDA administrative guidelines were critical and

--35, including the 5 major prescription drug producers, or 60 percent, of the 58 firms had critical deviations from GMPs on successive inspections.

FDA identifies critical deviations from GMPs as those deviations having the greatest probability of creating adulterated products. The 382 critical deviations included

--Raw materials not assayed

--Incomplete or no master formula or batch production record.

--Incomplete or no production and control procedures

--No laboratory controls

--No distribution records.

In most instances FDA relied on communication with the producers and reinspection to encourage voluntary corrective action. Although these steps may have resulted in some improvements, FDA inspection reports revealed that in most instances the action taken had not achieved compliance with GMPs.

The following three examples illustrate FDA's enforcement of GMPs, as noted during our review

Firm A is a drug producer with estimated annual drug sales of $200,000. FDA made four inspections of this firm during the 50-month period ended December 1971. In each instance FDA concluded that the firm was not in compliance with GMPs. The inspection reports revealed, as summarized below, a total of 34 deviations of which 15 were critical according to FDA guidelines.

Date	Conditions found	FDA action
Nov 1967	Seven deviations from GMPs including the following four critical deviations --No assay of raw materials --No controls over labeling --No manufacturing records other than master formula --Lot numbers not assigned to batches Also, firm did not clean bottles or caps used in packaging and did not have equipment to clean them	Deviations discussed with representative of firm Reinspection was scheduled for March 1968
Mar 1968	Inspection revealed no changes in firm's operations, owner made no effort to comply with previous inspector's oral recommendations Eight deviations from GMPs were identified, including the following four critical deviations --No assay of raw materials --No working formulas --No manufacturing records --No label controls	No listing of inspectional observations was issued Post inspection letter issued 40 days after inspection Letter did not cite any violation of the FD&C Act No response was requested or received Reinspection was scheduled for October 1968, but was not made until September 1969
Sept 1969	No improvements in manufacturing practices Six deviations noted, two critical --No assay of raw materials or finished products --No manufacturing records Also, failure to adequately clean packaging and labeling equipment	A list of inspectional observations was issued Post inspection letter was issued 22 days after the inspection Response was requested but not received Reinspection was scheduled for March 1970 but not made until June 1971
June 1971	Firm was not registered as required by the act Thirteen violations of GMPs were identified, five critical --No master production and control records --No batch production and control records --No laboratory control --No stability testing of finished product --Lot distribution could not be readily determined	A list of inspectional observations was provided No post inspection letter was issued Reinspection was to be scheduled, but no further action was taken as of December 31, 1971

In 1969 the inspector noted that for the previous several years management had a less than acceptable attitude toward compliance. He stated, "Specifically, the producer refuses or is incapable of complying with good manufacturing practices." Although the management had continually promised to comply with GMPs, according to the June 1971 inspection report, there was no evidence that its intent was sincere. Because of the lack of FDA action, this producer has been permitted to manufacture and market drugs which are considered adulterated under the FD&C Act.

Firm B is a producer with estimated annual sales of $30 million consisting primarily of medicated or extra relief cough drops. FDA inspected the producer's manufacturing practices twice during the 2-year period ended March 1971, each time concluding that the firm was not complying with GMPs. In its previous inspection, October 1968, FDA found that the producer failed to manufacture cough drops in compliance with GMPs. FDA had observed that no tests were performed on components or finished drugs and batch production records were not maintained.

In an April 1970 inspection, FDA observed that the producer continued to manufacture without batch production records, testing of components and finished products, as well as other critical deviations from GMP requirements. FDA, relying on the producer to voluntarily correct the deviations, scheduled the firm for reinspection in 5 months

In September 1970 FDA reinspected the producer and again concluded that it was not in compliance with GMPs. The inspection showed that the producer initiated a components testing system that did not insure conformity to appropriate standards of identity and strength. Furthermore the producer continued to manufacture without subjecting finished drugs to testing (i.e., identity and strength of active ingredients). In addition, distribution records were not maintained to determine the disposition of drugs manufactured. FDA, relying on the producer to voluntarily correct deviations, scheduled the firm for reinspection in 10 months, July 1971.

In April 1971 FDA visited the producer to follow up on a consumer complaint of a bristle-like object in cough drops. In reviewing the producer's complaint file, FDA noted at least eight other complaints on cough drops. The firm refused further review of its complaint file and FDA terminated its review without taking any action.

As of December 1971, FDA had not reinspected the firm to determine whether corrective action had been taken.

Firm C is a drug producer with an estimated annual sales of $80,000, consisting primarily of dental drugs. FDA inspected the producer's manufacturing practices three times during the 32-month period ended December 15, 1971--each time concluding that the producer was not complying with GMP requirements such as formula and production control records not being maintained. The number of deviations increased from 6 in the first inspection, to 23 in the second, to 49 in the third--including critical deviations of 5, 9, and 25, respectively. Although a total of 78 deviations were found, of which 39 were critical, FDA did not recommend that legal action be taken to correct them, it relied on communication with the producer and followup inspections to promote voluntary corrective action.

Although the producer corrected some of the deviations, the last inspection showed the producer had continued to manufacture drugs under conditions that did not conform to GMPs. An FDA supervisory inspector in this district advised us that they usually wait at least two inspections before recommending legal action to allow the firm to correct its deviations.

Reasons for infrequent use of legal sanctions

The Director of the Office of Compliance, Bureau of Drugs, told us that in his opinion when FDA inspectors find major deviations from GMPs, in almost all cases they will find an adulterated product. The Deputy Director, Office of Compliance, said that in 1971 FDA had increased its effort to enforce compliance with GMPs.

The Deputy Director said that a producer manufacturing or marketing a prescription or nonprescription drug which constitutes a health hazard and which continually deviates from GMPs should be prosecuted and/or enjoined. He added that injunctions place a considerable burden on FDA's manpower since the producer's products must be continually monitored. He said that, because of this, few producers have been enjoined and FDA has been oriented toward approving only those cases which are health hazards.

FDA officials also described the following problems in effectively using legal sanctions to enforce compliance with GMPs

--The lack of adequate guidelines for the use of seizure actions by the districts.

--The therapeutic insignificance of GMP violations by producers of nonprescription drugs.

--The need for embargo authority.

--The extremely slow judicial process.

Lack of adequate guidelines

According to the Director of the Office of Compliance, Bureau of Drugs, FDA has had difficulty providing guidelines to the field offices for implementing GMPs according to the law. He said GMPs require the user's interpretation. He acknowledged, however, that current guidelines for implementing GMPs should be revised and stated that staff resources limited this action.

FDA has not provided the districts with guidelines to assist in developing a sound case. In addition, the Director of the Division of Case Guidance, Bureau of Drugs, said that some district personnel did not know what was needed for compiling a sound case for legal action against violations of GMPs He said that as a result district recommendations were frequently disapproved because the cases lacked documentation and completeness rather than significance.

