to be discontinued. Additionally, the policy authorizes the services to make similar decisions concerning locally-procured drugs in this category or to delegate their authority to local P&T Committees.

The policy also authorizes the procurement of "possibly effective" drugs when no alternative means of therapy is available and final FDA determinations on their efficacy are expected to require a long period of time. However, both central and local procurements of these items are to be minimized to take into account the possibility that they may be finally determined by FDA to be ineffective and ordered removed from the market.

Shortly after June 1973, the military departments included the revised policy in their instructions for field installations together with up-to-date consolidated listings of FDA drug safety and effectiveness data for use by military medical personnel.

Under CHAMPUS, DOD has placed no restrictions on the drugs that may be prescribed and is not supplied detailed data concerning the specific drugs that are being paid for. Therefore, DOD could be paying for drugs under CHAMPUS which could not be procured for its direct care activities.

Actions Taken by the Veterans Administration

Since December 1970, VA's policy has continued to be that all "ineffective" drugs must be removed from VA hospitals except where special approval of the Central Office Executive Committee on Therapeutic Agents has been obtained. Also, VA's policy concerning "possibly effective" drugs continues to require that consideration be given to using an alternative product having a higher FDA effectiveness classification.

To strengthen the policy's implementation, the VA is furnishing a list of drugs ordered to be withdrawn from the market to the P&T Committees at each VA facility which buys or dispenses drugs. Further, a current statement of VA policy on the use of drugs is now being developed by the Central Office Executive Committee on Therapeutic Agents for distribution to all VA facilities.

Actions Taken by the Department of Health Education and Welfare

As we testified in May 1972, HEW's policy was that Federal funds shall not be spent for "ineffective" drugs except under approved clinical research projects, or for "possibly effective" drugs, except under similar projects or when alternative means of drug therapy are not available. In October 1971, HEW agencies involved in direct patient care were instructed to stop procurement and use of such drugs and to

advise their contract physicians of the Department's policy. These instructions remain in effect.

Although the policy was intended for use in all of the Department's programs, it has not yet been implemented for the Medicare and Medicaid programs. The Department, SSA, and SRS have each drafted proposed regulations to address this matter. We understand that the drafts of the proposed regulations are under review in the Department and that notices of proposed rule making will be published for comments by interested parties in the near future.

You may recall that we issued a letter to the Administrator, SRS, in May 1972 bringing the matter to his attention and asking him to advise us concerning SRS plans for implementing the Department's policy. In June 1972, the Administrator told us that a draft of a regulation implementing the Surgeon General's 1970 policy had been cleared in SRS and was being prepared for transmittal to the Office of the Secretary for publication as a proposed rule. The regulation was not published.

As part of our continuing review efforts concerning Medicaid activities, we have recently initiated a survey of the administration of the Medicaid drug program. We have

already noted that States were continuing to pay for "ineffective" and "possibly effective" drugs.

For example, in one month--September 1973--three States paid an estimated $692,000 for such drugs. Also, we contacted officials of two additional States--which were included in our 1972 review--and were informed that these States had not changed their policy concerning payment for "ineffective" and "possibly effective" drugs and would not do so until SRS issues its final regulations concerning this matter.

We have again brought this matter to the attention of HEW in a letter to the Secretary, dated February 15, 1974.

Mr. Chairman, this concludes my statement. We shall be happy to answer any questions that you or other members of the Subcommittee may have.

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.

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

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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 labbling. --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.

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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 nonaggressive 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

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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.

APPENDIX I

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

APPENDIX I

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.

APPENDIX I

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 manufacturers.

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.

APPENDIX II

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.

APPENDIX II

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.

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APPENDIX II

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.

APPENDIX III

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.

REPORT TO THE CONGRESS

How To Improve The Procurement And Supply Of Drugs In The Federal Government

B-164031(2)

Department of Defense
Veterans Administration
Department of Health, Education, and Welfare
Office of Management and Budget
General Services Administration

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

DEC. 6, 1973

COMPTROLLER GENERAL OF THE UNITED STATES
WASHINGTON, D.C. 20548

B-164031(2)

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

This is our report on how to improve the procurement and supply of drugs in the Federal Government.

We made our review 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; the Secretaries of Health, Education, and Welfare and of the Department of Defense; the Administrator, General Services Administration; and the Administrator, Veterans Administration.

Elmer B. Staats

Comptroller General
of the United States

Contents

ABBREVIATIONS

DMMB	Defense Medical Materiel Board
DOD	Department of Defense
DPSC	Defense Personnel Support Center
DSA	Defense Supply Agency
FDA	Food and Drug Administration
FSS	Federal Supply Schedule
GSA	General Services Administration
HEW	Department of Health, Education, and Welfare
OMB	Office of Management and Budget
PHS	Public Health Service
VA	Veterans Administration
VAMC	Veterans Administration Marketing Center

COMPTROLLER GENERAL'S REPORT TO THE CONGRESS

HOW TO IMPROVE THE PROCUREMENT AND SUPPLY OF DRUGS IN THE FEDERAL GOVERNMENT

Department of Defense
Veterans Administration
Department of Health, Education, and Welfare
Office of Management and Budget
General Services Administration
B-164031(2)

D I G E S T

WHY THE REVIEW WAS MADE

Because of congressional interest in, and the magnitude of Federal expenditures for, drugs, GAO reviewed procurement and supply practices of agencies responsible for most of the Government's direct procurement of pharmaceuticals.

Direct drug purchases exceeded $275 million in fiscal year 1972, and estimated indirect purchases for such programs as Medicare and Medicaid were more than double that amount. Principal agencies concerned were the Department of Defense (DOD) and the Veterans Administration (VA).

FINDINGS AND CONCLUSIONS

Greater cooperation and coordination in procuring drugs would result in savings

DOD and VA operate procurement and supply systems largely independently of each other.

Although they stock about 200 of the same drugs--frequently bought from the same suppliers--and support numerous field installations throughout the United States, these two large agencies have had little exchange of requirements data or coordination in their procurement. (See pp. 8 and 9.)

GAO tests of drug purchases during a 3-year period showed that, in many cases, DOD and VA had paid the same manufacturer different prices for large quantities of the same drugs within the same general time frames.

Since drug prices usually are lower for purchases in large quantities, substantial savings could be realized if VA and DOD were to procure drugs jointly. (See pp. 9 and 10.)

DOD and VA procedures for developing their drug requirements are similar. To consolidate procurement the requirements of the two systems could be coordinated without undue difficulty.

Medical facilities supported by the Defense Personnel Support Center may not order from VA central stocks drugs not stocked by that Center. Similarly, VA medical facilities may not order directly from that Center.

Consequently, these facilities purchase drugs they cannot obtain from their own central supply organization from Federal Supply Schedule

contracts or directly from vendors in small quantities at much higher prices. (See pp. 10 to 12 and app. I.)

About $420,000 could have been saved in the 3-year period if DOD and VA medical facilities had acquired drugs from one another's central stocks.

For example, from July 1970 to December 1971, military hospitals purchased macrodantin directly from the manufacturer for $555,000 because it was not carried in DOD's central stocks. At that time VA was purchasing this drug for its central stock and paying about 48 percent of the amount paid by the hospitals. (See p. 11.)

Uneconomical local procurements of drugs should be avoided whenever practicable. The availability of DOD and VA central stocks to all Federal field facilities should reduce the frequency of these procurements.

Benefits of specifications and central management in procuring pharmaceuticals

Specifications defining drug product characteristics encourage competitive procurement and should reduce the cost of drugs. Use of these specifications has expanded. A revised DOD policy for approving drugs for central management would improve drug procurement.

--From October 1970 to June 1972, the VA Marketing Center prepared and used 85 new specifications for procuring drugs. As a result it saved nearly $1 million annually. (See pp. 19 and 20.)

--Under its current policy DOD will not procure a drug by central procurement unless (1) data sufficient to develop specifications is available or (2) all three military services concur in designating a single procurement source.

GAO brought the macrodantin case to the attention of the Defense Medical Materiel Board. The Board's policy resulted in substantial excess costs being incurred because the drug was not bought centrally. Although the Board then authorized central management of the drug on a sole-source basis, it did not change its policy. (See pp. 11, 20, and 21.)

Savings should continue if specifications are developed for new drugs and those managed centrally for which no specifications have been prepared. DOD could also realize substantial savings if it would amend its policy for approving drugs.

Since many drugs for which the Defense Personnel Supply and VA Marketing Centers prepare specifications are basically the same and since the number of these items should increase, duplicate effort could be avoided and technical talent could be better used if the Centers cooperate in preparing specifications. (See p. 20.)

Uniform reporting of drugs bought locally and more effective use of related reports would improve selection of items for central management

Bulk purchases of drugs for central stocks are substantially lower priced than smaller purchases. The primary method of identifying drug items for central DOD and VA management is through review of reports from field

activities of purchases made directly from vendors. However:

--The reporting systems of the military services for local purchases differ in many important respects, exclude certain purchases, and hamper the identification of drugs for potential central management. (See pp. 24 and 25.)

--The voluminous VA report contains no summary by drug items to facilitate a review of purchase information. (See p. 26.)

Because of weaknesses in the reporting systems, VA are DOD may be procuring many drugs locally, instead of centrally, at unnecessairly high prices. (See pp. 24, 25, and 27.)

Overlapping quality assurance activities

DOD and VA have different systems for inspecting manufacturers' plants to insure that they qualify as supply sources and that the drugs are of required quality. These inspections are additional to those made by the Food and Drug Administration (FDA), which is responsible for checking manufacturing practices and conditions under which drugs are made in the United States.

RECOMMENDATIONS

To promote Federal agency cooperation in procuring drugs:

--The Director, Office of Management and Budget (OMB), should lead in developing--with representatives of the General Services Administration (GSA); DOD; VA; and the Department of Health, Education, and Welfare (HEW)--policies and procedures, including consolidating requirements, to increase agency cooperation in buying drugs and achieve substantial savings through large-volume buys. Field installations should be authorized to obtain their drug requirements from any centralized Government supply source. (See pp. 13 and 14.)

--The Administrator, VA, should develop specifications for (1) all new drugs which VA decides to manage centrally and (2) centrally managed drugs for which it currently has no specifications. (See p. 22.)

--The Secretary of Defense should revise DOD policy to insure that drugs will be obtained centrally whenever savings would result. (See p. 22.)

--The Secretary of Defense and the Administrator, VA, should consider jointly developing specifications which would satisfy all Federal agencies' requirements. (See p. 22.)

--The Secretary of Defense should (1) develop, for reporting local drug purchases, a uniform reporting system aimed at requiring all military activities with individual drug purchases exceeding specified criteria to report their purchases and (2) require centrally managed drugs purchased from other than a central manager to be reported. (See p. 28.)

--The Administrator, VA, should require that VA's Central Office Supply Service (1) prepare lists of summary and exception data from the information reported, (2) require local field stations to report their purchase data correctly and consistently, and (3) see that all vendors report detailed sales data when required by contracts. (See p. 28 and 29.)

--The Secretary of Defense and the Administrator, VA, should consider using a standardized coding system, such as the National Drug Code, for identifying local purchases of drugs not having Federal stock numbers. (See p. 29.)

--The Secretaries of Defense and HEW and the VA Administrator should review the frequency and type of inspections required and the related changes needed to facilitate the transfer to FDA of all quality assurance responsibilities pertaining to purchases of drugs by Federal agencies. (See pp. 33 and 34.)

AGENCY COMMENTS AND UNRESOLVED ISSUES

DOD, VA, GSA, and OMB expressed interest in and general agreement with these aims. OMB and VA pointed out the need to consider total economic costs in determining whether consolidated procurement would be economical. This data has not been developed, and it may be a long time before it is available.

Meanwhile, opportunities exist for effecting economies and improvements within the present state of management data and operating methods, and GAO believes that action to take advantage of the opportunities should not be delayed until such data becomes available.

DOD and VA expressed reservations as to whether FDA could provide the types of inspections they require on a timely basis. HEW stated that it would discuss with DOD and VA officials the quality assurance requirements, needed resources, and other pertinent matters. HEW also said that it would take necessary action to transfer to FDA all quality assurance activities if it found that this would be in the best interest of the Government.

MATTERS FOR CONSIDERATION BY THE CONGRESS

This report shows how Federal drug procurement, supply, and inspection functions could be improved and could save the Government money.

CHAPTER 1

INTRODUCTION

Government procurements of pharmaceuticals directly from drug companies are estimated to have exceeded $275 million in fiscal year 1972. The two largest buyers were the Defense Supply Agency (DSA) and the Veterans Administration (VA), but the Public Health Service (PHS) of the Department of Health, Education, and Welfare (HEW) also made fairly large purchases.

The Defense Personnel Support Center (DPSC), Philadelphia--a DSA activity--buys and stocks drugs for the Department of Defense (DOD) and provides supply support to military medical field facilities, to other DOD components, and to Federal agencies under interagency support agreements. DPSC bought about $95 million worth of drugs during fiscal year 1972.

The Defense Medical Materiel Board (DMMB), composed of the Surgeons General of the Army, Navy, and Air Force, in coordination with the military medical services and DPSC, adopts drugs for and deletes them from the DOD central supply system.

The General Services Administration (GSA) is responsible, under the Federal Property and Administrative Services Act of 1949 (40 U.S.C. 471), for procuring medical supplies for civil agencies. In 1960 GSA delegated to VA the buying and supplying of drugs, biologicals, and official reagents[1] for all civil agencies.

The VA Marketing Center (VAMC), Hines, Illinois--an activity of the VA Central Office Supply Service in Washington, D.C.--is the central VA purchasing organization. During fiscal year 1972 it bought about $37 million worth of drugs for central stock. VAMC determines which drugs should be adopted for or deleted from the VA supply system subject to approval of VA's Central Office. VA field stations requisition centrally stocked medical items from VA depots.

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[1]Chemical substances used in testing drugs.

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VAMC also awards and administers Federal Supply Schedule (FSS) contracts--those for supplying articles or services at stated prices for a given period--in accordance with regulations prescribed by the GSA Administrator.

PHS operates a central supply organization at Perry Point, Maryland, which purchases, stocks and issues drugs to all PHS hospitals, clinics, and outpatient offices.

The following table summarizes operations of DPSC, VAMC, and PHS within their own agencies.

	Number of drugs centrally managed	Number of depots where drugs are stocked	Number of medical facilities supported	Cost of fiscal year 1972 drug procurement	Drug inventory June 30, 1971
				(millions)	
DPSC	1,100	6	1,672	$95	$59
VAMC	450	3	[a]182	37	[b]18
PHS	600	1	60	[c]9	.5

[a]VA also sells centrally stocked drugs to other Government agencies and administers FSS contracts used by all agencies. In fiscal year 1972 VA sold about $3.5 million worth of depot drugs to other Government agencies. VA services about 270 additional medical facilities in this way.

[b]Includes about $9 million worth stored in VA field stations.

[c]Includes undetermined purchases from VA and DPSC.

The medical facilities supported by these agencies also buy drugs directly from manufactures, under FSS contracts, and from local vendors. During fiscal year 1971 total drug purchases under FSS contracts totaled about $64 million. The cost of local purchases could not be ascertained because of limitations in the reporting by medical facilities. (See ch. 4.) PHS obtains a large part of its drug requirements from, or under contractual arrangements made by, VAMC and DPSC.

PAST EFFORTS TO IMPROVE FEDERAL MANAGEMENT OF MEDICAL MATERIAL

Between 1963 and 1971 DOD and GSA separately and with other interested Government agencies studied the possibility of a single agency's having Government-wide responsibility for managing various categories of supplies, including medical material which includes pharmaceuticals.

Late in 1964 GSA and DOD entered into an agreement governing the supply management functions and relationships between the two agencies. Essentially the agreement contemplated studies to develop a unified national supply system eliminating unnecessary duplication between military and civil agencies in five commodity areas, including medical material.

The study on medical material concluded that further review and evaluation was necessary. Further review was completed during 1969 and 1970, and in February 1971 GSA and DOD approved a new agreement governing their supply management relationships.

Under the new agreement, several Federal stock classes were assigned to GSA and DSA for integrated management. The agreement provides for joint development of plans for assigning, identifying, and subsequently transferring necessary resources, funds, and personnel. Although medical material is included among the commodities assigned to DSA for integrated management, that assignment has been deferred pending the outcome of still another study.

This new study, proposed in June 1971 by the Office of Management and Budget (OMB), recognized that, although several agencies purchase and use medical items and although studies were previously made, no decision regarding unified management or a national system was reached. OMB believed that a further investigation should be undertaken before a final decision could be made on the best means of providing medical support to all Federal agencies. To reach a decision OMB has set up a steering group composed of a representative from OMB and each of four agencies--VA, DSA, GSA, and HEW--to study the functions, organization, and management practices in all Federal agencies involved in medical supply. The study was started in January 1972; the OMB representative chaired the study group. A report on this study was expected in June 1973 but has not yet been issued.