Also, the Director of the Division of Case Guidance, who is responsible for approving the district recommendations, said that his staff did not have guidelines for making case decisions. Rather, they rely on their expertise and judgment developed over a period of many years of experience The benefit of this experience, however, has not been passed on to the district offices in the form of written guidance for their consideration when developing recommendations. The following case illustrates the resultant confusion.

FDA officials in one district, which initiated 18 of the 51 seizure actions approved in the 2-year period ended June 1971, stated that it had become increasingly difficult to obtain headquarters approval of seizure recommendations. The officials said five seizure recommendations were disapproved during the 2-year period and showed us seven similar examples from fiscal year 1972. One of these examples follows.

Firm D produces drugs with estimated annual sales of $2 million. In December 1971 the district office completed an inspection during which it observed 26 deviations from GMPs. Production of two separate quantities of a drug were considered adulterated based on inspectional evidence showing they were not manufactured in conformity with current GMPs. Accordingly the district recommended seizure of both quantities of production. Consistent with provisions of the law and implementing regulations, no laboratory analysis was considered necessary to support the recommendation.

In disapproving the seizure action, FDA headquarters stated that the identified deviations were not significant without FDA analysis of the product or other evidence of widespread defects. Officials in the Bureau of Drugs stated

> The Administrative Guideline concerning critical and significant GMP deviations must not be taken as hard and fast rules, but must be interpreted concerning relative significance in light of the firm's actual practices and operations

They explained that supporting a seizure action based solely on not following GMPs must be more stringent, i e , deviations must be of greater significance since the burden of proof of deficiency is on FDA.

FDA district officials took strong exception to the reasons for disapproval stating that deviations from GMPs when considered in a group support the recommended seizure. Specifically, the district was concerned with the Bureau's position interpreting it to mean that in similar future instances there would be a need for FDA laboratory analysis showing a violation to support a seizure action District officials pointed out that the FD&C Act and GMPs permit seizure actions on the basis of inspectional evidence only, notwithstanding the need for or outcome of an FDA assay of the finished product.

Because of the confusion created by headquarters' disapproval, of this and other seizure recommendations, the district officials requested clarification in February 1972 of current FDA policy and guidelines for initiating legal action when inspections show firms are not complying with GMPs. The district officials told us that a headquarters' reply received in May 1972 did not provide the district with guidelines for future action. FDA advised us in October 1972 that the guidelines for implementing GMPs were being studied for improvement.

Therapeutic insignificance of nonprescription drugs

Neither the FD&C Act nor FDA guidelines preclude legal action against firms that deviate from GMPs when producing nonprescription drugs. FDA headquarter officials stated, however, that actions recommended and taken depended primarily on the demonstration of therapeutic significance or potential health hazard. Since nonprescription drugs usually do not pose a significant threat to the public health, FDA officials said they are reluctant to pursue legal actions for violations of GMPs on such drugs.

Need for embargo authority

Bureau of Drug officials have expressed a need to have embargo authority--authority to temporarily detain drugs suspected or known to be violative while seizure action is processed and accomplished Lacking such authority at present, drugs identified for seizure are often shipped to distributors before seizure action is approved. The Associate Commissioner for Compliance stated that FDA is unable to effectively remove a drug from the market after it has been widely distributed since a seizure action would have to be taken through each United States District Court having jurisdiction over the product location. The need for FDA to seek embargo authority is discussed in a previous GAO report to the Congress [1]

Slow judicial process

Some FDA officials consider the effectiveness of injunctions and prosecutions limited because the judicial process is extremely slow, and in the meantime firms continue to produce and market adulterated drugs During fiscal years 1970 and 1971, FDA approved a total of 51 seizures, 2 injunctions, and 5 prosecutions because of deviations from GMPs. It is evident from the national statistics that, only in a few instances FDA used either an injunction or prosecution to enforce GMPs of the FD&C Act.

One of the few injunction orders processed by FDA took 16 months Thirteen of the 16 months elapsed while the proposed injunction was being processed through FDA headquarters. By contrast, it took 2 months for the district to prepare the recommendation and 1 month for the United States District Court to approve the injunction after it was filed

Recent steps toward more aggressive enforcement

In February 1972, FDA's Associate Commissioner for Compliance issued a policy statement which resulted in the following instruction being provided to district offices

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[1] "Lack Of Authority Limits Consumer Protection Problems In Identifying and Removing From The Market Products Which Violate The Law." (B-164031(2), Sept. 14, 1972)

--In those instances where critical deviations are noted, seizure or citation will be recommended to headquarters.

This policy change indicates FDA's intention to enforce compliance with GMPs more aggressively since, before this instruction, recommendations to headquarters for seizure or citation were not mandatory.

CONCLUSION

FDA has not always aggressively enforced drug producers' compliance with GMPs, as indicated by the large number of producers in our samples with continuing deviations on successive inspections. As a result, many firms have continued to produce and market adulterated drug products The non-aggressive enforcement appears to have stemmed primarily from a lack of guidance on when legal actions should be taken and what should be documented and the resultant confusion between FDA personnel responsible for recommending legal action and those responsible for approving such action. In our opinion, FDA has not provided sufficient incentive to producers chronically deviating from GMPs to correct their practices.

FDA's recent policy changes indicate a step toward more aggressive enforcement of GMPs. FDA district offices have been directed to submit to headquarters, recommendations of citation for prosecution or of seizure in all cases of critical deviations. However, we believe the effectiveness of this change will be hampered by the lack of guidance available to district offices, the confusion surrounding the criteria for legal action, and the needed documentation to support a case in court.

RECOMMENDATION TO THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE

We recommend that the Secretary, HEW, direct the Commissioner, FDA, to establish more definitive guidelines to be followed by headquarters and district office personnel, specifying (1) when products should be seized--especially those posing a questionable health hazard, (2) the amount and type of documentation needed to adequately support the seizure action, and (3) when firms should be cited for prosecution

HEW concurred in our recommendation and advised us that the Bureau of Drugs is studying administrative guidelines for GMPs as well as the current good manufacturing practice regulations with assistance from a drug quality control expert consultant with extensive industry experience. HEW stated that the guidelines will be rewritten to more clearly delineate and define actions to be taken. In addition, training programs for field and headquarters officials will be intensified and will continue to insure that everyone making regulatory decisions has written guidelines to the fullest extent possible or has the experience to make judgments where guidelines are not possible.

HEW stated that the use of the term "critical deviations" throughout the report in referring to inspections of drug firms was unfortunate and possibly misleading HEW explained that in the administrative guidelines for GMPs, there is a list of critical areas with instructions on when to recommend regulatory actions where critical deviations are found and that these guidelines stress the importance of judgment in determining whether a situation exists that requires regulatory action. HEW stated that wherever truly critical deviations from GMPs are found it always acts to correct the situation.

We agree that certain types of deviations from GMPs are more significant than others and that judgment must be exercised in determining when regulatory actions should be taken. It should be noted, however, that the report shows the total number of deviations noted during the inspections of 73 drug producers. To show the extent to which serious deviations occurred, the report also identifies the number of deviations which were critical--according to FDA guidelines. This was done because FDA identifies critical deviations from GMPs as those deviations having the greatest probability of creating adulterated products

CHAPTER 3

NEED FOR MORE CORRECTIVE FOLLOWUP ACTIONS

When FDA inspections disclose deviations from GMPs, FDA district officials take certain followup procedures designed to obtain voluntary corrective action. These procedures involve giving notice of deviations to the drug firms and making followup inspections. Our review showed that the procedures were often not followed or, if followed, were not pursued in a timely manner. We believe that improvements in following up on deviations are needed if FDA expects drug firms to adopt a serious attitude toward its inspection efforts.

In most instances, FDA inspections identify deviations from GMPs. Before February 1972, FDA had established the following procedures in accordance with the FD&C Act to be followed by the districts in attempting to obtain voluntary corrective action

--Upon completion of an inspection, discuss the findings with a representative of the firm and provide a list of inspectional observations noting the objectional conditions or practices which deviate from GMPs

--Subsequently, notify the firm's management of deviations--either by a warning letter for minor violations or a post inspection letter for major violations.

--Make followup inspections to determine if adequate corrective action has been taken.

In February 1972, FDA issued a policy statement rescinding the use of post inspection letters, except for inspectional findings relating to insanitary conditions associated with food firms.

To review FDA's followup actions, we examined the inspection reports on the 58 drug producers with deviations from GMPs These inspections were made primarily during the 2-year period ended March 31, 1971. The 58 producers were inspected a total of 268 times, however, deviations were concentrated in 156 of the inspections.

POST INSPECTION COMMUNICATION OF FINDINGS

In nearly all instances FDA inspectors discussed their findings with producers' representatives but did not provide adequate written notification. We examined reports and other records relating to the 150 inspections (6 of the inspections were made before the post inspection letter guideline) on the 58 producers with deviations and noted that FDA issued a list of inspectional observations and a post inspection letter, as the guideline suggests, in only 65 instances or in about 43 percent of the inspections. FDA did not follow this procedure in the remaining 85 instances--issuing no written communications in 46 instances and only 1 of the 2 types of written communication in 39 instances.

Over the years, drug firms have complained that post inspection letters are the only means of notifying their top management of what needs to be corrected. They have maintained that inspectors' oral and written communications to immediate plant personnel do not always reach top management. Accordingly, in January 1968 FDA established procedures for issuing post inspection letters to top management. However, FDA issued post inspection letters in only 75 of the 150 inspections.

In addition, our review of 15 post inspection letters issued by one district office showed they usually were not issued in a timely manner On the average, the district took 41 days to issue the letter after completing the inspection. The range was 13 to 89 days. For example.

--Six inspections were made over a 37-month period of a drug manufacturer with annual sales of $4 million. A total of 34 deviations from GMPs were found, of which seven were critical. FDA issued a post inspection letter to the producer after each of the first four inspections but as shown below took more than 1 month to do so in three instances.

Date inspected	Number of deviations	Date of letter	Calendar days
11-27-68	5	2-24-69	89
6-12-69	6	7-24-69	42
11-06-69	4	12-05-69	29
1-08-70	9	3-13-70	64
3-13-70	9	none issued	-
11-17-70	1	none issued	-

Action taken on the fourth inspection indicates what can happen when post inspection letters are not issued timely. Upon completing the inspection on January 8, 1970, the inspector discussed his findings with plant personnel and issued a list of inspectional observations, indicating that the deviations identified could lead to product contamination. Nevertheless, the producer continued to manufacture the product and release it for distribution. Later FDA analysis of the product showed it had been contaminated with particulate matter

On March 13, 64 days after completing the inspection, FDA issued a post inspection letter reemphasizing that any one of the deviations could lead to product contamination. The producer was also reinspected on the same day. The inspection report stated that the management was apathetic to the indicated deviations and would not agree to any corrective action. Two weeks later, after receiving the post inspection letter, the producer stated in a written reply to FDA that it discontinued manufacturing this product and was in the process of correcting the deviations, and that the product produced in 1969 and 1970 had been recalled.

Delays in informing top management of drug producers of deviations are not conducive to prompt correction and may result in prolonging the exposure of consumers to adulterated drug products. According to FDA, optimum consumer protection requires that FDA report to the producer, in a timely manner, all significant inspection findings, and schedule an inspection to insure compliance.

FOLLOWUP INSPECTIONS

FDA's followup inspections to insure that producers have corrected deviations from GMPs have generally been

untimely, especially for small drug producers, which comprise the vast majority of the 6,400 producers

We reviewed 83 inspection cases involving deviations from GMPs for which followup inspections were scheduled and were to be made during a specific month before December 31, 1971. Twenty-five reinspections were made on time, i.e., when scheduled, 32 were made late and 26 were not made as of December 31, 1971. For example

--An inspection of a drug manufacturer with annual sales of $115,000 was completed in December 1967. FDA found five deviations from GMPs and scheduled a followup inspection for April 1968, 4 months later However, the firm was not reinspected until May 1969--17 months later--and four deviations were noted. Three were among the deviations identified during the December inspection. A routine followup inspection was scheduled for May 1971 but had not been made as of December 1971.

Other than the requirement of the FD&C Act for biennial inspection, FDA has no definitive guidelines for scheduling followup inspections of producers that deviate from GMPs. Instead, followup inspection depends on each district office's interpretation of the significance of its findings, the availability of resources, and the likelihood of the producer's voluntary corrective action.

FDA routinely schedules followup inspections at varying time intervals in those instances where inspectors note deviations. As the table shows, the scheduled time interval in one district varied from 1 to 24 months for 48 followup inspections scheduled to be made before December 31, 1971.

Scheduled time interval	Number of reinspections scheduled
Within 1 month	1
2- 3 months	1
4- 6 months	13
7- 9 months	6
10-12 months	7
13-15 months	3
16-18 months	2
19-21 months	8
22-24 months	7
	48

Of the 48 followup inspections scheduled, only 28 had been made as of December 31, 1971, and the average time before reinspection was 14 months. Fourteen reinspections were made within 12 months, 9 more within 24 months, and 5 more within 36 months. The remaining 20 had not been made at the end of 1971, although an average of 22 months had elapsed since the initial inspection.

FDA district officials stated that, although they attempt to make followup inspections of producers with significant deviations from GMPs, higher priority work many times precludes or delays the inspections. They said that there were no definitive guidelines for determining what work should be done first; priority was usually given to headquarters-directed programs and problem firms that produce drugs with significant health implications. Consequently, some producers are not given the attention that may be warranted because the annual volume or health implications of their drugs is insignificant compared with other producers.