CHAPTER 2

GREATER COOPERATION AND COORDINATION WOULD RESULT IN SIGNIFICANT SAVINGS IN PROCURING DRUGS

Lack of coordination between the central buying agencies and certain restrictions on interagency transactions increase the costs of drugs to the Government. In reviews of a limited number of the procurements during a 3-year period, we identified (1) costs of about $420,000 which could have been avoided through greater coordination between the procuring agencies and (2) price variances of $447,000 on Government purchases of the same items. A substantial portion of the differences could have been avoided and lower prices realized through greater coordination.

Although DOD and VA have established policies of using the most economical supply sources and have prescribed priorities of supply sources to be followed by their medical facilities, they operate their drug procurement and supply systems largely independently of each other. Further, there is little exchange of requirements data or coordination in procurement, even though the agencies centrally buy and stock about 200 of the same drugs and one or the other often obtains a lower price for the same item.

DSA-VA SUPPLY AGREEMENT

DSA and VA have an agreement whereby VAMC can purchase from DPSC medical material which DPSC manages centrally. The agreement establishes the procedures for requirements planning, material requisitioning and release, billing and collection, and other matters.

VAMC does not use the agreement extensively; in fiscal year 1970 it purchased only about $207,000 worth of drugs from DPSC. A drawback to more extensive use of the agreement is DPSC and VAMC surcharges which can total nearly 20 percent of the cost for drugs supplied to VA field stations. Also, the flow of drugs from DPSC depots or manufacturers to VAMC depots and then to VA field stations is cumbersome and results in extra handling and added transportation costs.

The agreement does not provide for DPSC to buy drugs from VAMC. We noted no procurements by DPSC from VAMC.

Military medical facilities may not obtain from VAMC stocks those drugs which DPSC does not carry, and VA facilities may not buy from DPSC those drugs that VAMC does not carry. In these cases these medical facilities have to buy such drugs under the FSS contracts or directly from vendors at much higher prices than those available from the central buyers.

DEVELOPMENT OF REQUIREMENTS DATA FOR PROCUREMENT

When either DPSC or VAMC approves a drug for central management, it procures an estimated quantity to cover anticipated needs for a limited period. Thereafter, quantities to be procured are based primarily on the quantity issued by depots since the last inventory replenishment. Computer reports are prepared periodically--monthly by VAMC and quarterly by DPSC (more frequently if predetermined reorder points or critically low inventory positions are reached)--and reviewed to determine items for which procurement or other supply action should be taken. Both agencies try to maintain inventory levels representing a number of months' use--in VAMC 5 to 7 months' supply and in DPSC about 9 months' supply--plus any special requirements.

Quantities of each drug are purchased to replenish stocks and fill requisitions. DPSC includes unfilled orders in calculating its reorder points, but VAMC does not.

Procedures for developing requirements under each system are quite similar, and it appears that, to consolidate procurement, requirements data under the systems could be coordinated without difficulty.

POSSIBLE SAVINGS THROUGH JOINT PROCUREMENT

DPSC and VAMC independently purchased, at different prices, many of the same drugs for central stock--in many cases from the same manufacturer and at about the same time. Several manufacturers have told us that large-volume purchases will generally reduce prices.

If VAMC and DPSC cooperated, they could forecast their annual drug requirements; consolidate their procurements, providing for any special needs for such things as packaging, labeling, and inspection; and, under joint procurement arrangements, take advantage of the most economical methods of contracting and supply sources. Apparently, if their requirements had been consolidated and bought under joint procurement arrangements, VA and DPSC could have realized significant savings.

For example, procurement records for 43 drugs showed that, during fiscal years 1970 and 1971, DPSC and VAMC paid different prices for the same drugs purchased within 30 days of each other. These variances totaled about $246,000, and each agency obtained the lower price in about half the cases.

We furnished information on these cases to DPSC and VAMC officials so that they could determine the reasons for the differences. Some vendors made voluntary refunds totaling $15,000 to DPSC because of pricing mistakes they had made during negotiations. Other vendors claimed that the differences were due to the type of contract negotiated, the varying quantities ordered, the frequency of orders, special labeling and packaging requirements, or additional quality control and testing requirements. One vendor suggested to DPSC that it and VAMC combine their buys to obtain lower prices.

Because of the possibility of long-term storage and shipments to countries with extreme climates, DPSC generally requires more protective wrapping for the drugs it buys than other buyers do. Despite this, DPSC has often paid identical or lower prices than VAMC for the same drugs purchased in similar or smaller quantities in the same period.

We also examined the sales records of four manufacturers. DPSC and VAMC paid two of them $91,000 additional because of different prices charged for the same items.

NEED TO PROMOTE INTERAGENCY TRANSACTIONS AT THE USER LEVEL

If drugs stocked by DPSC and VAMC could be made available to medical facilities of the system which does not stock such drugs, substantial savings could be realized. As shown

below, savings would result from eliminating buys through FSS contracts and buys directly from vendors at prices which, almost invariably, are substantially higher than those paid by central managers. (See app. I.)

The military departments have not arranged for their activities to purchase from VAMC depots drugs not centrally managed by DPSC. Also, VAMC has negotiated several special contracts which military and, in some cases, civil agencies cannot use. The prices under these contracts are lower than those for the same drugs sold under FSS contracts. VA field stations may not requisition directly from DPSC.

Effects on medical facilities

When individual medical facilities cannot obtain their required drugs from central stocks because of interagency restrictions or impediments, they purchase them through FSS contracts or directly from vendors in relatively small quantities and usually at much higher prices. Following are examples of the additional costs incurred in such circumstances.

1. From July 1970 to December 1971, military hospitals purchased macrodantin through FSS contracts for $555,000 because DPSC did not stock it. At this time, VAMC was purchasing the item for central stock and paying about 48 percent of the FSS price. After allowing for VAMC's 8-percent surcharge, the hospitals would have saved about $270,000 by purchasing the item from VAMC, which had procured it centrally in bulk quantities. After we brought this situation to DMMB's attention, it arranged for DPSC to centrally procure, stock, and manage this drug, and the prices negotiated were comparable to those negotiated by VAMC.

2. Sales records of purchases totaling about $6.1 million made from four vendors during a recent 2-year period showed that the Government incurred over $214,000 in excess costs because military and VA medical facilities bought many drugs directly from them or under FSS contracts at prices higher than those paid by DPSC and VAMC for the same drugs for central stock. Even after allowing for DPSC and VA

surcharges--amounting to 10-1/2 percent and 8 percent, respectively--about $150,000 would have been saved had the military and VA medical facilities purchased directly through DPSC or VA central supply points. For example, during calendar year 1970, VA field stations paid $46.07 for an 8-ounce jar of Aristocort Cream under the FSS contract. DPSC stocked this item and could have supplied it for $39.85 a jar, including all surcharges (18-1/2 percent), a savings of $6.22 a jar. Total savings on this item alone during calendar year 1970 would have amounted to over $4,600.

The need to promote interagency transactions extends to Government medical organizations other than those of VA and DOD. Our review at the four vendors' plants identified price variances of $110,000 because PHS and the National Institutes of Health, HEW, purchased drugs directly from these vendors at prices higher than those paid by DPSC and VAMC for the same items.

Under the existing GSA and DOD agreement, DOD issued a catalog, effective October 1, 1972, of selected items managed by its Defense Supply Centers for the use of civil agencies. About 600 drugs are listed which any Government agency can order from the cognizant Defense Supply Centers. The catalog states that other DSA-managed items included in supply catalogs may also be requisitioned so long as a Federal stock number is provided and appropriate requisitioning procedures are followed.

This is a step toward fostering interagency transactions. However, use of the catalog is not mandatory; consequently, the agencies will not necessarily use it as an alternative to more expensive local purchases.

CONCLUSIONS

Substantial savings and other advantages could result from an effective joint effort--including planning, consolidating procurement, and centrally procuring and supplying drugs--among DPSC, VAMC, and other agencies that buy drugs. Coordination should also enable these agencies to improve inventory management and better serve medical facilities Further, availability--under an interagency agreement--of the

VAMC and DPSC central supply stocks to all field facilities should reduce costly buys through FSS contracts and buys directly from vendors. Because central supply organizations supply drugs to other Federal agencies, as well as to the medical facilities they support, the overall benefits to the Government could be considerable.

To facilitate coordination, DPSC, VAMC, and other affected agencies may have to adjust their methods of determining requirements to insure that all work together with compatible supply levels and frequencies of review of inventory status. Contracts for procuring common drugs should include each agency's special requirements and delivery needs.

OMB should resolve the question of the type of joint arrangements that should be made for buying the common items and should make the solution a matter of record, in a DPSC-VAMC agreement or in appropriate regulations, by clearly setting forth the arrangements and how they should be implemented. The objectives of the arrangements should include (1) the elimination of avoidable duplication between the DPSC and VAMC procurement and supply systems and those of other Federal agencies that buy, store, and supply drugs and (2) a management plan permitting DOD and VA medical facilities to order from each other's central stocks when this would be beneficial.

Such an agreement could be patterned after the existing DSA-VA agreement, which prescribes necessary funding and material-requisitioning arrangements. To obtain maximum benefit from interagency transactions, the agreement should provide that interagency purchases be mandatory, except in emergencies.

Procurement consolidation would be a good first step toward eliminating duplication in procurement. This, and making the supply services available to all agencies, should also improve supply support for medical activities.

RECOMMENDATIONS

We recommend that the Director, OMB, lead in developing--with GSA, DOD, HEW, and VA representatives--policies and procedures to provide greater coordination and cooperation among Federal agencies in buying drugs. These policies and procedures should include agreements between the parties

or appropriate regulations providing for (1) periodic determinations of the joint requirements of the agencies--and others they support--for individual drugs and (2) joint procurement arrangements so that the most advantageous prices can be negotiated with suppliers for bulk quantities, with specified quantities delivered during a specified period (or other bases) direct to agency facilities where the drugs will be used or to Government storage and redistribution depots.

Within this framework, provision could be made for special requirements of the agencies, such as the special packaging and specifications for longer shelf life sometimes required for items for military use. Field installations should be authorized, except in emergencies or other justifiable circumstances, to obtain their drug requirements from any centralized Government supply source.

AGENCY COMMENTS AND GAO EVALUATION

DOD cited its current agreements with VA, GSA, and other civilian agencies as evidence of its interest in fostering interagency cooperation and coordination in the best interest of the Government. DOD stated that:

> "Pending final resolution of this matter DOD is willing to discuss further arrangements to prevent purchases of an item by one agency when the item is available from stock of the other agency, and to obtain the most advantageous prices in the purchase of pharmaceutical drugs."

In its comments VA stated that:

> "We agree with the major recommendation that there should be greater cooperation and coordination among Federal agencies buying drugs. Since the actual items involved will be determined by the nature of the programs served and will reflect the differences in mission, the degree of standardization will be limited by those factors. However, this should not limit other advantages to the Government which would stem from a viable program of interchange of procurement and supply techniques, ideas, and innovations."

In commenting on this report, OMB stated that it generally agreed that significant improvements could be made and economies could be achieved in procuring, inspecting, storing, and supplying drugs. However, OMB questioned whether mere consolidation of DOD and VA drug requirements and joint procurement would insure economies. Further, both OMB and VA pointed out that the total economic costs of procuring, storing, and issuing drugs under central procurement and local procurement systems and their relative cost effectiveness should be determined and considered before arriving at a decision to centrally buy and stock drug items. OMB also pointed out that quantity was only one of the factors which influenced drug prices.

We agree with the concept of relative cost effectiveness based on total economic costs, but "* * * the Government has failed to develop the data and techniques needed to measure the 'total economic cost' of fulfilling a Government need."[1] Further, it appears that substantial time may elapse before such management data for selecting the most cost-effective supply system for drugs will become available. We also agree with the Commission on Government Procurement's view that local procurement should be used whenever it is found to be economically feasible.

Since total economic cost data is not expected to be available in the near future, we believe the Government should use those opportunities which, with current management data and methods of operating, seem to indicate economies and improvements.

We are advocating the joint procurement of consolidated requirements, which does not necessarily include central storage and reissue. The decision whether or not to centrally stock drug items should be made on an item-by-item basis after considering all cost factors. Deliveries could be made direct to users, as is often done under centrally procured requirements-type contracts, thus obviating storage and related costs.

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[1]"Report of the Commission on Government Procurement," vol. 3 (Dec. 1972), p. 65.

We agree with OMB that quantity is not the only factor that affects the prices the Government pays for drugs. However, we believe that ordinarily it is a major factor, as evidenced by the differences in prices paid for the same drugs bought in relatively small quantities under FSS contracts or local procurements and those paid by a central procuring organization for large definite quantity contracts. (See app. I.) Our analysis of the prices paid for 68 drug items showed that the FSS prices for 29 items were from 5 to 366 percent higher than the definite-quantity-contract price. Also, in a study (B-164031(2), Nov. 22, 1972) comparing prices paid for the same drug items by DPSC and VA with those paid by nonprofit organizations that buy drugs on a group basis for private hospitals, we found that the Government paid lower prices for 28 of the 31 leading drug items which these organizations and the Government bought. The Government bought substantially larger quantities of 25 of these drug items. We believe this undoubtedly had some effect on the prices paid.

OMB stated that the preferable approach would be to combine the best aspects of each existing procurement system into one system. We do not disagree; however, as stated on page 7, the possibility of a single system has been under consideration since 1963 without result. We believe that, until a viable single system is designed, actions in line with our recommendations would improve the existing drug procurement and supply operations.

CHAPTER 3

BENEFITS OF SPECIFICATIONS AND CENTRAL MANAGEMENT IN PROCURING DRUGS

Efficient procurement and management of drugs depend largely on obtaining effective competition and sound policies for approving items that warrant central management. VA has improved its drug procurement by increasing the number of specifications available for procurement personnel to use in obtaining competition for VA's requirements. DOD could save more in procuring drugs by revising its policy for adopting items for central management.

DEVELOPING SPECIFICATIONS

VAMC and DPSC prepare drug specifications for procurement personnel to use in advising potential suppliers of the characteristics that drugs must meet and to generate competition for the Government's requirements. In many cases, however, due to patents or regulatory restrictions on the products the Government requires, procurement is limited to a single source.

However, our comparison of central procurements of 13 drugs by competition based on specifications and on a sole-source basis demonstrates the advantages of seeking broad competition. During a 2-year period lower average prices were obtained on 11 of these items when they were obtained competitively, and we estimated the Government would have saved about $338,700 on these 11 items had they been bought competitively in all instances. The quantities purchased by each method were different. This probably accounts for some of the price variation, but the primary reason seemed to be competition.

Preparing specifications can be difficult. For instance, the data for writing them is ordinarily obtainable only from manufacturers. Sometimes the manufacturers furnish incomplete information or none at all, especially for proprietary items, because they recognize that disseminating complete and accurate data in specifications will probably result in greater competition for Government, and possibly commercial, requirements for their drugs.

A further difficulty concerns data for formulating a drug. Even when the proper ingredients and quantities to be used are known, a product having a therapeutic effect different from that desired may be manufactured.

Thus, because of inadequate or incomplete data or the existence of patents, specifications are issued for many drugs that the Government buys which do not increase competition. Frequently, only one source can provide what the Government wants.

The degree of competition obtained in procuring drugs is less than that obtained for many other Government supply items. In fiscal year 1970 only about 7 percent of VAMC and DPSC dollar procurements for central stocks were made under formal advertised procedures. Much of the balance was procured under contracts negotiated with the sole source of supply or under contracts negotiated and awarded after proposals were solicited.

The primary reasons for the lack of competition are the large number of patented drugs and the Food and Drug Administration's (FDA's) requirements for approving drugs for manufacture. Some manufacturers have difficulty meeting these requirements because of the technical requirements and costs involved.

AVAILABILITY AND USE OF SPECIFICATIONS

DPSC generally will not approve a drug for central management unless (1) data sufficient to develop a competitive procurement specification is available or (2) all three military services concur in designating a single procurement source. Consequently DPSC has prepared specifications for nearly all the 1,100 drugs it manages. Only 1 percent of these items are intentionally bought noncompetitively from preselected sources.

Although DPSC attempts to buy competitively virtually all the drugs it manages, it has been successful only for about 51 percent of 1,100 items and the degree of competition on many of them is quite limited. The remainder, about 535 items, is supplied by single sources. FDA regulations, which disallow marketing without approved new drug applications or antibiotic certificates, or patents preclude or

restrict competition for 386 of these. But no apparent laws or regulations preclude interested firms from bidding for the remaining 149 drugs.