Post inspection letters to drug producers eliminated by policy statement

In February 1972 FDA's Associate Commissioner for Compliance issued a policy statement which provided the following instructions to district offices

--Use of warning letters will be continued in cases of minor violations (no impact on health or safety). The

letters will be issued after approval by headquarters and will request a response by the producer

--Use of post inspection letters will be continued only as the findings relate to insanitary conditions which could lead to violations of the FD&C Act. (Insanitary conditions are associated primarily with the food industry.) The firm will be requested to reply within 10 days.

We discussed these changes with the Deputy Associate Commissioner for Compliance He said the primary means of communication with drug producers regarding inspection findings would be the inspector's oral discussion with plant personnel and the list of inspectional observations. FDA district officials explained that, as a result of these changes, districts' top management are no longer authorized to notify producers' top management of significant adverse findings. Instead, they will recommend seizure or citation for prosecution to FDA headquarters.

In August 1972, subsequent to the completion of our fieldwork, FDA rescinded its policy statement of February 1972 and issued a new policy statement which (1) requires that post inspection letters be issued within 10 days of the completion of an inspection to all drug producers where critical deviations from GMP regulations are encountered and (2) allows the judicious use of regulatory letters in those cases where seizure actions are not practicable and injunctions or prosecutions are not warranted. The new policy statement also requires a response from the drug producers within 10 days, and prompt followup action by the District offices to insure that producers take corrective action. To maintain control, the Associate Commissioner for Compliance will receive copies of all regulatory letters issued and industry responses received.

However, the policy change does not provide instructions to insure that warning letters--unlike post inspection letters and regulatory letters--specify a time limit in which a drug producer must notify FDA of corrective actions planned or taken.

CONCLUSION

FDA's efforts to obtain drug producers' voluntary compliance with GMPs in many instances were not effective because proper and timely written notification of needed corrections was not provided to producers' top management. Followup inspections were usually untimely, if made at all, and were often ineffective when firms were found to have taken no action.

Proper implementation of the August 1972 policy statement regarding post inspection and regulatory letters should assist FDA in insuring that (1) district offices properly monitor drug producers' replies and (2) producers take needed corrective actions. However, we believe that FDA should also consider establishing a time limit for receipt of written responses requested in warning letters.

RECOMMENDATION TO THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE

We recommend that the Secretary, HEW, direct the Commissioner, FDA, to consider establishing a time limit for receipt of the written response requested in warning letters.

HEW concurred in our recommendation and advised us that instructions were issued in August 1972 to require a response to all warning letters to firms within 10 days.

Our review of the August 1972 instructions showed, however, that the 10-day response was required only for post inspection and regulatory letters, and was not required for warning letters. We believe FDA should clarify its instructions to also establish a specific time limit for receipt of the written responses requested in warning letters.

CHAPTER 4

SOME DRUG PRODUCERS NOT INSPECTED AS OFTEN AS REQUIRED

The FD&C Act requires all drug producers to (1) register annually with FDA and (2) be inspected by FDA at least once in the 2-year period beginning with the date of registration and at least once every 2 years thereafter FDA inspections are made to determine if GMPs are being followed in actual practice. FDA considers its inspections to be an integral part of its defense against adulterated drugs reaching the consumer

However, FDA has not inspected some producers as often as required At least 213--perhaps as many as 336[1]--of the 1,300 drug producers in the three districts included in our review had not been inspected during the 2-year period April 1969 through March 1971 FDA officials acknowledged during May 1971 hearings before the Subcommittee on Intergovernmental Relations, House Committee on Government Operations, that about 26 percent of the registered pharmaceutical manufacturers were not inspected during the 32-month period July 31, 1968, through March 31, 1971

Failure to inspect some producers as often as required can be attributed to weaknesses in the inspection scheduling process, the priority given to reinspecting other producers that had a history of deviating from GMPs, diversion of manpower to crisis situations and headquarters-directed work, and the lack of available manpower

FIRMS SUBJECT TO INSPECTION

FDA maintains a narrative inspection history, in the form of a computer printout, on all producers subject to inspection. For the three districts included in our review, the printout showed that 609 of the 1,539 firms classified as drug producers were not inspected during the 2-year period ended March 31, 1971.

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[1]See discussion on p 31

Because of numerous errors in printout information, we found, with FDA's assistance, that only 213 of the 609 firms were properly classified and had not been inspected. Although another 123 of the 609 firms were shown as not inspected, district officials did not have records to verify that these firms were subject to the 2-year inspection requirement. FDA district office boundaries were realined in 1971 and records on the 123 firms could not be located. We also found that 34 of the firms shown as not inspected on the printout had been inspected during the 2-year period The remaining 239 firms not inspected were either (1) out of business, (2) not currently producing drugs (inactive), or (3) misclassified as to establishment type; i.e., classified as a drug producer when the firm was either a distributor, a warehouse (storage facility), a dealer (i.e., drug store), or a shipper (jobber), and not required to be inspected biennially.

We randomly selected and reviewed inspection records on 98 of the 213 producers not inspected during the 2-year period ended March 31, 1971, to determine the firms' size, kind of products produced, and past inspection history.

As of March 31, 1971, an average of 36 months had elapsed since 74 of the producers were last inspected. As the following table shows, some had not been inspected for as long as 5 years.

Elapsed time between date of last inspection and March 31, 1971	Number of firms
25-30 months	30
31-36 months	11
37-42 months	15
43-48 months	8
49-60 months	7
Over 5 years	3
Total	74

The remaining 24 of the 98 producers in our random selection had registered for the first time during the 2-year period and were not required to be inspected by March 31, 1971. The 24 producers had been registered an average of 9 months--seven for over 12 months. FDA has no established

guidelines on how soon newly registered producers should be inspected after registration. Since these producers are permitted to produce and distribute drugs for consumer use, we believe FDA should consider making an earlier initial inspection of such producers

TYPES OF FIRMS NOT INSPECTED AND PRIOR DEVIATIONS

Generally, the drugs produced by most of the 74 producers could be purchased by consumers without a prescription. Many of the producers manufactured or repacked drugs such as vitamins, liniments, salves, bulk drugs, medicinal gases, and reducing tablets Thirty-nine were small drug producers with annual sales of less than $10,000 Five had annual sales of over $1 million.

Many of the findings during prior inspections related to labeling and misbranding However, deviations from GMPs included

--failure to prepare control records for each quantity of drugs produced,

--failure to establish production and control procedures to insure the quality of the drug produced,

--failure to code finished products to determine, if necessary, the history of the manufacture and control of the drug, and

--inadequate laboratory controls to insure that components and finished products conform to appropriate standards of identity, strength, quality and purity

A brief inspection history follows on one of the 74 producers.