Thus, although DPSC has developed specifications for virtually all the 1,100 items, it has obtained competition for only about half of them. The specifications on the remainder, although not necessarily generating competition, do define what is wanted and minimize misunderstanding and contractor failure to satisfy Government requirements. DOD considers this benefit of specifications to be significant. It further believes that specifications should be developed in restricted competitive procurement so that DOD will be ready to go into the competitive market when a patent expires, when it legally buys around a patent, or when additional manufacturers conform to the regulations for manufacturing a drug.

Before October 1970 VA generally bought its required drugs on a brand-name basis and did not develop specifications for drugs it bought on a sole-source basis.

At that time about 70 percent of the drugs VA centrally stocked were designated for sole-source procurement to obtain specified brand-name drugs. Also, a large percentage of FSS contracts were for making manufacturers' product lines available to the Government at less than market prices. However, these contracts were negotiated without specifications or competition.

At that time also, VA ordinarily developed specifications only when the demand for a generic drug was sufficient to warrant central management or for drugs for which no patents existed or the patents had expired. Generally this meant that procurement was made from preselected sources which obviated the need for specifications.

In October 1970, however, VA began to develop specifications for 110 of the 450 drugs it managed centrally, for which it considered competition feasible. This effort has primarily consisted of obtaining industry comments on DPSC specifications which VA has rewritten as proposed VA specifications. After suggested revisions were considered, the specifications were written in final form.

On June 21, 1972, VA officials testified before the Subcommittee on Monopoly, Senate Select Committee on Small Business, concerning VA efforts to expand competitive procurement of its centrally managed drugs. VA indicated that it had developed specifications for 85 of 133 items it had determined suitable for competitive procurement and that specifications for 34 of the items were being developed. VA officials stated that 14 of the 133 items were being deleted and that, although it was too early to establish the total potential savings, annual savings of almost $940,000 had resulted from using the 85 specifications that had been issued as of June 1972.

COORDINATION POTENTIAL IN DEVELOPING SPECIFICATIONS

Several Government agencies buy many of the same drugs, and, as new drugs are developed and adopted for use, this number should increase. As previously indicated, specifications are extremely beneficial in obtaining competition and drugs that conform to required quality standards.

VA and DPSC are not required to coordinate in preparing specifications for identical or nearly identical drugs they both manage centrally. This situation leaves potential for duplicate effort in preparing specifications (1) for new items for which neither organization has yet prepared specifications and (2) for those items currently managed centrally by VAMC without specifications if VAMC decides it can, and should, issue specifications for such items and if DOD also decides to use and centrally manage the same items.

When identical and near-identical items are adopted for central management, DPSC and VAMC, and possibly other agencies, should jointly develop specifications for such items to avoid possible duplicate effort and to make the best possible use of the available talent to do this important work.

NEED TO REVISE DOD POLICY FOR ADOPTING ITEMS FOR CENTRAL MANAGEMENT

In considering an item for central management, DMMB requests the manufacturer to furnish information on the item's essential characteristics. DPSC evaluates this

information to determine whether it can prepare a specification. DMMB's policy provides that an item not be adopted for central management unless (1) data sufficient to develop acceptable specifications is available or (2) all three military services concur in designating a single procurement source. Substantial costs were incurred because of this policy.

The macrodantin case (see p. 11) illustrates the effect of this policy. In June 1969 the Air Force proposed this drug for central management. The Navy concurred, but the Army did not because it considered satisfactory a similar drug which was centrally managed. The brand-name manufacturer of the proposed items refused to provide technical data, and, because specifications could not be developed, the Air Force and Navy withdrew their recommendations.

Without concurrence by all three services, DMMB did not adopt the item for central management on a sole-source basis. Consequently, military activities continued to purchase it under the FSS contract, and during the 18 months from July 1, 1970, through December 31, 1971, they purchased $555,000 worth of the drug. During this time VAMC was purchasing the drug for its central stocks at less than half the FSS price. Had the military adopted the item for central management, military medical activities could have saved about $291,000, assuming the purchases could have been made at the same price VA paid.

We brought this matter to DMMB's attention in March 1971, and after DMMB concurred it authorized DPSC in July 1971 to centrally manage and procure the item on a sole-source basis. The first contract was awarded in December 1971.

CONCLUSIONS

Substantial savings resulted from VA's expanded use of specifications in procuring its centrally managed items. Savings should continue if specifications are developed to the extent practicable and beneficial on new items and on those centrally managed items for which specifications have not been prepared. DOD could also realize substantial savings by revising its policy for adopting items for central management. Further, since many drugs Federal agencies use

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for which DOD and VA prepare specifications are basically the same and since the number of such items should increase, VA and DOD could cooperate in preparing specifications for such drugs. Such cooperation would avoid duplicate effort and best use technical talent in preparing specifications.

RECOMMENDATIONS

We recommend that the VA Administrator arrange, as soon as practicable and beneficial, for specifications to be developed for (1) all new items which VA decides to manage centrally and (2) centrally managed items for which it currently has no specifications.

Also, since cooperation and coordination can be valuable in developing specifications, we further recommend that the Secretary of Defense and the Administrator consider jointly developing specifications which will satisfy all agencies' requirements. The effort should consider the requirements of all Federal agencies which procure drugs so that specifications will be issued, when possible, for those items for which the aggregate quantity required justifies central management.

We recommend that the Secretary of Defense revise DOD policy to insure that drugs will be adopted for central management whenever savings will result. Controls on sole-source drugs will be necessary to (1) insure that the sole-source designation is not misused, (2) insure that specifications are developed as soon as possible, and (3) encourage, when appropriate, the use of lower cost alternative drugs.

AGENCY COMMENTS AND GAO EVALUATION

VA stated that it considered joint development or mutual use of specifications an important element of the increased agency cooperation advocated in our report. It did not, however, comment on the need to develop specifications for some of the items it currently manages centrally and for new items it selects to manage centrally in the future.

DOD stated that DMMB would be specifically asked to coordinate the development of specifications with DSA and VA and to recommend appropriate action providing for the "* * * joint coordination/preparation of medical material having common usage within DOD and VA."

Regarding the recommendation that DOD revise its policy for adopting items for central management, DOD stated that, in addition to monetary savings, decisions were based on such factors as drug efficacy and storage requirements. However, it said that it would review the criteria and the standardization procedure used for adopting items for central management.

Although DOD policy provides for central procurement when savings apparently will result, the policy can be nullified by the requirement that the three military services concur in a sole-source designation. We believe that DOD should evaluate this requirement in its review of the standardization and procedures.

CHAPTER 4

UNIFORM REPORTING AND MORE EFFECTIVE USE OF RELATED REPORTS WOULD IMPROVE SELECTION OF ITEMS FOR CENTRAL MANAGEMENT

The primary method of identifying drugs for possible DPSC and VAMC central management is reviewing field activities' reports of purchases from FSS contracts and local suppliers. Each military service has a different system for reporting medical items purchased locally, and neither DMMB nor DPSC reviews these reports. VAMC reports local procurements, but its voluminous reports contain many errors and no summary. VAMC could use these reports more effectively.

MILITARY DEPARTMENT REPORTS

The following table summarizes pertinent aspects of the systems the military services use to obtain data from their medical facilities on procuring medical items, including drugs.

	Number of medical facilities reporting	Frequency of reporting	Medical items required
Army	19	Semi-annually	Those on which expenditures totaled $1,000 or more.
Navy	93	Quarterly	Those accounting for the highest expenditures during the reporting period. The number ranges from 10 to 50, depending on the reporting facility, but at least 50 percent must be drugs.
Air Force	26	Semi-annually	Those representing the top 15 items purchased with locally assigned stock numbers
Air Force	70	Semi-annually	Those listed in a special catalog of non-centrally stocked medical material

These reports are sent to field offices which organize the data and consolidate the reports for each service, but the field offices do not review and evaluate the items reported. The offices of the respective Surgeons General that select and recommend items to DMMB for centralized management make such reviews and evaluations. No single authority reviewed all of these reports at the time of our review, but a DOD official advised us that, after we examined this situation, arrangements were made for all the military departments to send their consolidated reports to DMMB for its review and use in evaluating new items for standardization.

The Army and Navy Surgeons General have no written definitive criteria for evaluating and selecting drugs to be recommended for central management. The Army, however, does have a written procedure stating that reports of local purchases will be reviewed to identify items used in sufficient quantity to warrant central management, but what constitutes such a quantity is not defined.

The Air Force has definitive written criteria for identifying drugs as candidates for central management. Generally the Air Force considers recommending items purchased by three or more facilities which have aggregate semiannual expenditures exceeding $1,000.

The Army's and the Navy's lack of these definitive criteria can result in failure to identify drugs purchased by their medical facilities in sufficient quantities to warrant DMMB evaluation. For example, Army and Navy medical organizations may purchase a drug exceeding $1,000 in value and the item may not be considered for central management; whereas, in similar circumstances, the Air Force normally considers the item for central management. Also, reports do not include purchases of centrally managed items from sources other than the central manager. The services could use this information to monitor field activities to insure that they were purchasing such drug items from DPSC as prescribed by service regulations.

VA REPORTS

Under authority GSA delegated in 1960, VA awards and administers FSS contracts and obtains semiannual reports

from vendors on the volume of drugs they have sold Federal agencies under (1) advertised contracts and (2) negotiated FSS contracts.

VA requires its field stations to report all local purchases of drugs to the VA Data Processing Center, Austin, Texas, which lists the data in the quarterly Drug Acquisition Report. This report is sent to VAMC for review and evaluation to determine whether the field stations are (1) purchasing locally drugs which could be supplied more economically if they were available in depot stocks or (2) purchasing in ways VAMC previously designated, such as from depot stocks, through special contracts providing for decentralized procurement and through FSS contracts.

VA's basic criterion for considering whether a drug should be centrally stocked is that local purchases should amount to $10,000 or more a year. All items that qualify under the criterion are not assured of being considered. In part, this is due to (1) the sheer volume of the Drug Acquisition Report--approximately 120,000 transactions listed on 4,500 pages, (2) the lack of item summaries and exception data, and (3) errors and inconsistencies due to VA field stations' failure to adhere to prescribed reporting requirements. One individual reviews the report.

To test the report's effectiveness, we had to devise a special computer program to isolate and summarize purchase data on potential candidates for central management. This test covered the reports for September 1970 through May 1971 and revealed 273 items which were not being centrally stocked although they satisfied the local purchase criterion. VA officials explained that 219 of the items were inappropriate for central stocking because some needed refrigeration, some were blood derivatives, and different intravenous systems required various types and sizes of intravenous solutions. VA officials said that, of the remaining 54 items, 24 were already being studied for central stocking and 30 would be considered.

In September 1972 VA officials informed us that, of the 30 items, 8 had not been selected for central stocking for such reasons as declining purchases, insufficient price break for bulk procurement, and the delay in waiting for FDA efficacy determinations. Of the remaining items, 9 were still being studied and 13 had been or were being centrally

stocked. Of the 13 items, 5 had been centrally purchased; VA forcasted savings of almost $36,000 for fiscal year 1973 on these items.

FSS contracts for pharmaceuticals are let in two sections and are labeled section A and section B contracts. Section A contracts are generally used for generic items and section B contracts for brand-name items. Section A contracts ordinarily are let for individual drugs, but section B contracts generally are let for the complete product lines that drug manufacturers produce.

The reports to be submitted by FSS contractors on section A contracts are useful to VA in considering items for central management because VA needs information on individual items in determining whether the volume of procurement of single items warrants consideration for central management. The reports on section B contracts are generally not usable because they relate to a complete product line.

Some contractors were not furnishing the reports of orders received, contrary to contract requirements. To the extent the reports are not received, the volume of purchases Federal agencies make is understated; therefore, drugs that qualify may not be identified or considered for central procurement. Also, the lack of usable data submitted in reports on a product-line basis under section B contracts could result in failure to identify items with potential for substantial savings through central management.

NEED FOR STANDARDIZED CODING SYSTEM

Under current reporting practices of both VA and military medical facilities, reports may include data for drugs under identification methods when an item does not have a Federal stock number. For such items the manufacturer's number, the hospital's number, or other types of identification are used.

In such a situation, purchase data on the same item may possibly be reported in two or more ways and the fact that the same drug is involved may be overlooked. If such purchase data is not consolidated, potential items for central management may be bypassed. A national drug code

number has been assigned to every drug, and these numbers could be used when a Federal supply number has not been assigned.

CONCLUSIONS

Both the military services' and VA's reporting systems for local purchases have weaknesses. Specifically, the lack of uniform reporting, the lack of evaluation criteria, the failure to evaluate many items that qualify for consideration for central management, and omissions from the local purchase reports suggest that many items that should be centrally managed are not and are therefore being procured locally at unnecessarily high prices.

To implement its stated policy of buying from the most economical source, DOD should establish a uniform reporting system for local drug purchases, including centralized review and evaluation of the reports of all the services, probably by DPSC. Candidates for central procurement should be recommended to DMMB.

RECOMMENDATIONS

We therefore recommend that the Secretary of Defense have DMMB:

--Develop, for reporting local drug purchases, a uniform system aimed at requiring all activities which made specified total dollar purchases of individual drugs during the reporting period to report their purchases.

--Require that centrally managed drugs purchased from other than the central manager be reported.

Although the basic concept of VA's Drug Acquisition Report is sound, it could be more effectively used. We therefore recommend that the Administrator, VA, require (1) the Central Office Supply Service to prepare lists of summary and exception data from the information reported and (2) local field stations to report their purchase data correctly and consistently. Further, we recommend that the Administrator see that vendors report their sales under FSS contracts on an individual-item basis when this is required by such contracts and, when not required, negotiate such

requirements into future FSS contracts when reasonable and practicable.

We also recommend that DOD and VA, to improve reporting, consider using a standardized coding system, such as the National Drug Code, for identifying, in their reports of local purchases, those drugs which do not have Federal stock numbers. This would avoid the possibility under current procedures of either the manufacturer's or possibly some other identification number's being used for a particular drug. In this case data relating to identical items may not be recognized, and as a result, potential items for central management may be overlooked.

AGENCY COMMENTS

DOD stated that all military departments now submit consolidated reports to DMMB for its review and use in evaluating new items for standardization action.

DOD stated also that one of its objectives was a uniform reporting system incorporating the points in our recommendation. However, it considers near-term achievement impracticable and too costly because of the differing systems. DOD further stated that action would be taken to insure that each military department followed standard reporting criteria and that, as soon as practicable and cost effective, a uniform reporting system for all local purchases of pharmaceuticals would be implemented.

VA acknowledged the need for the recommended improvements in its reporting system on field station drug purchases but did not comment on our recommendation to use a standardized drug coding system. DOD stated that it had been considering using the National Drug Code. There has been coordination among the military departments, DSA, and FDA. The intent is to implement either the National Drug Code or a comparable system which will facilitate consolidation of purchase data on pharmaceuticals.

CHAPTER 5

OVERLAPPING QUALITY ASSURANCE ACTIVITIES AND OBSTACLES TO ELIMINATING THEM

FDA monitors the manufacturing practices and conditions under which drugs are made by inspecting the plants of drug firms, reviewing their quality assurance controls, and testing product samples. Under the Food, Drug, and Cosmetic Act (21 U.S.C. 301), antibiotics, insulin, and certain veterinary drugs may not be marketed until FDA has tested each batch for strength, quality, and purity and has issued individual certificates of approval to the manufacturer. For all other drugs, FDA periodically tests products through surveillance sampling programs to insure that the items meet the purity, strength, and identity standards provided in the act.

DPSC and VAMC also operate quality assurance programs to insure that the drugs they buy are acceptable in purity, safety, strength, and other considerations. These programs differ both in qualifying manufacturers as supply sources for drugs and in procedures for insuring that the respective supply systems accept only quality products.

In these circumstances, two or all three agencies could be conducting quality assurance inspections simultaneously at the same plant.

DIFFERENCES IN APPROVING FIRMS TO SUPPLY DRUGS AND IN INSPECTING PRODUCTS

Qualification of suppliers

The DPSC quality assurance program includes evaluating the contractor's ability to supply each required drug. This is done by surveying manufacturing plants and by testing product samples before awarding contracts.

Preaward plant surveys and preaward samples are generally required when a firm's ability to manufacture a specific drug is unknown or a doubt exists about the firm's quality control, housekeeping procedures, or financial position. A manufacturer may be disqualified for failing to satisfy certain requirements of quality control, housekeeping, acceptability of subcontractors, plant capacity, or

financial condition, but the disqualification pertains only for the specific procurement for which the manufacturer failed to meet DPSC requirements. A satisfactory plant inspection or demonstrated ability to manufacture a specific item is not a prerequisite for being placed on the the DPSC bidders list.

Unlike DPSC, VAMC requires that a plant survey or inspection be made of each prospective supplier before it can be placed on the list of approved suppliers for VA contracts, including FSS contracts. Reinspections are made approximately every 5 years, unless required sooner because of customer complaints or other problems.

DPSC and VAMC inspection procedures use standards for manufacturing and processing drugs patterned on the Good Manufacturing Practices published by FDA. However, although VA and FDA standards are essentially the same, DPSC standards are more specific. For example, FDA and VA personnel standards require that persons who direct the manufacture and control of a drug be adequate in number, education, training, and experience to insure that the drug has the safety, identity, strength, quality, and purity that it purports to possess. DPSC standards go further and set specific personnel requirements, qualifications, and responsibilities.

The following table summarizes the results, during fiscal years 1969 through 1971, of preaward surveys by DPSC and plant inspections by VAMC to qualify suppliers for their bidders list.

	DPSC		VAMC	
	Number	Percent	Number	Percent
Qualified	238	53	265	76
Disqualified	213	47	84	24
	451	100	349	100

DPSC disqualifies more manufacturers partially because of its policy of surveying individual products, which may result in disqualifying a firm only for one item being purchased.

Product inspections

After a contract has been awarded, DSA, through the Defense Contract Administration Services, monitors the quality of products being bought by inspecting the contractor's plant during the contract period. This quality assurance concept is designed to determine, before supplies are accepted, that the contractor has fully complied with contractual requirements for product quality.

Detailed instructions give procedures for the Quality Assurance Representatives to follow in inspecting products. Basically, they must review the contractor's manufacturing and testing procedures and verify that control of manufacturing processes is adequate and that deficiencies are corrected. The inspections are performed on a lot-by-lot basis using statistically selected samples. Deficiencies are reported to the contractor. During fiscal year 1971, 67 deficiency reports were issued; copies were sent to FDA.

In contrast to the DSA product inspection system, VAMC requires that items purchased for depot stockage be inspected after receipt in the depot but before Government acceptance. FDA performs these inspections on a cost-reimbursable basis, and they are required for each lot of generic drugs purchased but for only one lot of each brand-name product purchased during the year. Items purchased through FSS contracts are not subjected to any Government inspections other than those normally performed by FDA under the Food, Drug, and Cosmetic Act.

During fiscal years 1969 through 1971, FDA tested for VAMC 544 brand-name drugs and 1,882 generic lots of drugs furnished by commercial suppliers. FDA rejected 78 lots (all generic drugs), or 3.2 percent of all lots inspected.

OBSTACLES TO ELIMINATING OVERLAPPING QUALITY ASSURANCE ACTIVITIES

We discussed the overlapping DOD, VA, and FDA quality assurance efforts with responsible officials. The officials indicated that they were prepared to consider a centralized quality assurance program under FDA direction.

Officials of DOD and VA have reservations, however, and stated that it would be imperative that such a program (1) be at least as effective as their present programs and (2) fully recognize the agencies' special requirements; for example, shelf life and packaging of items for military use.

The FDA Commissioner testified on January 19, 1971, before the Subcommittee on Monopoly, Senate Select Committee on Small Business, that drug inspection by three Federal agencies was duplicative and that the resources used by other agencies for drug inspection should be allocated to FDA.

CONCLUSIONS

The present DSA, VA, and FDA drug inspection systems are not as efficient as they could be, because several Federal agencies survey the plants and inspect the products of the same vendors and sometimes the same items. Also the agencies differ in their degrees of inspection for both plants and products.

DSA makes preaward surveys and in-plant product inspections for the majority of the drugs bought for military use--those items that are centrally managed. However, military hospitals make substantial procurements commercially, either under FSS contracts or from local vendors, of which no inspections are made, other than those by FDA. VA augments FDA inspection to a lesser degree than DSA does and still seems to obtain satisfactory results.

RECOMMENDATION

Advantages should stem from having a single agency responsible for quality assurance activities pertaining to purchases of drugs by Federal agencies. Since FDA has statutory responsibilities pertaining to the manufacture of drugs, it seems to be the logical choice for this centralized responsibility. The additional responsibility should facilitate the performance of its other responsibilities relating to drug manufacturers.

Accordingly, we recommended that the Secretary of HEW; the Secretary of Defense; and the Administrator, VA, review the frequency and type of inspections required and the related staffing, organization, and administration changes

that would be needed to facilitate the transfer to FDA of all quality assurance responsibilities pertaining to purchases of drugs by Federal agencies.

AGENCY COMMENTS

DOD doubted FDA's capability to perform the types of inspections it requires.

VA stated that it would use the service when FDA was capable of performing inspections on a timely basis. HEW stated that it would discuss the requirements, resources needed, and pertinent issues for carrying out our recommendation with the interested agencies, and, if it found that it would be in the best interests of the Government, it would take the necessary actions to arrange for the transfer to FDA of all quality assurance responsibilities pertaining to purchases of drugs by Federal agencies.

We believe there is a demonstrated need for serious consideration of transferring drug procurement quality assurance inspection activities to FDA. Although discussions of requirements, resources needed, and pertinent issues are a first and important step, we believe that such discussions should be held with the objective of exploring alternatives that, if proven feasible, would facilitate the transfer to FDA.

CHAPTER 6

SCOPE OF REVIEW

We limited our review primarily to pharmaceuticals and did not include medical equipment and other supplies. We:

--Reviewed the direct procurement of drugs by Federal agencies.

--Compared selected aspects of the procurement and supply systems of DSA and VA--the two major buyers and suppliers of drugs to Federal medical facilities.

--Evaluated DSA and VA procurement philosophies and practices and determined the extent of interagency coordination and its effect on drug prices paid.

--Reviewed laws and other authorities which control or influence the manufacture, inspection, and sale of drugs.

--Reviewed pertinent policies, procedures, and practices and talked with representatives of organizations involved directly or indirectly in Federal drug procurement.

--Examined records and transactions concerning the matters reviewed.

The organizations we visited or with whose officials we talked were:

DOD:
- DMMB, Washington, D.C.
- Department of the Army:
  - Office of the Surgeon General, Washington, D.C.
  - U.S. Army Medical Materiel Agency, Phoenixville, Pa.
  - Walson Army Hospital, Fort Dix, N.J.
- Department of the Navy:
  - Bureau of Medicine and Surgery, Washington, D.C.
  - Bureau of Medicine and Surgery, Field Branch, Philadelphia, Pa.
  - U.S. Naval Hospital, Philadelphia, Pa.

Department of the Air Force:
Office of the Surgeon General, Washington, D.C.
Medical Materiel Field Office, Phoenixville, Pa.
Malcolm Grow United States Air Force Medical Center, Andrews Air Force Base, Washington, D.C.
DSA:
Headquarters, Cameron Station, Alexandria, Va.
Defense Personnel Support Center, Philadelphia, Pa.

VA:
Department of Medicine and Surgery, Washington, D.C.
VAMC, Hines, Ill.
Veterans Administration Hospital, Washington, D.C.
Veterans Administration Hospital, Hines, Ill.

OTHER ORGANIZATIONS:
Committee on National Formulary, Washington, D.C. (prepares the National Formulary drug compendia)
Committee of Revision, The United States Pharmacopeial Convention, Inc., Washington, D.C. (prepares the U.S. Pharmacopeial drug compendia)
HEW:
Social Security Administration, Washington, D.C.
FDA, Rockville, Md.
GSA:
Federal Supply Service
Arlington, Va.
OMB, Washington, D.C.

We also visited (1) four pharmaceutical firms and examined their records of sales to Federal agencies, to evaluate the agencies' procurement practices, and (2) three private hospitals, to discuss their drug selection, drug procurement, and quality control procedures.

APPENDIX I

COMPARISON OF HIGHEST PRICE PAID UNDER DEFINITE-QUANTITY CONTRACT BY VA OR DPSC WITH THE FSS PRICE FOR DRUGS, MARCH 1968 TO DECEMBER 1969

	Definite-quantity contract		FSS price	Difference	
	Buying agency	Highest price		Amount	Percent
Psyllium hydrophilic mucilloid with dextrose 6505-050-4567	VA	$ 0.87	$ 2.22	$ 1.35	155
Carisoprodol tablets 6505-062-4833	DPSC	3.79	6.60	2.81	61
Isoproterenol hydrochloride (HCL) and phenylephrine 6505-071-7861	DPSC	2.10	2.64	.54	26
Chlorthalidone tablets 6505-074-9914	DPSC	4.19	4.38	.19	5
Quinidine sulfate tablets 6505-138-7400	DPSC	1.96	2.50	.54	28
Tripelennamine HCL tablets 6505-148-9000	VA	6.32	22.41	16.09	254
Chloramphenicol capsules 6505-160-0495	VA	5.41	8.03	2.62	48
Prednisolone tablets 6505-559-6734	DPSC	5.69	10.00	4.31	77
Phenazopyridine HCL tablets 6505-582-5344	VA	32.16	39.84	7.68	24
Sodium diphenylhydantoin capsules 6505-584-2338	VA	2.89	4.65	1.76	61
Pentaerythritol tetranitrate tablets 6505-584-4297	VA	9.05	12.45	3.40	38
Pentaerythritol tetranitrate tablets 6505-597-7341	VA	4.72	8.30	3.58	76
Potassium phenoxymethyl penicillin tablets 6505-656-1612	DPSC	1.60	7.46	5.86	366
Sodium aminobenzoate, sodium salicylate and ascorbic acid 6505-660-1746	VA	7.49	8.81	1.32	17
Pentaerythritol tetranitrate tablets 6505-680-2326	DPSC	15.36	24.90	9.54	62
Nitrofurantoin tablets 6505-685-1972	VA	75.54	180.00	104.46	138
Etholeptazine citrate and aspirin tablets 6505-687-7901	DPSC	14.71	20.50	5.79	39
Propoxyphene HCL capsules 6505-725-6992	DPSC	6.45	13.62	7.17	111
Phenelzine sulfate tablets 6505-753-9702	VA	3.11	3.98	.87	28
Theophylline ephedrine HCL and phenobarbital tablets 6505-753-4766	VA	8.61	23.74	14.13	147
Povidone-iodine solution 6505-754-0374	DPSC	9.86	9.90	.04	-
Ampicillin capsules 6505-770-8343	DPSC	5.40	10.45	5.05	93
Methocarbamol and aspirin tablets 6505-775-5708	DPSC	18.47	21.00	2.53	14
Propoxyphene HCL, aspirin, caffeine and phenacetin 6505-784-4976	DPSC	12.75	28.97	16.22	128
Chlorpropamide tablets 6505-817-2279	DPSC	12.39	17.28	4.89	39
Imipramine HCL tablets 6505-853-4799	DPSC	4.47	4.81	.34	8
Erythromycin estalate capsules 6505-890-1388	DPSC	3.43	14.98	11.55	308
Sodium phosphate and sodium citrate solution	DPSC	.28	.30	.02	7

APPENDIX I

	Definite-quantity contract				
	Buying agency	Highest price	FSS price	Difference Amount	Percent
Sodium coliatimethate for injection 6505-890-1582	VA	$ 3.51	$ 5.23	$ 1.72	50
Carisoprodol tablets 6505-904-3256	VA	4.65	6.40	1.75	37
Dexbrompheniramine maleate and pseudo-ephedrine sulfate tablets 6505-926-9019	DPSC	3.82	6.00	2.18	57
Propoxyphene HCL capsules 6505-458-2364	DPSC	12.38	27.79	15.41	124
Nystatin, gramicidine, neomycin sulfate and triamcinolone 6505-961-5504	VA	1.70	2.05	.35	21
Butalbital, aspirin, caffeine and phenacetin tablets 6505-962-4375	DPSC	8.58	16.40	7.82	91
Propoxyphene HCL, aspirin, caffeine and phenacetin 6505-967-8735	DPSC	6.82	15.92	9.10	133
Isoproterenol sulfate inhalation, nonaqueous 6505-023-6481	DPSC	1.23	1.68	.45	37
Guanethidine sulfate tablets 6505-062-4829	DPSC	6.23	7.84	1.61	26
Triamcinolone acetonide cream 6505-064-3940	DPSC	39.20	48.00	8.80	23
Glyceryl guaiacolate syrup 6505-064-8765	VA	.35	.53	.18	51
Isosorbide dinitrate tablets 6505-072-9346	DPSC	2.03	2.80	.77	38
Glyceryl guaiacolate syrup 6505-079-6269	VA	11.99	15.04	3.05	25
Nitrofurazone ointment 6505-130-1960	VA	2.28	5.10	2.82	124
Neomycin sulfate powder 6505-299-9527	VA	.48	.90	.42	88
Dibucaine ointment 6505-299-9535	VA	.22	.52	.30	136
Test paper and color chart 6505-559-6859	DPSC	.81	1.10	.29	36
Diphenhydramine HCL capsules 6505-582-4868	VA	2.94	7.22	4.28	146
Propantheline bromide tablets	DPSC	14.10	36.00	21.90	155
Promethazine HCL injection 6505-584-3280	DPSC	.63	1.00	.37	59
Perphenazine tablets 6505-584-3669	DPSC	17.15	27.87	10.72	63
Acetone test tablets 6505-616-7861	DPSC	1.48	1.67	.19	13
Chlorpheniramine maleate tablets 6505-655-8460	VA	7.02	27.90	20.88	297
Senna pod extract tablets 6505-656-1468	DPSC	1.27	1.70	.43	34
Triamcinolone acetonide cream 6505-682-8194	DPSC	.86	1.52	.66	183
Meglumine diatrizoate injection 6505-734-0658	VA	1.31	1.81	.50	38
Simethicone aluminum hydroxide gel 6505-735-1742	DPSC	.80	1.10	.30	37
Isosorbide dinitrate tablets 6505-761-1506	DPSC	11.21	15.46	4.25	38
Dipyridamole tablets 6505-764-9014	DPSC	42.93	49.68	6.75	16
Acetylcysteine solution 6505-767-9111	DPSC	4.38	5.60	1.22	28
Isosorbide dinitrate tablets 6505-781-3111	DPSC	6.04	8.33	2.29	38
Oxyphenbutazone tablets 6505-786-8747	DPSC	42.29	49.68	7.39	17
Bisacodyl tablets 6505-889-9034	DPSC	21.98	25.92	3.94	18

APPENDIX I

	Definite-quantity contract				
	Buying agency	Highest price	FSS price	Difference Amount	Difference Percent
Isoxsuprine HCL tablets 6505-890-1321	DPSC	$ 29.99	$ 42.91	$ 12.92	43
Flurandrenalone cream 6505-890-1554	VA	.98	1.25	.27	28
Dioctyl calcium sulfosuccinate capsules 6505-890-1627	VA	32.65	44.80	12.15	37
Fluocinolone acetonide cream 6505-905-9041	VA	24.00	30.60	6.60	28
Sodium ampicillin for injection 6505-946-4700	DPSC	.37	1.10	.73	197
Methenamine mandelate tablets 6505-982-5429	DPSC	3.48	4.65	1.17	34
Fluocinolone acetonide cream 6505-985-7110	DPSC	1.10	1.52	.42	38
Total		$655.31	$1,067.31	$412.00	74

APPENDIX II

ASSISTANT SECRETARY OF DEFENSE
WASHINGTON, D. C. 20301

HEALTH AND
ENVIRONMENT

14 AUG 1973

Mr. Gregory J. Ahart
Director, Manpower and Welfare Division
United States General Accounting Office
Washington, D. C. 20548

Dear Mr. Ahart:

On behalf of the Secretary of Defense we have carefully reviewed the findings, conclusions, and recommendations contained in the GAO Draft Report, dated 1 June 1973, "Opportunities to Improve the Procurement and Supply of Pharmaceutical Drugs" (OSD Case #3636).

The Department of Defense subscribes to the principles set forth in your report that greater cooperation and coordination between the Veterans Administration and the Department of Defense in the development of drug requirements data for procurement purposes, development of common specifications and the possibility of joint procurements for centrally managed common drug items could result in savings to the government. The following discussion provides specific comments on each of the report's recommendation.

DEVELOP POLICIES AND PROCEDURES DESIGNED TO PROVIDE GREATER COORDINATION AND COOPERATION AMONG FEDERAL AGENCIES BUYING DRUGS

As stated in your report, interagency agreements between DoD and civil agencies are now in being which provide for supply support to civil agencies to include centrally managed drug items. Specifically, the following documents are currently in existence relative to interagency support of medical materiel: (a) DoD/GSA Agreement, February 1971, subject: Agreement Between the Department of Defense and the General Services Administration Governing Supply Management Relationships Under the National Supply System; (b) Federal Supply Catalog (C2510 to 9999CA), effective 1 October 1972, a catalog provided by DSA for use by Federal civil agencies which

includes items in Federal Supply Group 65 (Medical Materiel) that are available to civil agencies; (c) DSA/VA Interagency Supply Support Agreement, 4 November 1968, subject: Medical and Non-perishable Subsistence, which provides for DSA support of VA with drug items centrally managed by DPSC. These are evidence of DoD interest in fostering interagency cooperation and coordination in the best interests of the government.