Firm E primarily manufactures high-purity laboratory chemicals and solvents. On special order it produces a drug for peptic ulcers which FDA estimated annual sales of $45,000. FDA inspected the producer in March 1969 and found that the producer was using adequate control procedures. However, the drug for peptic ulcers was not being manufactured at the time of inspection FDA scheduled the producer

for another inspection in June 1970. FDA did not perform this inspection or the rescheduled inspection for March 1971.

Because the drug produced by the firm was to be used by the military services, the Defense Supply Agency inspected the producer in June 1971, and identified nine findings which were deviations from GMPs including:

--Inadequate control of raw materials, as written specifications are not established for all raw materials, raw materials are not tested, and approved raw materials are not isolated and distinctly labeled for ready identification as fit for use.

--Possibility of contamination from other products exists in the manufacturing operations.

--All equipment is not routinely inspected and cleaned before each use and promptly cleaned thereafter.

--Positive identification of material is not maintained during processing operation.

--Plant was not clean and orderly. Windows and doors in plant were not screened to prevent entrance of insects and other pests.

The Defense Supply Agency communicated its inspection results to FDA by letter in July 1971. As of April 1972 FDA had not reinspected the producer. The deterioration in the producer's control procedures during the period FDA did not inspect it illustrates the importance of inspecting all producers biennially.

REASONS GIVEN FOR NOT INSPECTING ALL DRUG PRODUCERS

We noted a lack of controls to insure that producers are rescheduled and inspected biennially. FDA Bureau of Drugs officials told us that no one at headquarters had been assigned responsibility for insuring that all drug producers were inspected every 2 years, although the Bureau has responsibility for this activity. Several officials said that headquarters did not maintain records on statistics identifying drug producers inspected for GMPs. Also, the districts

did not maintain records showing the firms inspected for GMPs.

FDA headquarters officials told us that district directors had been assigned the responsibility for insuring that all drug producers were inspected biennially as required The Deputy Executive Director for Regional Operations told us that guidelines on the frequency of inspections had not been given to district personnel He did not believe such guidelines were necessary since the FD&C Act required biennial inspections.

We were told that some producers were not inspected because they were either overlooked during the scheduling process or judgmentally deleted when available manpower was needed on higher priority work. For example, we found that 17 of 30 producers not inspected were scheduled for inspection one or more times during fiscal years 1970 and 1971. These 17 producers were scheduled for inspection a total of 25 times, with one producer being scheduled for inspection a total of 6 times The remaining 13 firms were not scheduled for inspection.

At the completion of each inspection, the producer is normally scheduled for another inspection within 2 years. Reinspection dates are fed to the district data processing unit, which prints out a bimonthly schedule of producers to be inspected during the period. However, FDA district office personnel must often delete and reschedule producers at a future date because of such higher priority assignments as special inspection or sampling programs imposed by headquarters and emergency product recalls. A recent emergency recall involved a toxic bacteria in a food product In this instance, all scheduled drug inspections were delayed at least a month.

During our review, a new procedure was initiated in one FDA district to insure biennial inspection of all drug producers. Under this procedure a producer is scheduled for reinspection within 18 months of the last inspection This procedure provides a 6-month leadtime to reinspect within the required 2-year period.

CONCLUSIONS

FDA lacks an effective means to insure biennial inspection of all drug producers. Although we found that noninspected firms generally were small producers of nonprescription drugs, the FD&C Act clearly requires that FDA inspect all drug producers regardless of size or product type.

We believe that FDA should develop an effective means for insuring biennial inspection of all drug producers and headquarters should monitor the district offices more closely to insure that the 2-year requirement is met. FDA may want to consider the procedure discussed on page 34 for wider implementation. An up-to-date listing of producers not inspected would aid in providing needed control.

Also, FDA should make a more timely initial inspection of newly registered producers since these producers are permitted to market drugs.

RECOMMENDATIONS TO THE SECRETARY, HEALTH, EDUCATION, AND WELFARE

We recommend that the Secretary, HEW, direct the Commissioner, FDA, to

--Establish an inspection scheduling system monitored by FDA headquarters to insure that all drug producers are inspected biennially.

--Establish guidelines to insure timely initial inspection of newly registered drug producers.

HEW concurred in our recommendations and advised us that FDA will develop a system (to be monitored at the headquarters level) for scheduling biennial inspections of all drug producers. HEW stated that full implementation of the system, however, will depend on an increase in inspection resources presently available to FDA and on other competing priorities for the manpower to perform such inspections

HEW pointed out that most of the firms not inspected biennially were manufacturing nonprescription drugs which

usually do not pose a significant threat to the public health. HEW conceded that these firms should have been inspected in a more timely manner, but advised us that FDA's limited manpower precluded reaching this goal. HEW stated that the decision was made to use this manpower in inspecting those plants and those operations that do or could pose a significant health hazard to the consumer.

HEW advised us that instructions will be issued to the field to inspect newly registered drug producers as promptly as possible. The instructions will cover not only newly registered firms but new firms which have failed to register and which come to FDA's attention through other means. These firms will be required to register.

HEW also stated that it was unfortunate that the scope of our audit was not such that a number of approaches taken by FDA to protect the consumer were not commented on in the report. HEW cited FDA's new Quality Assurance Program which calls for large numbers of samples to be analyzed before inspection to detect specific flaws. HEW stated that under this approach, inspectors can focus on the conditions in a firm that led to these flaws.

The Quality Assurance Program was implemented subsequent to our review and is an attempt by FDA to make its drug inspections more efficient by obtaining preinspection information through product analysis. This program, if properly implemented and carried out, should assist FDA in improving the effectiveness of its inspection activities.

CHAPTER 5

NEED FOR IMPROVEMENT IN FDA'S REGISTRATION LISTING AND OFFICIAL ESTABLISHMENT INVENTORY

Our review showed that two master listings--the registration listing and the official establishment inventory (OEI)--maintained by FDA for management and control purposes, were inaccurate and incomplete, and that FDA had neither monitored nor enforced annual registration of drug producers. The purpose of the registration listing is to identify all drug producers subject to biennial inspection. The OEI is FDA's official record of all firms that fall into FDA's regulatory purview. The OEI is one tool headquarters uses in deciding on the annual allocation of inspection manpower resources within each district We were told that data in the OEI is assumed to be correct.

In our opinion, the usefulness of the listings has been significantly reduced as a basis for management decisionmaking and control. Both listings for calendar year 1971 contained inaccurate and incomplete information The registration listing included firms that were not subject to registration and inspection. The OEI listed some firms, which were not included on the registration listing, as drug producers subject to registration and inspection. Conversely, drug producers shown on the registration listing were not included on the OEI. Also, some firms on the OEI list had gone out of business. In addition, we found little use made of the registration listing as a means of control.

REGISTRATION LISTING

Annual registration is to identify firms that produce drugs and are subject to FDA biennial inspections. Each November, FDA mails registration forms to all producers that registered during the prior year. Other drug establishments, including new drug producers, may request registration forms. Completed forms are returned to FDA headquarters for review and distribution, with copies going to the responsible district offices.