Your report notes that the 1971 DoD/GSA Agreement specifically assigns Government-wide support for medical materiel, which includes pharmaceuticals, to DoD and that the Agreement pertaining to this commodity has not been implemented pending the outcome of a study being led by the Office of Management and Budget. Pending final resolution of this matter DoD is willing to discuss further arrangements to prevent purchases of an item by one agency when the item is available from stock of the other agency, and to obtain the most advantageous prices in the purchase of pharmaceutical drugs.

DEVELOP SPECIFICATIONS ON ITEMS CENTRALLY PROCURED BY VA

DoD will assist the VA in any manner deemed appropriate. The DSA currently provides VA a copy of all specifications developed on pharmaceuticals.

REVISE DOD POLICY ON ADOPTING ITEMS FOR CENTRAL PROCUREMENT

DoD policy provides for central procurement whenever the expected volume/demand indicates a savings will result. There are other factors such as generic equivalency, drug efficacy, expiration periods, and special storage requirements which influence the adoption of pharmaceuticals and must be considered in arriving at the final decision to catalog a pharmaceutical item. The Defense Medical Materiel Board (DMMB) is currently receiving and reviewing consolidated reports on local purchases from the military departments. The Board evaluates this data along with the above mentioned factors in finalizing a decision on standardization. DoD will again review the criteria used and the standardization procedure for cataloging pharmaceuticals to insure compliance with the intent of the basic policy.

APPENDIX II

DEVELOP JOINT DOD/VA SPECIFICATIONS

A joint effort between the VA, GSA, DOD and other federal agencies to use common specifications for drug procurement has been implemented on a limited degree through the Intra-Governmental Professional Advisory Council on Drugs and Devices (IPADD) and the exchange of DoD developed specifications with VA. While this effort results in a separate specification for each agency, the technical data contained in the specification is normally the same for all agencies. Also, a mechanism is currently available to assist in the development of common Federal Specifications. DSM 4120.3M, Defense Standardization Manual, January 1972, prescribes policies and procedures for the preparation of specifications within DoD. In part, this reference states that "Federal specifications shall be developed for materials, products or services, used or for potential use by two or more Federal Agencies, at least one of which is an agency other than DoD. The common policy of the GSA and DoD provides a basis for determining whether a standardization document is eligible for inclusion in the Federal series. DoD policy governs military participation in the preparation and coordination of Federal specifications and standards, and prohibits the issuance of a military document which duplicates a suitable Federal document.

The Defense Medical Materiel Board has the function to maintain liaison and coordinate with the Defense Supply Agency and other government agencies in all professional-technical matters involving medical materiel. This activity will be specifically tasked to coordinate this matter with DSA and VA and recommend appropriate policy/agreements which will provide for the joint coordination/preparation of specifications for medical materiel having common usage within DoD and VA.

ESTABLISH A UNIFORM REPORTING SYSTEM FOR LOCAL PURCHASES

A uniform reporting system incorporating the points contained in your report is a DoD objective. To completely achieve this objective in the near term is considered impractical and too costly since the automated supply systems of the military departments differ and many of the smaller medical supply activities are operating a manual system. Currently the USAF reports all purchases while the U.S. Army and U.S. Navy report high dollar value purchases. As a result

of the DMMB action in April 1972 all military departments submit consolidated reports to the Board for review and their use in evaluating new items for standardization action. Continued action will be taken to insure standard reporting criteria are followed by each military department and that as soon as it is considered practical and cost effective a uniform reporting system for all local purchases of pharmaceuticals will be implemented.

IMPROVE THE VA's DRUG ACQUISITION REPORT

No comment.

CONSIDER UTILIZING A STANDARDIZED CODING SYSTEM

The utilization of the National Drug Code (NDC) for identifying all purchases of non-cataloged pharmaceuticals has been and is under consideration. Coordination with the military departments, Defense Supply Agency and the Food and Drug Administration has been effected and as a result a future meeting is being planned. Several system and other procedural matters remain to be resolved, however, the intent is to implement either the NDC system or a comparable system which will facilitate the consolidation of purchase data for pharmaceuticals.

ASSUMPTION OF THE PHARMACEUTICAL PROCUREMENT INSPECTION FUNCTION BY HEW

Reservation is expressed regarding your recommendation that the FDA assume quality assurance responsibilities pertaining to purchases of pharmaceuticals by Federal agencies. The basic questions as to whether this consolidation would result in savings or whether the FDA would be able to meet the unique ASPR and operational requirement of DoD have not been resolved. The report does not provide a sufficiently detailed analysis for decision concerning these matters, therefore, suggest that the recommendation be modified to require a further examination of the feasibility of consolidating this function. The fundamental concerns of DoD are responsiveness to the needs of the military departments and the maintenance of an effective quality assurance program. DoD cannot concur in any course of action which would fragment the current integrated procurement

APPENDIX II

and quality assurance system or detract from the high quality inspection standards currently maintained.

We appreciate the objectivity and the many helpful comments regarding means to improve the procurement and supply of pharmaceuticals contained in the draft report.

George J. Hayes
Major General, MC USA
Principal Deputy

APPENDIX III

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

SEP 18 1973

Mr. Gregory J. Ahart
Director, Manpower and
Welfare Division
General Accounting Office
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your letter of June 1 which requested our views and comments on your draft report to the Congress entitled, "Opportunities to Improve the Procurement and Supply of Pharmaceutical Drugs". As you may know, Department officials met with General Accounting Office representatives to discuss the report; in particular, the conclusions reached that the Food and Drug Administration of this Department should assume quality assurance responsibilities pertaining to purchases of pharmaceutical drugs by Federal agencies.

This will confirm for your records that we agreed to discuss this matter with other interested agencies (Defense and Veterans Administration). At such time we will determine their particular requirements; discuss the resources needed; and other like pertinent issues. If, based on these discussions we find it will be in the best interest of the Government to do so, we will take such actions as are necessary to arrange for transfer to FDA all quality assurance responsibilities pertaining to purchases of pharmaceutical drugs by Federal agencies.

The opportunity to review this report in draft form has been much appreciated.

Sincerely yours,

James B. Cardwell
Assistant Secretary, Comptroller

APPENDIX IV

VETERANS ADMINISTRATION
OFFICE OF THE ADMINISTRATOR OF VETERANS AFFAIRS
WASHINGTON, D.C. 20420

JULY 25 1973

Mr. Frank M. Mikus
Assistant Director, Manpower
and Welfare Division (801)
U. S. General Accounting Office
Room 137, Lafayette Building
811 Vermont Avenue, N. W.
Washington, D. C. 20420

Dear Mr. Mikus:

We have reviewed your draft report entitled "Opportunities to Improve the Procurement and Supply of Pharmaceutical Drugs - Department of Defense and Veterans Administration" (Code 88016).

We agree with the major recommendation that there should be greater cooperation and coordination among Federal agencies buying drugs. Since the actual items involved will be determined by the nature of the programs served and will reflect the differences in mission, the degree of standardization will be limited by those factors. However, this should not limit other advantages to the Government which would stem from a viable program of interchange of procurement and supply techniques, ideas, and innovations.

The report rests heavily on the premise that consolidation of the agencies' requirements will result in larger quantities purchased at lower prices, and that a mandatory requirement for use of control stocks would be economical. However, the need should be stressed to consider all costs involved in procurement decisions. Savings would not result until the centralized agency sources prove to (1) be economic in terms of their location and number, (2) price their items to recover all costs to the Government, and (3) be competitive with alternate sources of supply. It is possible that more consideration would need to be given to shelf-life, special packaging, and labeling for respective agencies before blanket standards could be set and before specific savings could be ascertained.

APPENDIX IV

Mr. Frank M. Mikus
Assistant Director, Manpower
and Welfare Division
U. S. General Accounting Office

Also, the coordination of stock requirements and monitoring of stock levels could offset some of the advantages of inventory consolidation. [22][1]

With regard to the recommendation on page 34b, we consider the joint development of specifications or the mutual use of existing specifications as an important element of the increased interagency cooperation advocated by this report.

We acknowledge the need for improvement of our reporting system on field station acquisitions, as recommended on page 40.[28] With reference to the recommendation on page 50,[33] the VA will utilize such service exclusively when the Food and Drug Administration is capable of performing inspections on a timely basis and furnishing us with copies of its reports.

With reference to the leadership role of the Office of Management and Budget, we have been informed that all OMB personnel involved with supply programs and management were recently transferred to the General Services Administration. This reorganization could have a marked effect on future interagency coordination efforts. [6][1]

On page 13 of the report, 182 is listed as the number of medical facilities supported by VA; apparently, no credit has been given to our serving other civil agencies, under the GSA assignment, which would raise the VA total to approximately 450. Also, on the same page, under the "Drug Inventory" entry, it should be noted that VA's central stocks are turned four times a year, instead of twice as is the case with the Defense Personnel Support Center. [7][1]

On page 14 of the report, reference is made to a review which preceded a February 1971 agreement between the General Services Administration and the Department of Defense. Having understood, from involvement in studies previous to that date, that we, as a party of interest, would be involved in any future determinations, we were surprised by the February 1971

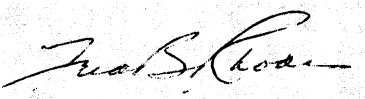
APPENDIX IV

Mr. Frank M. Mikus
Assistant Director, Manpower
and Welfare Division
U. S. General Accounting Office

action. We have not been able to determine what studies were made and would appreciate a copy of the review.

Thank you for the opportunity to review this draft. If you have any questions concerning our comments my staff will be available.

Sincerely,



FRED B. RHODES
Deputy Administrator

GAO note 1: Numbers in brackets refer to page numbers in this final report.

APPENDIX V

UNITED STATES OF AMERICA
GENERAL SERVICES ADMINISTRATION
WASHINGTON, D.C. 20405

JUL 6 1973

Honorable Elmer B. Staats
Comptroller General of the
United States
General Accounting Office
Washington, D.C. 20548

Dear Mr. Staats:

Thank you for the opportunity to comment on the draft report to the Congress on "Opportunities to Improve the Procurement and Supply of Pharmaceutical Drugs."

The draft report cites efforts to improve the management of medical material made by the General Services Administration (GSA) and other Federal agencies in the past and in conjunction with the recent Office of Management and Budget study of medical and nonperishable subsistence commodities. In addition, the General Accounting Office report should note that GSA currently is working closely with the Veterans Administration (VA) on a project to improve the present method of procuring drugs.

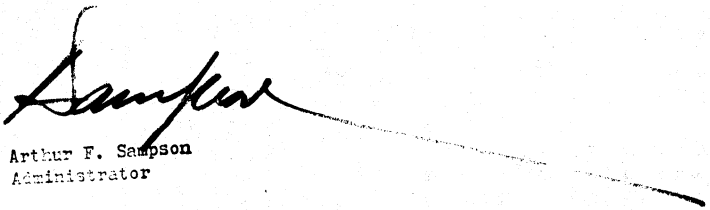
A coordinated study has been made to identify high dollar volume items and to utilize this information to improve the method of contracting. We are also addressing ourselves to the feasibility of developing a continuing system for accumulating demand data to support continued efforts to improve our contracts.

The collection of data on high dollar volume drug items required developing coding techniques for item identification. The preliminary experience and information gained on this study should be useful

APPENDIX V

Although we have assigned the procurement responsibility for drugs and pharmaceuticals to the VA, we do retain broad responsibility for management of this class and are very much concerned about the resolution of the problems outlined in your report.

Sincerely,



Arthur F. Sampson
Administrator

APPENDIX VI

EXECUTIVE OFFICE OF THE PRESIDENT
OFFICE OF MANAGEMENT AND BUDGET
WASHINGTON, D.C. 20503

JUL 20 1973

Mr. Gregory J. Ahart, Director
United States General Accounting Office
Washington, D.C., 20548

Dear Mr. Ahart:

This is in response to your letter to the Director requesting our comments on the GAO draft report entitled "Opportunity to Improve the Procurement and Supply of Pharmaceutical Drugs."

We are in general agreement with the thrust of the draft report that significant improvements can be made and economies achieved in the procurement, inspection, storage and supply of pharmaceutical drugs. While we have no objection to the recommendation in the draft report that the Office of Management and Budget take the leadership in an interagency effort to effect these improvements, it should be pointed out that such an effort has been underway for some time under OMB leadership, and we expect the results to provide the basis for decisive action with respect to the procurement and supply of medical material and nonperishable subsistance as well as drugs and pharmaceuticals.

The conclusions and recommendations contained in the draft report with respect to the consolidation of requirements, single procurement, central storage and inventory management seem more far-reaching than a careful examination of the facts may warrant. Specifically, we question whether there is adequate support for the conclusion that mere consolidation of requirements would assure more economical procurement. The analysis in the draft report of the reasons for different prices received by DOD and VA for similar purchases does not indicate that the lower price in each instance was related to a larger quantity procurement.

APPENDIX VI

If, as the facts seem to indicate, the lower prices were due to other causes, then the act of consolidating procurement would be not only an inappropriate response to the problem but would also remove the advantage of the current practice which permits the measuring of relative cost effectiveness of the DOD and VA supply support operations through comparative examination of the competing systems. We do not question that some savings can normally be achieved by consolidating requirements, but we believe the procurement system or technique used in many instances can have even greater impact on the total economic cost of the procurement. It would seem preferable to seek the best from each of the procurement systems and only after these are identified for incorporation in a single system should we recommend consolidated procurement with reasonable assurance that it would be an appropriate and timely step.

In addition to the above, we would also suggest that further consideration be given to portions of the draft report which encourage central storage and issue as the means of providing supply support. By omitting any recognition of the expenses of the Government that should be weighed in comparing costs of local purchase versus central storage and issue the draft report would give undue emphasis to the latter method of support to the detriment of total cost effectiveness. The omission in the draft report is one that commonly occurs in Government according to the report of the Commission on Government Procurement. In Part D, Chapter 6 of the Commission's report which deals with total economic costs, the Commission states its finding that the practice throughout the Government in the procurement of commercial products was to focus on the price paid the supplier rather than on the total cost of satisfying a requirement. The result, according to the Commission, is that"the Government has failed to develop the data and techniques needed to measure the total economic cost of fulfilling a Government need." Generally, these costs should include the price of the product, procurement personnel costs, warehousing, distribution, obsolescence, taxes foregone, and costs arising through use or consumption.

Failure of the draft report to give consideration to these factors results in a stronger preference for central storage and issue than may be justified. As a minimum, it would seem desirable for the draft report to refer to the results of the Commission's extensive study in this problem area.

We appreciate this opportunity to comment on the draft GAO report. If you would like to discuss this matter with OMB staff or if there are any questions regarding the above comments, please contact Mr. James D. Currie, 395-5193.

Sincerely,

Dudley C. Mecum

Dudley C. Mecum
Assistant Director
Management and Organization

32-814 (Pt. 24) O - 74 - 46

APPENDIX VII

PRINCIPAL VA AND DOD OFFICIALS RESPONSIBLE FOR THE MAJOR PORTION OF THE DIRECT PURCHASES OF PHARMACEUTICALS FOR THE GOVERNMENT

	Tenure of office	
	From	To
VETERANS ADMINISTRATION		
ADMINISTRATOR OF VETERANS AFFAIRS:		
Donald E. Johnson	June 1969	Present
DIRECTOR, SUPPLY SERVICE:		
Donald P. Whitworth	Jan. 1965	Present
DEPARTMENT OF DEFENSE		
SECRETARY OF DEFENSE:		
James R. Schlesinger	July 1973	Present
Elliot L. Richardson	Jan. 1973	July 1973
Melvin R. Laird	Jan. 1969	Jan. 1973
ASSISTANT SECRETARY OF DEFENSE (HEALTH AND ENVIRONMENT) (note a):		
Dr. Richard S. Wilbur	Aug. 1971	Present
Dr. Lewis H. Rousselot	Jan. 1968	July 1971
DIRECTOR, DEFENSE SUPPLY AGENCY:		
Lt. Gen. Wallace H. Robinson, Jr., USMC	Aug. 1971	Present
Lt. Gen. Earl C. Hedlund, USAF	July 1967	Aug. 1971
COMMANDING OFFICER, DEFENSE PERSONNEL SUPPORT CENTER:		
Maj. Gen. Abraham J. Dreiseszun, USAF	July 1972	Present
Maj. Gen. Robert E. Hails, USAF	Aug. 1971	July 1972
Col. Donald J. Bussey, USAF	June 1971	Aug. 1971
Brig. Gen. William M. Mantz, USAF	Nov. 1967	May 1971

APPENDIX VII

	Tenure of office	
	From	To
DEPARTMENT OF THE ARMY		
SECRETARY OF THE ARMY:		
Robert F. Froehlke	July 1971	Present
Stanley R. Resor	July 1965	June 1971
SURGEON GENERAL:		
Lt. Gen. H. B. Jennings, Jr.	Oct. 1969	Present
DEPARTMENT OF THE NAVY		
SECRETARY OF THE NAVY:		
John H. Chafee	Jan. 1969	May 1972
John W. Warner	May 1972	Present
SURGEON GENERAL OF THE NAVY:		
Vice Adm. George M. Davis	Feb. 1969	Feb. 1973
Vice Adm. D. L. Custis	Feb. 1973	Present
DEPARTMENT OF THE AIR FORCE		
SECRETARY OF THE AIR FORCE:		
Robert C. Seamens, Jr.	Jan. 1969	Present
SURGEON GENRAL:		
Lt. Gen. Robert A. Patterson	Aug. 1972	Present
Lt. Gen. Alonzo A. Towner	May 1970	July 1972
Lt. Gen. K. E. Pletcher	Dec. 1967	Apr. 1970

[a] This position was formerly entitled "Deputy Assistant Secretary of Defense (Health and Medical)" under the Assistant Secretary of Defense (Manpower and Reserve Affairs). The change was effective in June 1970. Dr. Rousselot occupied the position under both titles.

EXHIBITS PROVIDED BY THE FOOD AND DRUG ADMINISTRATION

STATEMENT

BY

ALEXANDER M. SCHMIDT, M.D.

COMMISSIONER

FOOD AND DRUG ADMINISTRATION

PUBLIC HEALTH SERVICE

DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

BEFORE

THE

SUBCOMMITTEE ON MONOPOLY

SELECT COMMITTEE ON SMALL BUSINESS

UNITED STATES SENATE

FEBRUARY 20, 1974

Mr. Chairman:

We are pleased to have this opportunity to appear this morning to discuss Food and Drug Administration drug quality assurance programs and the effect these programs may have on other Government agencies involved in drug procurement and reimbursement.

FDA QUALITY ASSURANCE PROGRAMS

Let me begin by stating that the pharmaceutical industry must bear the primary responsibility for assuring the production of high quality drug products. The Food and Drug Administration's (FDA) role is to assure that manufacturers meet this responsibility. We do so by setting appropriate standards for the manufacture of drugs, and by carrying out surveillance activities such as factory inspections and analysis of selected products. When firms do not meet their responsibilities, the Federal Food, Drug, and Cosmetic Act (FDC Act) provides us with authority to take certain measures to bring about correction and/or to remove offending products from the market.

Our quality assurance programs for drugs are aimed at providing optimal assurance of drug quality to all physicians and consumers. These programs employ a major portion of our field manpower available for drug work and range in approach from continuing surveys of the manufacturing practices of selected drug firms, to intensified targeted programs such as certification of specific products or plant inspection and analyses involving a certain product with identified problems.

Inspection of Drug Manufacturing Establishments

The Federal Food, Drug, and Cosmetic Act requires inspection of every drug firm at least once every two years. A major portion of our field inspection time is expended in our efforts to comply with this mandate. In FY 1973, we inspected 2,700 registered human drug establishments and made some 7,000 inspections of registered and related drug establishments. This level of inspectional activity will be maintained during the current fiscal year. It will allow us to inspect not only those firms with identifiable problems, but also 97 percent of major manufacturers of prescription legend drugs, responsible for about 95 percent of marketed prescription legend drugs.

A primary objective of the inspectional program is to determine whether drug manufacturers are following what the law refers to as current good manufacturing practices (GMP's). GMP's are spelled out in regulations, and serve to guide our inspectors when reviewing plant operations.

In addition to providing routine surveillance on a scheduled basis, GMP inspections may be made on a selective basis. We often schedule inspections as a result of information obtained from our own product analysis, or other reports of defective products. A pending new drug application or request for certification of an antibiotic by a firm may also trigger an inspection, as a determination of compliance with GMP is a required condition for approval.

Monitoring Marketed Drugs

A second basic approach to assuring the quality of drugs is a monitoring program involving the sampling and analysis of marketed drugs to determine their adherence to compendial standards, as well as standards established in New Drug Applications (NDA).

Criteria used in selecting drugs for examination are:

--Therapeutic Significance - drugs prescribed for serious conditions or diseases.

--Complexity of Compounding - for instance, drug products in which the active ingredient of a potent drug makes up a small portion of the total weight of a solid dosage form.

--Product History - drugs for which quality failures have occurred, or which have a potential for degradation or decomposition.

The objectives of this program are to:

--Identify defective batches of drug products and remove them from the marketplace.

--Help determine the reasons for batch failures and assure that manufacturing procedures are corrected as necessary to eliminate the problems.

--Provide a means for measuring changes in the quality of drugs and the relationship of such changes to FDA actions.

--Provide a statistically valid evaluation of the quality of selected drugs under study.

The analytical work under this program is carried out by FDA's National Center for Drug Analysis in St. Louis or one of our 18 field laboratories. Where feasible, drugs of similar composition are assigned to a single laboratory for analysis, increasing laboratory efficiency by permitting use of mass production techniques. During FY 73, we analyzed over 9,000 human drug samples. During the current fiscal year, we plan to analyze 15,000 samples of human drugs. In general, we have found that only a small percentage of drugs analyzed are defective. All those that are defective are followed-up by our field offices to remove them from the market and to ascertain the cause of the defect. Also, we publish the results of our drug quality surveys in the FDA Drug Compliance Information Letter, a copy of which I would like to submit for the record.

When our monitoring activities reveal problems with an entire class or type of drug, specific intensive programs are established. Our recent efforts to assure digoxin content uniformity and dissolution and sterility of large volume parenteral solutions (LVP) are examples of such programs.

In 1970, to assure digoxin content uniformity, we established an industry-wide voluntary certification program. Until a firm

demonstrated that it could consistently manufacture digoxin in compliance with standards, it had to obtain a batch-by-batch analysis and FDA release prior to marketing.

When we later received information concerning variation in bioavailability of digoxin manufactured by different firms, and a new United States Pharmacopeia (USP) dissolution rate standard was adopted, we instituted a certification program similar to that employed in the content uniformity problem.

New regulations pertaining to the marketing of digoxin became effective on January 22, 1974; a copy is submitted for the record. The regulations require batch-by-batch certification of digoxin until the firm demonstrates that its product consistently meets the new USP dissolution standards. These regulations also require that all firms intending to continue the marketing of digoxin must present evidence of bioavailability within 180 days after filing such notice of intent.

In the case of the large volume parenterals (LVP), we instituted a special program in response to continuing reports of nonsterile products. The program evaluates the quality control and manufacturing procedures in all plants of all firms producing large volume parenterals in the United States. Ten manufacturing plants, representing the four manufacturers (Abbott, Baxter, McGaw, and Cutter) were inspected during May and June of 1973.

After careful evaluation of the inspection reports and review of the scientific literature pertaining to principles of sterilization, etc., we met with the individual firms during September and October of 1973. In these technical sessions, we identified problem areas and separated them into those which could and should be corrected immediately and those which would require longer-term improvements in production practices.

The FDA then prepared summary papers identifying the significant problem areas and proposed solutions. These have subsequently been commented upon by each firm, and we have now prepared a summary document designed to establish common standards for the industry as a whole.

The latter has been submitted to all the firms (in January 1974) for final comment. The FDA expects that from this program will evolve specific guidelines for FDA inspections of LVP manufacturers and revisions of our good manufacturing practice regulations.

Drug Product Defect Reporting Program

Another program for monitoring drug quality is a joint effort involving various pharmaceutical associations, the United States Pharmacopeia and FDA. Under this program, pharmacists across the Nation report apparent product defects or problems to the USP.

Copies of these reports are furnished to the manufacturer or other distributor of the product in question, and to FDA. Based on evaluation of these reports, we issue investigatory assignments to the field when indicated, or in some cases institute special programs or surveys.

During FY 1973, we received 2,750 program reports. The program is expanding at a rapid rate as demonstrated by the fact that we have already received 2,350 reports for the first half of FY 1974.

The kind of correction this program may bring about is illustrated by the interesting story of nitroglycerin. A pharmacist questioned the suitability of a plastic, pen-shaped container for nitroglycerin tablets. Our investigation revealed that the drug was rapidly absorbed into the container walls and after 30 days only seven percent of the tablet potency remained, i.e., the drug was practically worthless. FDA contacted the manufacturer and the plastic, pen-shaped containers were recalled.

We have since issued a regulation requiring that nitroglycerin be packaged in glass containers and dispensed only in the original unopened container.

ADDITIONAL ACTIVITIES CARRIED ON BY FDA TO ASSURE UNIFORMLY HIGH DRUG QUALITY

In conjunction with our total quality assurance program, the Agency conducts a number of programs which help assure a uniformly high quality for the Nation's drug supply, including:

Establishment and Product Inventory

Essential to any national drug quality assurance plan is full information concerning the pharmaceutical industry and its drug products. This is necessary in order to plan and schedule work assignments efficiently and accurately, both at the headquarters and regional levels, and to evaluate our performance.

As you know, all drug manufacturers must register annually with FDA. During the past two years we have improved our data systems and we continuously review our Official Establishment Inventory list of registered firms to verify its accuracy and to insure that all registered firms are active.

The Drug Listing Act of 1972 authorizes us for the first time to require information that will result in a comprehensive inventory of all marketed pharmaceutical products. We are currently processing submissions under this Act and expect this file to be active within a few months. This will provide an important resource for other agencies, as well as for the FDA, and will enable us to use in other areas field manpower formerly needed for gathering information on drug products.

New Drug Approval

As you of course know, all new drugs introduced into the market since 1938 must be shown to be safe and effective. What is less well known, perhaps, is that the approval process also applies to quality control procedures and other manufacturing practices. Before a new drug application may be approved, our Bureau of Drugs must have assurance, through inspections, that the applicant can and will manufacture the drug under conditions of current good manufacturing practice. In addition, the new drug approval imposes requirements for the maintenance of certain records, including periodic reports regarding clinical experiences with the drug. Important changes in manufacturing processes or controls must be approved by the FDA before they can be implemented. The new drug approval process is therefore an important and essential part of our overall quality assurance program.

Drug Efficacy Study Implementation (DESI)

Under the Federal Food, Drug, and Cosmetic Act enacted in 1938, safety was the sole consideration for obtaining approval to market a new drug. The Drug Amendments of 1962 extended the requirements

to include substantial evidence of effectiveness and also required a review of the effectiveness of all drugs approved between 1938 and 1962.

The Food and Drug Administration contracted with the National Academy of Sciences/National Research Council (NAS/NRC) to carry out a review of the pre-1962 drugs and we have used the results of the NAS/NRC advisory study in making our own final determinations of efficacy.

As a result of this program, some 5600 ineffective drug products have been removed from the market, ineffective indications for use have been deleted from drug labeling, and where drugs have been shown to be possibly or probably effective, manufacturers have been provided an opportunity to supply data that will establish their effectiveness.

In addition, manufacturers of many products not previously covered by new drug applications (NDA) have been required to submit abbreviated NDA's. Before such applications are approved, we require compliance with current good manufacturing practice regulations. As in the case of NDA submissions, this is determined by a plant inspection. This program has greatly increased our inspection activities in small and medium-size firms in the past and has resulted in substantial improvement in compliance

with the requirements of the good manufacturing practice regulations.

This program also has improved and promoted the exchange of information between FDA and Defense Personnel Support Center (DPSC) regarding drug efficacy status and has a marked influence on the purchasing policies of of various Government agencies such as the DPSC. The impact of the program is remarkably broad. For example, the Secretary of DHEW has directed that Federal funds will not be expended for the purchase of drugs classified under the DESI program as no greater than "possibly effective" for use in certain of the Department's programs, such as Direct Care Programs, Contract Care Programs, and Federal Grant Programs.

With the Drug Enforcement Administration (which includes the former Bureau of Narcotics and Dangerous Drugs) we have established procedures for implementing the large-scale DESI review follow-up action against amphetamine-containing drugs not in compliance with current requirements (regulation 130.46).

These drugs are under the jurisdiction of both DEA and FDA. Although this cooperative action has not been completed, some 1,755 amphetamine-containing drugs manufactured by 351 firms have been effectively removed from the market. This regulatory action involved 549 drug recalls and also five seizure actions under the FDC Act. With cooperating State

health officials, a high degree of success has been achieved in the removal of these violative drugs from pharmacy shelves throughout the country.

Liaison for exchange of DESI Program information has been established with the Chief Pharmacy Officer, Public Health Service. In addition, we have received numerous communications from State, foreign government, and United Nations health officials about drug status under the DESI Review Program. Copies of the DESI announcements are routinely forwarded to several Government agencies.

Batch Certification

The Federal Food, Drug, and Cosmetic Act requires that samples of each batch of antibiotics and insulin be tested and certified by FDA before these products are released for sale. Batch certification is also imposed for other products when it is needed to assure uniform quality. As previously discussed, digoxin has been subjected to batch certification since our drug surveillance program revealed significant variances from official standards.

Current Good Manufacturing Practice Regulations (GMP)

FDA regulations set standards for the facilities and conditions under which drugs are manufactured. Because good manufacturing practices should be "current" and change as drug technology changes, these regulations are periodically updated. The regulations were last revised

in 1970 and are currently under further revision. Among changes being actively considered is a requirement that all drug products bear an expiration date based on adequate stability data, and also addition of GMP regulations for specific classes of products such as large volume parenterals.

Bioavailability and Bioequivalency

It has been shown in recent years that in a few instances chemically equivalent drugs, even though they meet all official standards, produce significantly different blood levels in man. In scientific terms they differ in bioavailability or, to use another term, they are lacking in bioequivalency.

To assure the bioequivalency of chemically equivalent drugs we are taking three steps:

First, we will shortly publish in final form regulations describing standards and procedures to be followed in conducting bioavailability studies.

Second, we will shortly publish proposed regulations requiring bioavailability studies for all drugs of the following kinds:

--Those for which the precise dosage is particularly critical and where a bioavailability problem would create a health hazard.

--Those formulations with previously documented biovailability problems.

And last, we will also publish in the near future a notice concerning the procedures we will follow in calling for and reviewing data about the potential for bioavailability problems with other drugs (i.e., those without previously well-documented bioavailability problems).

In my opinion, the issue of bioequivalency is being overdrawn. As we have learned more about non-equivalency problems, it has become clearer that they are limited in number and are manageable.

RELATIONSHIP WITH OTHER GOVERNMENT AGENCIES

Many Government agencies are involved in the procurement of drugs. An organization called the Intra-Governmental Professional Advisory Council on Drugs and Devices (IPADD) was established to provide these agencies with a forum for the timely interchange of medical-technical information, and, through cooperative efforts, to improve the quality of drugs furnished to the agencies. Types of information exchanged include specifications, standards, and those involving quality control and inspection. FDA is a charter member of IPADD.

Working groups have been established within IPADD for indepth exploration of appropriate subjects and areas. These groups meet every 4 to 6 months, which provides an opportunity for informal contact and exchange of information of mutual interest.

FDA supplies the Defense Personnel Support Center (DPSC) with copies of FDA Daily Action Reports identifying all seizures, prosecutions, injunctions, and recalls involving drugs. Since September of 1973, we have also been supplying DPSC with unevaluated copies of all Notices of Observations, the form supplied to all drug firms by our inspectors at the end of inspections. These documents represent the individual inspector's raw unreviewed observations.

Representatives of the Bureau of Drugs maintain frequent contact with the various Federal purchasing agencies and continually respond to inquiries, both written and telephone, from DPSC, Defense Medical Material Board, Veterans Administration (VA), General Services Administration, and Public Health Service Stock Pile Management, concerning firms and products. These inquiries generally involve such matters as the adequacy of labeling, "new drug" status, FDA inspectional and laboratory results, and tests, procedures, or other data in new drug applications that have been submitted to us.

In addition, when a drug is to be recalled from the market and we determine from distribution reports that the firm has supplied the drug to DPSC, VA, or other Government agency, FDA notifies that agency of the recall. It is then the responsibility of that agency to insure appropriate recall of the drug under its control.

When we receive a report through our Drug Defect Reporting System, the DPSC is notified whenever the report originated from a Federal hospital or other Federal installation, and also where a "Federal Stock Number" is part of the labeling of the product.

GENERAL ACCOUNTING OFFICE (GAO) REPORTS

The Food and Drug Administration has completed actions to implement the recommendations of the March 1973 GAO report on Enforcement of Good Manufacturing Practices for Drugs. We have developed a monitoring system to identify (1) new drug firms that require inspection, (2) existing firms that failed to reregister for the current year, and (3) firms that require an inspection to fulfil the statutory requirement for biennial inspection. In addition, FDA has revised the Administrative Guideline for GMP's to provide more specific guidance to FDA personnel in determining the need for regulatory action. That guideline is under current consideration for further revision.

The more recent GAO report (December 1973) on Improving the Federal Procurement of Drugs recommended that the separate quality assurance activities of the Department of Defense, the Veterans Administration and FDA should be consolidated into a single organization. We believe this is a sound recommendation that will enhance the efficiency of Federal quality assurance efforts. We also feel that the Food and Drug Administration is the most logical focal point for this responsibility.