If a firm has not registered previously, the district office prepares a master card on the firm, recording the information submitted in the registration form and sometimes classifying the firm as to the type of establishment, e.g., drug producer, distributor, or warehouser. If the firm has previously registered, the master card is updated. The updated master card forms the basis for OEI changes. Firms are recorded on the registration listing when the district office returns the registration form to FDA headquarters.

We identified 161 firms shown as drug producers on the registration listing for the three districts included in our review that were not on the OEI. Our review of district records for 65 of the firms showed that 15 were not drug producers and therefore not required to register or be inspected. FDA headquarters officials told us that registration forms were issued on request without determining that the firms were subject to registration and inspection.

Our review showed that the districts prepare master cards without screening the firms. We were told by a district supervisor that only limited information is requested of the drug firm on the registration form. The supervisor said that this lack of information sometimes makes it necessary to guess at what the firm's classification should be, e.g., a drug producer and subject to the biennial inspection or a distributor or warehouser not subject to the inspection Rather than guessing, we believe the information should be verified and, if needed, enlarged upon via a telephone call or visit before the firm is classified in FDA's information systems. We were told visits or telephone calls for such purpose were made infrequently.

We were told that, if an inspection later shows that the firm was improperly classified, the inspector would have to prepare a change slip to correct the master card and the OEI. Since the registration listing is a separately maintained system, the change would also have to be furnished to FDA headquarters. Such changes were not always made

We reviewed the inspection records at one FDA district office for 31 of the 124 firms that distribute drugs in the district. Twelve of 13 firms that were registered were misclassified and did not have to register. FDA did not correct the misclassification until we brought its to their attention.

It appears that little emphasis has been placed on the importance of insuring the accuracy of the registration listing and little use has been made of it. The Director, Division of Case Guidance, stated that the annual registration requirement is not strictly enforced by FDA because once the firm registers, it is maintained on the OEI listing. Further, we were told by FDA headquarters officials that they rely on district office personnel to monitor the listing. However, guidelines have not been provided to the district offices instructing them how to perform the monitoring.

OFFICIAL ESTABLISHMENT INVENTORY

FDA officials told us that the OEI is a useful, essential management tool, and that it is used in resource allocation and inspection planning. A district official said, however, that the OEI contains firms erroneously classified as drug producers, and thus portrays a false image of firms requiring biennial inspections.

A total of 1,396 firms were classified as drug producers on the 1971 OEI listing for the 3 districts included in our review.[1] However, 368 of these firms did not appear on FDA's registration listing. District records of 204 of the 368 firms showed 67 had not registered, 25 had registered but were not on the list, and 105 were misclassified on the OEI and not required to be registered or inspected biennially. Information was inadequate to determine the classification of 6 of the remaining 7 firms and 1 firm was listed twice.

A data processing supervisor in one FDA district attributed the inaccurate and incomplete information to

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[1]The difference between the total number of firms identified by the OEI and the narrative inspection history as discussed previously on p.30 had not been reconciled by FDS at the time of our review. FDA has contracted with a private credit organization to obtain data on establishments whose products may be subject to FDA regulatory authority. The contract required the data to be reconciled with current FDA inventory records.

--misclassification of firms by inspection personnel,

--failure of inspectors to submit data needed to change the OEI when reclassification or other changes are made to the firm's central records, and

--clerical errors in processing and maintaining data.

We also noted that FDA instructions for classifying firms on the OEI requires that firms be classified in a manner which will best indicate the overall type of establishment. Thus, firms have been classified, for example, as a food establishment even though they may also manufacture or repack drugs. Of the 65 firms whose district file records were reviewed, 30 were properly listed as drug producers on the registration listing but were classified on the OEI as other types of producers, such as foods, cosmetics, etc.

The OEI is one source of information used by headquarters in preparing district offices' annual work plans. The work plans include an allocation of each district's manpower resources to the basic problem areas, i.e., foods, drugs, cosmetics, etc., based on the number of firms in the district and priorities which the FDA Commissioner establishes. Actual selection of drug producers to be inspected is left to the district offices. We believe the usefulness of the OEI in making such resource allocations is reduced by listing drug producers as other types of producers and by the various other misclassification errors we found

CONCLUSIONS

The usefulness of the registration listing and the OEI as tools for management decisionmaking and control has been reduced because the lists have not been complete or accurate. Firms incorrectly listed on the OEI as drug producers inflate the number of firms subject to biennial inspection. Conversely, firms which produce or repackage drugs but whose primary business is other than drugs, may not be subject to biennial inspection.

FDA has not adequately monitored or enforced the annual registration of drug producers required by the FD&C Act. As a result some firms have registered unnecessarily and some have not registered although required to do so.

Because of the lack of emphasis placed on registration, it appears that little effort has been made to insure the listing is corrected when inspections disclose that firms were originally misclassified and need not register. We believe that enforcement and adequate monitoring of the registration would enable FDA to cross-check OEI accuracy and completeness.

We believe FDA needs complete and accurate drug firm inventory and registration listings

--to identify drug producers subject to biennial inspection and

--to insure proper resource allocation to each district's inspection workload.

RECOMMENDATIONS TO THE SECRETARY OF HEALTH, EDUCATION, AND WELFARE

We recommend that the Secretary, HEW, direct the Commissioner, FDA, to

--properly enforce the annual drug producers registration requirement and effectively monitor the accuracy and completeness of the registration listing to permit its use as a cross-check on the OEI listing and

--correct the inventory of drug producers subject to biennial inspection so that FDA will have complete and accurate knowledge of the scope of its inspection responsibilities.

HEW concurred in our recommendations and advised us that FDA headquarters' staff will quarterly match the OEI file with the drug registration file and provide the district offices with a list of "non-matches." The two sources of information, according to HEW, will be used to increase the accuracy of both files. HEW advised us that additional inventory data will automatically update the list of drug manufacturers.

According to HEW, FDA has contracted with a major private concern to compare the establishment inventory with the inventory of firms dealing in commodities subject to the FD&C Act. FDA will resolve discrepancies between these two lists

by June 1973. Other sources of commercial information will also be used by the district offices to correct the inventory. Updates will be received from the contractor at regular intervals and will become part of prescribed OEI updatings.

DEPARTMENT OF HEALTH EDUCATION AND WELFARE
OFFICE OF THE SECRETARY
WASHINGTON D C 20201

JAN 8 1973

Mr. Morton A Myers
Assistant Director
Manpower and Welfare Division
General Accounting Office
Washington, D.C 20548

Dear Mr. Myers·

The Secretary asked that I reply to your letter of September 28, in which you asked for our comments on a draft of a GAO report to the Congress entitled, "Problems in Obtaining and Enforcing Compliance with Good Manufacturing Practices for Drugs."

Enclosed are our comments which set forth the actions taken or planned on the matters discussed in the report.