To explore the feasibility of consolidation, we have already held discussions with representatives of the Assistant Secretary of Defense (Health and Environment) and the Veterans Administration. These discussions are continuing.

We have requested from Department of Defense (DOD) and VA information as to precisely what resources they now expend for drug quality assurance. We expect that within 30 days of receipt of such data, we can prepare and circulate a proposed program to both those agencies.

CONCLUSION

At the present time, FDA directs essentially all of its human drug budget, approximately $43 million, to assuring that the drugs in the marketplace are safe and effective. During the last two years,

we have analyzed thousands of drug samples in both certification and surveillance programs, and have inspected 97 percent of those manufacturers of human prescription legend drugs who are responsible for about 95 percent of the marketed drugs. We believe that the impact of our quality assurance programs on the drug industry has made that industry one of the most quality-control conscious industries in the country. This has resulted in a drug supply for this Nation that is of the highest quality in the world.

We plan to take any necessary measures to further strengthen our quality assurance program in the months ahead. We know we will find problems in the future and this is to be expected. When they are found, we will correct them, and thereby take one more step toward the goal of a consistently and uniformly high quality drug supply.

We will be pleased to respond to any questions you or your Subcommittee may have.

FDA DRUG COMPLIANCE INFORMATION LETTER

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE
Public Health Service
FOOD AND DRUG ADMINISTRATION
Bureau of Drugs
Office of Compliance

February 28, 1973

TO: Manufacturers, Repackers, and Relabelers of Drug Products

RE: Drug Surveillance Reports

The Food and Drug Administration, as part of its regulation of the American drug supply, routinely conducts drug quality surveys. FDA now intends to publish the results of its drug quality surveys, and to send copies to all manufacturers, repackers and relabelers of drug products. In this way, the industry will be advised concerning FDA's laboratory findings on batches of different classes of marketed drugs. This is in line with FDA's attempts to provide to the public and the regulated industries as much valuable information as it can within the scope of the Freedom of Information Law. It is hoped that information of this nature will lead to better compliance by regulated industries. Each report will include pertinent information such as scope of survey, sampling information, laboratory tests and summary of results.

The analytical methods used are either those specified by the United States Pharmacopeia (U.S.P.) and National Formulary (N.F.), or automated procedures developed by FDA or adapted from published methods and validated. Many of the methods may be found in the FDA's "Drug Autoanalysis Manual," available from the Division of Industry Liaison. Samples analyzed and found defective by non-official methods are check-analyzed by U.S.P., N.F., or other official methods such as those of the Association of Official Analytical Chemists (AOAC). Defective samples are followed up by FDA Field Offices so as to remove offending batch(es) from the market either by legal action, voluntary recall, or destruction, or cooperative action by State or local authorities.

Test results may or may not be indicative of the quality of other lots of the same product or other products produced by the listed manufacturer.

The first survey report is on central nervous system stimulants.

T. E. Byers, Director
Office of Compliance
Bureau of Drugs

REPORT ON CENTRAL NERVOUS SYSTEM STIMULANTS

Scope of the Survey

This survey covered Dextroamphetamine Sulfate Tablets U.S.P. XVIII, marketed as a single active ingredient product in tablet form in the following dosages: 2.5 mg., 3.0 mg., 4.0 mg., 5.0 mg., 10.0 mg., 12.0 mg., and 15.0 mg.

Of the 24 domestic formulators known to produce Dextroamphetamine Sulfate Tablets, samples of batches from 22 firms were collected in this survey. FDA's District Offices reported a total annual production between September 1, 1970, and September 1, 1971, by all 24 firms of about 104 million Tablets representing 175 batches. Batches varied in size from slightly less than 100,000 Tablets to slightly more than 2,000,000 Tablets. Fifty-two batches from 22 firms or 30 percent of all batches were tested. This represented a range of from 6 to 100 percent of the batches produced by individual firms. The output of two firms, Cord Laboratories and Riverton Laboratories, was unavailable for sampling.

Sampling Information

Samples were collected under FDA's FORDS (Formulator-Oriented Rx Drug Studies) Program from the formulators (manufacturing plant or primary distribution warehouse) or from their branch warehouses or major accounts. No collections were made at locations more than once removed from the manufacturer. Samples were collected from batches released for distribution by the firms' quality control.

Laboratory Tests

Sufficient tests were conducted to determine whether samples met compendial requirements. Individual Tablets were analyzed by a semiautomated procedure as described under Method No. 3 of the FDA Drug Autoanalysis Manual. Testing was performed on each of six sub-samples from each batch. Where outside of compendial limits, results were verified by the U.S.P. Method.

Summary of Results

Of the 52 samples analyzed (see Table 1) two samples, one 5 mg. and the other 10 mg. Tablets, were found defective with a sample defect rate for the survey of 3.8 percent. No samples of other dosage strengths were defective.

Table 1.--Testing Results "FORDS" Study
Dextroamphetamine Sulfate Tablets U.S.P. XVIII

[Survey Period - September 1971-January 1972]

Manufacturer	Declared potency (mg.)	Number batches sampled and analyzed	Number defective samples
American Pharmaceutical Co.	5	2	0
George N. Bell, Mfg. Chemists	5	2	0
Bolar Pharmaceutical Co.	5	4	0
	10	2	1 (a)
	15	3	0
The C. M. Bundy Co.	5	1	1 (b)
Columbia Pharmaceutical Corp.	5	1	0
	15	1	0
Don Hall Labs., Inc.	2.5	1	0
	5	1	0
	10	1	0
E. W. Heun Co.	3	1	0
	5	3	0
	10	1	0
Invenex Pharmaceuticals	5	1	0
	10	1	0
Kasar Labs.	5	1	0
Kirkman Labs., Inc.	5	1	0
The Lannett Co., Inc.	5	1	0
Linden Labs., Inc.	15	1	0
Mills Pharmaceuticals, Inc.	5	1	0
Philips Roxane Labs., Inc.	5	1	0
Premo Pharmaceutical Labs., Inc.	5	2	0
Rondex Labs., Inc.	5	1	0
Smith, Kline, & French Labs.	5	8	0
Stayner Corp.	5	1	0
Towne, Paulsen & Co., Inc.	5	1	0
	10	2	0
West-Ward, Inc.	5	1	0
West Coast Labs.	4	1	0
	12	1	0
The Zemmer Co.	10	2	0
Totals		52	2

(a) Defective due to subpotency (88.8% of declared), and lack of content uniformity (three tablets; 84.5%, 83.3%, and 84.8% of declared). Lot destroyed under State supervision. (b) Defective due to lack of content uniformity (two tablets; 128.6% and 116.8% of declared). Lot voluntarily removed by manufacturer from distribution channels.

FDA drug compliance information letter

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • Public Health Service • FOOD AND DRUG ADMINISTRATION
Bureau of Drugs • Office of Compliance

May 7, 1973

TO: Manufacturers, Repackers, and Relabelers of Drug Products

RE: Drug Surveillance Reports

The Food and Drug Administration, as part of its regulation of the American drug supply, routinely conducts drug quality surveys. FDA now intends to publish the results of its drug quality surveys, and to send copies to all manufacturers, repackers and relabelers of drug products. In this way, the industry will be advised concerning FDA's laboratory findings on batches of different classes of marketed drugs. This is in line with FDA's attempts to provide to the public and the regulated industries as much valuable information as it can within the scope of the Freedom of Information Law. It is hoped that information of this nature will lead to better compliance by regulated industries. Each report will include pertinent information such as scope of survey, sampling information, laboratory tests and summary of results.

The analytical methods used are either those specified by the United States Pharmacopeia (U.S.P.) and National Formulary (N.F.) or automated procedures developed by FDA or adapted from published methods and validated. Many of the methods may be found in the FDA's "Drug Autoanalysis Manual," available from the Division of Industry Liaison. Samples analyzed and found defective by non-official methods are check-analyzed by U.S.P., N.F., or other official methods such as those of the Association of Official Analytical Chemists (AOAC). Defective samples are followed up by FDA Field Offices so as to remove offending batch(es) from the market either by legal action, voluntary recall, or destruction, or cooperative action by State or local authorities.

Test results may or may not be indicative of the quality of other lots of the same product or other products produced by the listed manufacturer.

The second survey report is on Ethinyl Estradiol.

T. E. Byers, Director
Office of Compliance
Bureau of Drugs

REPORT ON ETHINYL ESTRADIOL

Scope of the Survey

This study covered Ethinyl Estradiol Tablets U.S.P. XVIII, marketed as a single active ingredient product in tablet form, in the following dosages: 0.02 mg., 0.05 mg., and 0.5 mg.

Of the seven domestic formulators known to produce Ethinyl Estradiol Tablets, samples of batches from four firms were collected in this survey. Batches varied in size from slightly under 200,000 tablets to slightly more than 2,000,000 tablets. Eight batches from four different firms were tested. The output of three firms (Ferndale Laboratories, Inc.; Organon Inc.; and Marshall Pharmacal) was unavailable for sampling.

Sampling Information

Samples were collected under FDA's FORDS (Formulator-Oriented Rx Drug Studies) Program from the formulators (manufacturing plant or primary distribution warehouse) or from their branch warehouses or major accounts. No collections were made at locations more than once removed from the manufacturer. Samples were collected from batches released for distribution by the firms' quality control.

Laboratory Tests

Samples were analyzed by semi-automated procedure as described under Method No. 24 of the FDA Drug Autoanalysis Manual. Testing was performed on each of six sub-samples from each batch. Where outside of compendial limits, results were verified by the U.S.P. Method.

Summary of Results

Of the eight samples analyzed (see Table 1) one sample of 0.05 mg. tablets was found defective due to lack of content uniformity, with a sample defect rate for the survey of 12.5 percent. No samples of other dosage strengths were defective.

Table 1.--Testing Results "FORDS" Study
Ethinyl Estradiol Tablets U.S.P. XVIII

[Survey Period - May 1, 1970-May 1, 1971]

Manufacturer	Declared potency (mg.)	Number batches sampled and analyzed	Number defective samples
Heun, E. W. Company.....	0.05	1	0
Linden Laboratories, Inc.	0.05	1	1 (a)
Schering Corporation	0.02	1	0
	0.05	1	0
	0.5	1	0
Upjohn Company	0.05	3	0
Totals		8	1

(a) Defective due to lack of content uniformity (25 tablets defective ranging from 26.5 percent to 183.6 percent of declared). The average for all 30 tablets check analyzed was 75.4 percent of declared. The lot was voluntarily removed by manufacturer from distribution channels.

FDA drug compliance information letter

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • Public Health Service • FOOD AND DRUG ADMINISTRATION
Bureau of Drugs • Office of Compliance

July 18, 1973

TO: Manufacturers, Repackers, and Relabelers of Drug Products

RE: Drug Surveillance Reports

The Food and Drug Administration, as part of its regulation of the American drug supply, routinely conducts drug quality surveys. FDA now intends to publish the results of its drug quality surveys, and to send copies to all manufacturers, repackers and relabelers of drug products. In this way, the industry will be advised concerning FDA's laboratory findings on batches of different classes of marketed drugs. This is in line with FDA's attempts to provide to the public and the regulated industries as much valuable information as it can within the scope of the Freedom of Information Law. It is hoped that information of this nature will lead to better compliance by regulated industries. Each report will include pertinent information such as scope of survey, sampling information, laboratory tests and summary of results.

The analytical methods used are either those specified by the United States Pharmacopeia (U.S.P.) and National Formulary (N.F.) or automated procedures developed by FDA or adapted from published methods and validated. Many of the methods may be found in the FDA's "Drug Autoanalysis Manual," available from the Division of Industry Liaison. Samples analyzed and found defective by non-official methods are check-analyzed by U.S.P., N.F., or other official methods such as those of the Association of Official Analytical Chemists (AOAC). Defective samples are followed up by FDA Field Offices so as to remove offending batch(es) from the market either by legal action, voluntary recall, or destruction, or cooperative action by State or local authorities.

Test results may or may not be indicative of the quality of other lots of the same product or other products produced by the listed manufacturer.

The third survey report is on Psychostimulants.

T. E. Byers, Director
Office of Compliance
Bureau of Drugs

REPORT ON PSYCHOSTIMULANTS

Scope of the Survey

This survey covered five psychostimulant drugs marketed as single active ingredient drugs each in one or two dosage forms as follows: Amitriptyline HCl Tablets and Injection, U.S.P. XVIII; Desipramine HCl Tablets and Capsules, N.F. XIII; Imipramine HCl Tablets, U.S.P. XVIII; Nortriptyline HCl Capsules, N.F. XIII; and Protriptyline HCl Tablets.

Of the seven domestic formulators known to produce these drugs, samples of batches from five firms were collected in this survey. The output of two firms, Standard Pharmacal Company and Taylor Pharmacal, was unavailable for sampling.

Sampling Information

Samples were collected under FDA's FORDS (Formulator-Oriented Rx Drug Studies) Program from the formulators (manufacturing plant or primary distribution warehouse) or from their branch warehouses or major accounts. No collections were made at locations more than once removed from the manufacturer. Samples were collected from batches released for distribution by the firms' quality control.

Laboratory Tests

Samples were analyzed for compliance with the specifications in the compendial monograph or NDA by the appropriate semi-automated procedure or other method of analysis deemed appropriate by the National Center for Drug Analysis. Testing was performed on each of six sub-samples from each batch.

Summary of Results

Of the 42 samples analyzed (see Table 1), no samples were found defective.

Table 1.--Testing Results "FORDS" Study Psychostimulants

[Survey Period - May 1972-September 1972]

Manufacturer	Declared potency (mg.)	Number batches sampled and analyzed	Number defective samples
Amitriptyline HCl Tablets:			
Merck Sharp & Dohme	10.0	3	0
	25.0	3	0
	50.0	3	0
Totals		9	0
Amitriptyline HCl Injection:			
Merck Sharp & Dohme	10.0 mg/ml	2	0
Totals		2	0
Desipramine HCl Tablets:			
K-V Pharmacal	25.0	2	0
	50.0	3	0
Totals		5	0
Desipramine HCl Capsules:			
U.S. Vitamin	25.0	4	0
	50.0	1	0
Totals		5	0
Imipramine HCl Tablets:			
Ciba-Geigy Corp.	10.0	2	0
	25.0	1	0
	50.0	3	0
Totals		6	0
Nortriptyline HCl Capsules:			
Eli Lilly & Company	10.0	3	0
	25.0	6	0
Totals		9	0
Protriptyline HCl Tablets:			
Merck Sharp & Dohme	5.0	3	0
	10.0	3	0
Totals		6	0

FDA drug compliance information letter

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • Public Health Service • FOOD AND DRUG ADMINISTRATION
Bureau of Drugs • Office of Compliance

October 5, 1973

TO: Manufacturers, Repackers, and Relabelers of Drug Products

RE: Drug Surveillance Reports

The Food and Drug Administration, as part of its regulation of the American drug supply, routinely conducts drug quality surveys. FDA now intends to publish the results of its drug quality surveys, and to send copies to all manufacturers, repackers and relabelers of drug products. In this way, the industry will be advised concerning FDA's laboratory findings on batches of different classes of marketed drugs. This is in line with FDA's attempts to provide to the public and the regulated industries as much valuable information as it can within the scope of the Freedom of Information Law. It is hoped that information of this nature will lead to better compliance by regulated industries. Each report will include pertinent information such as scope of survey, sampling information, laboratory tests and summary of results.

The analytical methods used are either those specified by the United States Pharmacopeia (U.S.P.) and National Formulary (N.F.) or automated procedures developed by FDA or adapted from published methods and validated. Many of the methods may be found in the FDA's Drug Autoanalysis Manual, available from the Division of Industry Liaison. Samples analyzed and found defective by nonofficial methods are check-analyzed by U.S.P., N.F., or other official methods such as those of the Association of Official Analytical Chemists (AOAC). Defective samples are followed up by FDA Field Offices so as to remove offending batch(es) from the market either by legal action, voluntary recall, or destruction, or cooperative action by State or local authorities.

Test results may or may not be indicative of the quality of other lots of the same product or other products produced by the listed manufacturer.

The fourth survey report is on Antiemetics.

T. E. Byers, Director
Office of Compliance
Bureau of Drugs

REPORT ON ANTIEMETICS

Scope of the Survey

This survey covered four different drugs marketed as single active ingredient preparations; three in tablet form and one in both capsule and injectable form. Drugs in this study were: Cyclizine HCl Tablets U.S.P. XVIII, Meclizine HCl Tablets U.S.P. XVIII, Dimenhydrinate Tablets U.S.P. XVIII, and Trimethobenzamide HCl Capsules and Injection N.F. XIII.

Of the twelve domestic formulators known to produce these drugs, samples of batches from eleven firms were collected and analyzed in the survey. The output of one firm, Bowman Pharmaceutical, was unavailable for sampling.