Sincerely yours,

James B Cardwell
Assistant Secretary, Comptroller

Enclosure

Comments of the Department of Health, Education, and Welfare on the GAO Draft Report entitled, "Problems in Obtaining and Enforcing Compliance With Good Manufacturing Practices for Drugs"

General

We concur in the recommendations offered by GAO. FDA with its limited resources has, and will continue to seek ways to best protect the consumer. Manufacturers and processors, however, must strictly comply with the provisions of the Food, Drug and Cosmetics Act if the consumer is to be assured of quality, safety and wholesomeness in their products.

With respect to this report, GAO faults FDA for the limited number of inspections made of firms manufacturing non-prescription drugs. Elsewhere in the report, however, it is brought out that such drugs usually do not pose a significant threat to the public health. We concede that these firms should have been inspected in a more timely manner -- but want to point out that FDA's limited manpower precluded our reaching this goal. Instead, decision was made to use this manpower in inspecting those plants and those operations that do or could pose a significant health hazard to the consumer.

We believe it is unfortunate the scope of the audit was not such that a number of approaches taken by FDA to protect the consumer were not commented on in this report. For example, the agency's new Quality Assurance Program which calls for large numbers of samples to be analyzed prior to inspection to detect specific flaws. Under this approach, inspectors can focus on the conditions in a firm that led to these flaws.

Finally, we believe that the use of the term "critical deviations" throughout the report in referring to inspections of drug firms is unfortunate and possibly misleading In the Administrative Guidelines for Good Manufacturing Practices (GMPs), there is a list of "Critical Areas" with instructions on when to recommend regulatory actions where critical deviations are found These guidelines stress the importance of judgement in determining whether a situation exists that requires regulatory action. Wherever truly critical deviations from GMPs are found we always act to correct the situation.

GAO Recommendation

--Establish more definitive guidelines to be followed by FDA headquarters and district office personnel, specifying (i) when products should be seized -- especiallly those posing a questionable health hazard, (ii) the amount and type of documentation needed to adequately support the seizure action, and (iii) when firms should be cited for prosecution.

Department Comment

We concur. The Administrative Guidelines for GMPs as well as the current good manufacturing practice regulations themselves, are under study by the

Bureau of Drugs with assistance from a drug quality control expert consultant with extensive industry experience. The Guidelines will be rewritten to more clearly delineate and define actions to be taken. Training programs for field and headquarters officials will be intensified and continuing to assure that everyone making regulatory decisions has written guidelines to the fullest extent possible and the experience to make judgments where guidelines are not possible.

GAO Recommendation

--Consider establishing a time limit for receipt of the written response requested in warning letters

Department Comment

We concur Instructions were issued in August 1972 to require a response to all "warning" letters to firms within ten days These letters include (i) Regulatory Letters, (ii) Reports of Inspectional Findings, and (iii) Section 306 Warning Letters. In addition, FDA's inspectors who issue a report of their GMP findings (FD-2275) to an official other than the firm's principal executive, will also send a copy to the principal executive of the firm

GAO Recommendation

--Establish an Inspection scheduling system monitored by FDA headquarters, to assure that all drug producers are inspected at least every two years.

Department Comment

We concur in that FDA will develop a system (for monitoring at the headquarter's level) for scheduling inspections of all drug producers at least every two years. Its full implementation, however, will depend upon whether the inspection resources presently available to FDA are increased and on other competing priorities for the manpower to perform such inspections.

GAO Recommendation

--Establish guidelines to assure timely initial inspection of newly registered drug producers.

Department Comment

We concur. Instructions will be issued to the field to inspect newly registered drug producers as promptly as possible. The instructions will cover not only newly registered firms but new firms which have failed to register and which come to our attention through other means. These firms will be required to register.

GAO Recommendation

--Properly enforce the annual drug producers registration requirement and effectively monitor the accuracy and completeness of the registration listing to permit its use as a cross-check on the OEI listing

Department Comment

We concur. Each quarter (headquarters') staff will match the Official Establishment Inventory (OEI) file with the drug registration file and provide the district offices a list of "non-matches." The two sources of information will be used to increase the accuracy of both OEI and registration files When the Drug Listing Act and voluntary inventory data become available these data will automatically update the list of drug manufacture

GAO Recommendation

--Correct the inventory of drug producers subject to the 2-year inspection requirement so that FDA will have complete and accurate knowledge of the scope of its inspection responsibilities.

Department Comment

We concur. As part of the first major Official Establishment Inventory validation since 1963, we have contracted with a major private concern to compare FDA's establishment inventory with their inventory of firms dealing in commodities subject to the FD&C Act. Discrepancies between these two lists will be resolved by FDA's District Offices by June 1973 Other sources of commercial information will also be used by the Districts to correct the inventory. Updates will be received from the contractors at regular intervals, and will become part of prescribed OEI updatings.

COPY
GOOD MANUFACTURING PRACTICE REGULATIONS -- DRUGS

Good manufacturing practice regulations set forth in 21 CFR 133.3 - 133.15 are used as the criteria for determining whether the method used in, or the facilities or controls used for, the manufacture, processing, packaging, or holding of a drug conform to or are operated or administered in conformity with GMPs. Compliance with GMPs is intended to insure that a drug meets the requirements of the FD&C Act as to safety, and has the identity and strength and meets the quality and purity characteristics which it purports or is represented to possess, as required by section 501(a)(2)(B) of the FD&C Act. A brief description of each GMP regulation follows.

CFR Section

133.3 Buildings

Buildings in which drugs are manufactured, processed, packaged, labeled, or held shall be maintained in a clean and orderly manner and shall be of suitable size, construction, and location in relation to surroundings to facilitate maintenance and operation for their intended purpose.

133.4 Equipment

Equipment used for the manufacture, processing, packaging, labeling, holding, or control of drugs shall be maintained in a clean and orderly manner and shall be of suitable design, size, construction, and location in relation to surroundings to facilitate maintenance and operation for its intended purpose.

133.5 Personnel

The key personnel involved in the manufacture and control of the drug shall have a background of appropriate education and/or appropriate experience for assuming responsibility to insure that the drug has the safety, identity, strength, quality, and purity that it purports to possess.

133.6 Components

Components used in the manufacture and processing of drugs, regardless of whether they are intended to appear in the finished product, shall be identified, handled, and otherwise controlled in a manner to insure that they conform to appropriate standards of identity, strength, quality, and purity, and are free of contaminants at time of use. Adequate measures shall be taken to prevent mixups and cross-contamination affecting drugs and drug products. Components shall be withheld from use until they have been identified, sampled, and tested for conformance with established specifications and are released by a materials approval unit.

133.7 Master and batch production and control records

For each drug product, master production and control records shall be prepared, endorsed, and dated by a competent and responsible individual and shall be independently checked, reconciled, endorsed, and dated by a second competent and responsible individual. These records shall include specified information concerning, among other things, identity of the product, dosage, labeling, identity and weight and measure of ingredients; containers, closure, packaging, and finishing materials; and manufacturing and control instructions, procedures, specifications, special notations and precautions to be followed.

A separate batch-production and control record shall be prepared for each batch of drugs produced and shall be retained for at least 2 years after distribution has been completed or at least 1 year after the batch expiration date, whichever is longer The batch production and control record shall be numbered to permit the identification of all laboratory-control procedures and results on the batch and all lot or control numbers appearing on the labels of drugs from the batch. The records must also show an accurate reproduction of the appropriate master-formula record, checked and endorsed by a competent, responsible individual

133.8 Production and control procedures

Production and control procedures shall include all reasonable precautions, to insure that the drugs produced have the identity, strength, quality, and purity they purport to possess.

Each significant step in the process, such as the selection, weighing, and measuring of components, the addition of active ingredients during the process, weighing and measuring during various stages of the processing, and the determination of the finished yield shall be performed by a competent, responsible individual and checked by a second competent, responsible individual. If such steps in the processing are controlled by precision automatic mechanical or electronic equipment, their proper performance shall be adequately checked by one or more competent, responsible individuals.

133.9 Product containers and their components

Suitable specifications, test methods, cleaning procedures, and, when indicated, sterilization procedures shall be used to insure that containers, closures, and other component parts of drug packages are suitable for their intended use. They shall not be reactive, additive, or absorptive so as to alter the safety, identity, strength, quality, or purity of the drug or its components beyond the official or established requirements and shall furnish adequate protection against deterioration or contamination of the drug.

133 10 Packaging and labeling

Packaging and labeling operations shall be adequately controlled to insure that only those drugs that have met the standards and specifications established in their master production and control records shall be distributed, to prevent mixups between drugs during the filling, packaging, and labeling operations, to insure that correct labeling is employed for the drug, and to identify finished products with lot or control numbers that permit determination of the history of the manufacture and control of the batch of drug.

133.11 Laboratory controls

Laboratory controls shall include the establishment of adequate specifications and test procedures to insure that components, drug preparations in the course of processing, and finished products conform to appropriate standards of identity, strength, quality, and purity. Laboratory controls shall include the establishment of master records containing appropriate specifications for the acceptance of each lot of each component used in drug production and a description of the sampling and testing procedures used to check them. Samples shall be representative and adequately identified. Such records shall also provide for appropriate retesting of materials subject to deterioration. In addition, a reserve sample of at least twice the quantity of the drug necessary to perform most of the required tests and stored under conditions consistent with product labeling shall be retained at least 2 years after the drug distribution has been completed or at least 1 year after the drug's expiration date, whichever is longer. Also, the controls shall include the establishment of a master record of appropriate finished-product specifications and a description of sampling procedures to check them. In addition, the controls should include adequate provision to check the reliability, accuracy, precision, and performance of laboratory test procedures and laboratory instruments used.

133.12 Distribution records

Complete records shall be maintained of the distribution of each batch of drug in a manner that will facilitate its recall if necessary. Such records shall be retained for at least 2 years after distribution of the drug has been completed

or 1 year after the expiration date of the drug, whichever is longer, and shall include the name and address of the consignee, the date and quantity shipped, and the lot or control numbers identifying the batch of drug.

133.13 Stability

Adequate provision shall be made to insure the stability of finished drugs.

133.14 Expiration dating

Labels of all drug products liable to deterioration shall have suitable expiration dates which relate to stability tests performed on the product to insure that such drug products meet appropriate standards of identity, strength, quality, and purity at the time of use.

133.15 Complaint files

Records shall be maintained of all written or verbal complaints for each product. Complaints shall be evaluated by competent and responsible personnel and, where indicated, appropriate action shall be taken. The record shall indicate the evaluation and action.

ENFORCEMENT ALTERNATIVES AVAILABLE TO THE FOOD AND DRUG ADMINISTRATION

CRIMINAL PENALTIES

Section 301 of the FD&C Act sets forth those actions which are prohibited under the law. Section 303 provides that any person who violates a provision of section 301 be imprisioned for not more than 1 year or fined not more than $1,000, or both. For second and subsequent convictions, the imprisonment and fine are increased to no more than 3 years or $10,000, or both

Citation

Section 305 of the FD&C Act provides that, before any violation of the FD&C Act is reported for institution of a criminal proceeding, the person against whom such proceeding is contemplated be given appropriate notice and an opportunity to present his views, either orally or in writing, with regard to such contemplated proceeding To comply with this provision a Notice of Hearing, often referred to as a citation, is mailed to the alleged violator(s) and a date for response designated

INJUNCTION

Section 302 of the FD&C Act provides for injunction to restrain violations of section 301. An injunction enjoins the firm or individual from performing or not performing some act.

SEIZURE

Section 304 of the FD&C Act provides that seizure proceedings may be initiated against any food, drug, device, or cosmetic that is adulterated or misbranded when introduced into or while in interstate commerce.

Recall

A recall is described as voluntary action by a firm to remove from the market those products that present a threat to the safety or well-being of the consumer Although such

action is not provided for in the FD&C Act, FDA policy statements indicate that, over the years, recalls have been the most effective method of removing from the marketplace all units of products found to be in violation of Section 301 of the FD&C Act.

WARNING LETTER

Section 306 of the FD&C Act, under the caption "Report of Minor Violations" states that

> "Nothing in this Act shall be construed as requiring the Secretary to report for prosecution, or for the institution of libel or injunction proceedings, minor violations of this Act whenever he believes that the public interest will be adequately served by a suitable written notice of warning."

APPENDIX IV

PRINCIPAL OFFICIALS OF THE DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE RESPONSIBLE FOR THE ACTIVITIES DISCUSSED IN THIS REPORT

	Tenure of office	
	From	To
SECRETARY OF HEALTH, EDUCATION, AND WELFARE		
Caspar W. Weinberger	Feb. 1973	Present
Frank C. Carlucci (acting)	Jan. 1973	Feb 1973
Elliot L Richardson	June 1970	Jan 1973
Robert H. Finch	Jan. 1969	June 1970
Wilbur J. Cohen	Mar 1968	Jan. 1969
John W Gardner	Aug. 1965	Mar. 1968
ASSISTANT SECRETARY (HEALTH) (note a)		
Richard L. Seggel (acting)	Dec. 1972	Present
Merlin K. Duval, Jr.	July 1971	Dec. 1972
Roger O. Egeberg	July 1969	July 1971
Philip R. Lee	Nov 1965	Feb. 1969
COMMISSIONER, FOOD AND DRUG ADMINISTRATION		
Charles C. Edwards	Feb 1970	Present
Herbert L Ley, Jr.	July 1968	Dec 1969
James L. Goddard	Jan. 1966	June 1968

[a]Before November 1972 this position was designated as Assistant Secretary for Health and Scientific Affairs