Sampling Information

Samples were collected under FDA's FORDS (Formulator-Oriented Rx Drug Studies) Program from the formulators (manufacturing plant or primary distribution warehouse) or from their branch warehouses or major accounts. No collections were made at locations more than once removed from the manufacturer. Samples were collected from batches released for distribution by the firms' quality control.

Laboratory Tests

Samples were analyzed for compliance with the chemical specifications in the compendial monographs. Initial chemical analyses were performed by methods deemed appropriate by the National Center for Drug Analysis. Testing was performed on each of six sub-samples from each batch.

Summary of Results

Of the 33 samples analyzed (see Table 1) no defective samples were found.

Table 1.--Antiemetics
[Survey Period - February 1972-June 1972]

Manufacturer	Declared potency (mg.)	Number batches sampled and analyzed	Number defective samples
Cyclizine HCl Tablets:			
Burroughs Wellcome Co.	50.0	6	0
Total		6	0
Dimenhydrinate Tablets:			
Cord Laboratories, Inc.	50.0	2	0
Paul B. Elder Co.	50.0	2	0
The Lannett Co., Inc.	50.0	1	0
Linden Labs., Inc.	50.0	1	0
Phoenix Labs., Inc.	50.0	1	0
Richlyn Laboratories	50.0	1	0
G. D. Searle & Co.	50.0	6	0
West-Ward, Inc.	50.0	1	0
Total		15	0
Meclizine HCl Tablets:			
Pfizer, Inc.	25.0	4	0
Total		4	0
Trimethobenzamide HCl Capsules:			
Hoffman-La Roche Inc.	100.0	1	0
	250.0	4	0
Total		5	0
Trimethobenzamide HCl Injection:			
Hoffman-La Roche Inc.	100.0 mg/cc	3	0
Total		3	0

FDA drug compliance information letter

U.S. DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE • Public Health Service • FOOD AND DRUG ADMINISTRATION
Bureau of Drugs • Office of Compliance

January 23, 1974

TO: Manufacturers, Repackers, and Relabelers of Drug Products

RE: Drug Surveillance Reports

The Food and Drug Administration, as part of its regulation of the American drug supply, routinely conducts drug quality surveys. FDA now intends to publish the results of its drug quality surveys, and to send copies to all manufacturers, repackers and relabelers of drug products. In this way, the industry will be advised concerning FDA's laboratory findings on batches of different classes of marketed drugs. This is in line with FDA's attempts to provide to the public and the regulated industries as much valuable information as it can within the scope of the Freedom of Information Law. It is hoped that information of this nature will lead to better compliance by regulated industries. Each report will include pertinent information such as scope of survey, sampling information, laboratory tests and summary of results.

The analytical methods used are either those specified by the United States Pharmacopeia (U.S.P.) and National Formulary (N.F.) or automated procedures developed by FDA or adapted from published methods and validated. Many of the methods may be found in the FDA's Drug Autoanalysis Manual, available from the Division of Industry Liaison. Samples analyzed and found defective by nonofficial methods are check-analyzed by U.S.P., N.F., or other official methods such as those of the Association of Official Analytical Chemists (AOAC). Defective samples are followed up by FDA Field Offices so as to remove offending batch(es) from the market either by legal action, voluntary recall, or destruction, or cooperative action by State or local authorities.

Test results may or may not be indicative of the quality of other lots of the same product or other products produced by the listed manufacturer.

The fifth survey report is on Progestins.

T. E. Byers, Director
Office of Compliance
Bureau of Drugs

REPORT ON PROGESTINS

Scope of the Survey

This survey covered seven drugs, each marketed as a single active ingredient product in one to three dosage forms. Dosage forms covered were tablets and injections or injection suspensions. The following drugs were programmed in the study:

1. (a) Progesterone Tablets N.F.[1]
   (b) Progesterone Injection (Aqueous or oil vehicle) N.F.
   (c) Progesterone Injection (Sterile Suspension) N.F.

2. (a) Medroxyprogesterone Acetate Tablets U.S.P.
   (b) Medroxyprogesterone Acetate Injection (Sterile Suspension) U.S.P.

3. Hydroxyprogesterone Caproate Injection (oil vehicle) U.S.P.

4. Dydrogesterone Tablets N.F.

5. Ethisterone Tablets N.F.

6. Norethindrone Tablets N.F.

7. Norethindrone Acetate Tablets N.F.

Of the 20 domestic formulators known to produce these drugs, samples of batches from 16 firms were collected in this survey. Unavailable for sampling was production from E. W. Heun Company, Maizel Laboratories, and Organics Inc. The result from sampling of Parke Davis' Progesterone Injection Suspension, 25.0 mg/ml, is not listed in Table 1 as a defective sample since an apparent syringeability problem interfered with the analysis.[2]

Sampling Information

Samples were collected under FDA's FORDS (Formulator-Oriented Rx Drug Studies) Program from the formulators (manufacturing plant or primary distribution warehouse) or from their branch warehouses or major accounts. No collections were made at locations more than once removed from the manufacturer. Samples were collected from batches released for distribution by the firms' quality control.

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1. Not available for sampling.
2. See Table 1, Footnote c.

Laboratory Tests

Samples were analyzed by the National Center for Drug Analysis for compliance with the specifications in the official compendial monographs (except sterility requirements). Initial analyses were performed by methods deemed appropriate by NCDA. Check analyses, as required, were made by the official method. Testing was performed on each of six sub-samples from each batch.

Summary of Results

Of the 51 samples of these drugs that were analyzed (see Table 1) two samples of Progesterone Injection, one labeled 25.0 mg/ml and the other labeled 50.0 mg/ml were found defective due to substrength.

Table 1—Progestins
(Survey Period - May 1972-September 1972)

MANUFACTURER	DECLARED POTENCY	NUMBER BATCHES SAMPLED AND ANALYZED	NUMBER DEFECTIVE SAMPLES
Progesterone Injection (Aqueous or oil):			
Bel-Mar Labs., Inc.	25.0 mg/ml	2	0
	50.0 mg/ml	1	0
	100.0 mg/ml	1	0
D-M Pharmaceuticals	50.0 mg/ml	1	0
Elkins-Sinn, Inc.	25.0 mg/ml	1	1 (a)
	50.0 mg/ml	1	1 (b)
Gotham Pharmaceutical Co., Inc.	50.0 mg/ml	1	0
Eli Lilly & Co.	25.0 mg/ml	2	0
	50.0 mg/ml	1	0
Maurry Biological Co., Inc.	50.0 mg/ml	1	0
Medical Chemicals Corp.	50.0 mg/ml	1	0
Myers-Carter Labs., Inc.	50.0 mg/ml	1	0
	100.0 mg/ml	1	0
Parke, Davis & Co.	25.0 mg/ml	1	0 — (c)
	50.0 mg/ml	1	0
Pasadena Research Labs., Inc.	50.0 mg/ml	1	0
	100.0 mg/ml	1	0
Schering Corporation	50.0 mg/ml	1	0
Titan Pharmacal Co., Inc.	50.0 mg/ml	1	0
TOTAL		20	2
Progesterone Injection Suspension:			
Elkins-Sinn, Inc.	25.0 mg/ml	1	0
	50.0 mg/ml	1	0
Hallmark Laboratories	25.0 mg/ml	1	0
	50.0 mg/ml	1	0
Maurry Biological Co., Inc.	50.0 mg/ml	1	0
Medical Chemicals Corp.	25.0 mg/ml	2	0
	50.0 mg/ml	1	0
	100.0 mg/ml	1	0
Pasadena Research Labs., Inc.	25.0 mg/ml	1	0
Titan Pharmacal Co., Inc.	25.0 mg/ml	1	0
	50.0 mg/ml	1	0
TOTAL		12	0
Medroxyprogesterone Acetate Tablets:			
The Upjohn Co.	2.5 mg	1	0
	10.0 mg	3	0
TOTAL		4	0
Medroxyprogesterone Acetate Injection Sterile Suspension:			
The Upjohn Co.	50.0 mg/ml	3	0
	100.0 mg/ml	2	0
TOTAL		5	0
Hydroxyprogesterone Caproate Injection:			
E.R. Squibb & Sons Inc.	250.0 mg/ml	1	0
TOTAL		1	0
Dydrogesterone Tablets:			
Philips Roxane Labs., Inc.	5.0 mg	1	0
	10.0 mg	2	0
TOTAL		3	0
Ethisterone Tablets:			
Schering Corporation	10.0 mg	1	0
TOTAL		1	0
Norethindrone Tablets:			
Parke, Davis & Co.	5.0 mg	1	0
TOTAL		1	0
Norethindrone Acetate Tablets:			
Parke, Davis & Co.	5.0 mg	3	0
TOTAL		3	0
GRAND TOTAL		51	2

(a) Defective due to subpotency in five of six sub-samples. The average potency was 86.6 percent of declared for the sample. Removed from distribution channels by seizure action.

(b) Defective due to subpotency in each of six sub-samples. The average potency for the sample was 85.8 percent. Removed from distribution channels by seizure action.

(c) The result on this sample is not listed as defective because an apparent syringeability problem interfered with the analysis. Because of this problem, the firm voluntarily recalled the batch.

TITLE 21--FOOD AND DRUGS

CHAPTER I--FOOD AND DRUG ADMINISTRATION,
DEPARTMENT OF HEALTH, EDUCATION, AND WELFARE

SUBCHAPTER C--DRUGS

PART 130--NEW DRUGS

CONDITIONS FOR MARKETING OF DIGOXIN PRODUCTS

In April, 1970, the Food and Drug Administration inaugurated a program to systematically test marketed batches of digoxin tablets after the agency became aware of an apparent potency problem with this cardiac glycoside. As a result of this testing program, from April to November, 1970, there were 79 recalls of digoxin products. In October, 1970, a voluntary certification program was initiated whereby participating manufacturers agreed not to release new batches of digoxin tablets until samples of the batches were tested by the Food and Drug Administration and found to meet The United States Pharmacopeia (USP) requirements for potency and content uniformity.

In December, 1971, John Lindenbaum, M.D. and his colleagues published a paper in The New England Journal of Medicine (Lindenbaum, J., Mellow, M. G., Blackstone, M. D., Butler, V. P., "Variation in Biologic Availability of Digoxin from Four Preparations," The New England Journal of Medicine, 285:1344, 1971) describing a study of the biologic availability in

normal human volunteers of 4 batches of commercially marketed digoxin tablets. The study noted marked differences in serum digoxin levels achieved with tablets produced by different manufacturers. Significant variation between different batches prepared by a single manufacturer was also observed. Lindenbaum conducted the study after observing low serum digoxin concentrations in several patients receiving unusually large maintenance doses of digoxin.

The tablets used in the study had not been analyzed for compliance with compendial specifications including potency and content uniformity. Subsequently, the Food and Drug Administration analyzed tablets from batches used in the Lindenbaum study and found that the two batches which gave acceptable serum digoxin levels met these compendial specifications. One batch which had given very low serum digoxin levels did not meet these compendial specifications varying from 76 to 152 percent of labeled potency. At that time sufficient tablets of the other batch which gave low serum digoxin levels could not be found for analysis. On this basis, it was the Food and Drug Administration's view that the problem identified by Lindenbaum may have been one of potency and not bioavailability (Vitti, T. G., Banes, D., Byers, T. E., "Bioavailability of Digoxin", The New England Journal of Medicine, 285:1433, 1971).

Somewhat prior to this, the Food and Drug Administration had begun a systematic investigation of several formulations of the cardiac glycosides. John G. Wagner, Ph.D., Professor of Pharmacy, Upjohn Center for Clinical Pharmacology, University of Michigan, Ann Arbor, Michigan,

under an extramural contract with the Food and Drug Administration, had just completed a pharmacokinetic evaluation of digitoxin when the agency learned of the results of the Lindenbaum study. Dr. Wagner then proceeded to study the bioequivalence of digoxin tablets. In addition to conducting a bioavailability study on digoxin tablets made by two different manufacturers, Dr. Wagner developed a reproducible in vitro dissolution test which showed significant correlation with in vivo bioavailability test results. The results of the Wagner study were published in The Journal of the American Medical Association in April, 1973 (Wagner, J. G., et al., "Equivalence Lack in Digoxin Plasma Levels," Journal of the American Medical Association, 224:199-204, 1973).

In the meantime, sufficient tablets of the second batch of digoxin tablets which gave low serum digoxin levels in the Lindenbaum study were located for chemical analysis. The Food and Drug Administration's analysis showed that the tablets met the compendial specifications for content uniformity. It was therefore apparent that the problem identified originally by Lindenbaum and his colleagues was attributable to bioavailability and not to potency (Skelly, J. and Knapp, G., "Biologic Availability of Digoxin Tablets," Journal of the American Medical Association, 224:243, 1973).

The Food and Drug Administration recognized that very few well controlled digoxin bioavailability studies had been performed and was aware of data which indicated that even the possibility of batch-to-batch bioavailability inconsistency could not be discounted. The agency continued to implement studies to determine the dimension of the problem and to provide the basis for a systematic regulatory approach to assure the

uniformity of all digoxin products. In addition to inaugurating additional in vivo studies under the extramural contract program, the agency, in its own laboratories, adapted, modified, and validated several dissolution procedures in both acid and water media based on the method originally developed by Dr. Wagner. Samples of digoxin tablets produced by all known manufacturers were obtained for laboratory analysis. A dissolution profile was obtained on all the tablets which met compendial requirements for potency and content uniformity. A satisfactory correlation existed with the available in vivo data.

The USP in conjunction with the FDA have initiated studies to determine the correlation between bioavailability in vivo and the dissolution rate of digoxin tablets in vitro. As a result of the available data from all such studies showing a satisfactory correlation between bioavailability and dissolution, the USP monograph for digoxin tablets has been revised to include a requirement for dissolution. This revision is included in the USP XVIII Sixth Interim Revision Announcement which became effective on November 15, 1973. The dissolution method described in the revision involves the use of a rotating basket in an acid dissolution medium.

The Commissioner has determined that the solution to the problem of the bioavailability of digoxin products will involve three separate but related actions. As a first step, immediate action will be taken to remove from the market those digoxin products which, on the basis of dissolution test results, are not adequately bioavailable. The second action will include procedures to assure that manufacturers conduct the in vivo tests needed to demonstrate the bioavailability of those digoxin

products which meet all compendial requirements including dissolution. The third action will involve procedures to monitor digoxin product reformulations in order to assure that orderly progress is made towards the marketing of digoxin products which are 100 percent bioavailable. The third action will include means of adequately advising practitioners of changes in digoxin bioavailability resulting from product reformulations.

The Food and Drug Administration is prepared to take the actions necessary to assure the removal from the market of all batches of digoxin tablets in the channels of commerce after November 15, 1973, which do not meet all compendial requirements. The agency has initiated a program for sampling and analyzing batches of digoxin tablets in the channels of commerce. Manufacturers of batches of digoxin tablets which are found not to be in compliance with the compendial requirements will be requested by the Food and Drug Administration to initiate recall of the subject batches from the market. Violative batches which are not promptly and effectively recalled will be subject to regulatory procedures.

Data indicate that a significant number of manufacturers will need to reformulate their digoxin tablets to assure that their digoxin tablets meet the new compendial requirement for dissolution. Because of the narrow margin between therapeutic and toxic levels of digoxin and the potential for serious risk to cardiac patients using digoxin products which may vary in bioavailability, the Commissioner has determined that immediate actions must be taken to assure better uniformity of all digoxin products for oral use. These actions include:

1. Procedures to remove from the market all batches of digoxin

products which do not meet current good manufacturing practice and compendial requirements.

2. Procedures to require manufacturers to submit samples of all new batches of digoxin tablets to the Food and Drug Administration for analysis and certification prior to release of these batches for distribution.

3. Procedures to monitor digoxin product formulations to assure that any reformulation will result in compliance with all in vitro test requirements and in uniform batch-to-batch bioavailability.

4. Procedures to require manufacturers to conduct in vivo bioavailability tests.

5. Procedures to assure uniformity in the labeling of all digoxin products for oral use.

The Commissioner is of the opinion that, in view of the questions that have been raised regarding the bioavailability of digoxin products and the need for some manufacturers to reformulate their products to meet the new requirements for dissolution, these drug products cannot properly be considered generally recognized as safe and effective within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act. Therefore, all digoxin products for oral use are new drugs for which approved new drug applications are required. All persons marketing such drug products must submit an abbreviated new drug application for these products on or before (insert date 30 days after the date of publication in the FEDERAL REGISTER) if marketing is to continue. After this date, any such drug product then on the market which is not the subject of an abbreviated new drug application submitted for such drug product will be

subject to regulatory procedures under section 505 of the act.

The Commissioner has determined that, in view of the questions raised regarding the bioavailability of digoxin products for oral use, there is sufficient evidence to invoke the authority under section 505(j) of the act to fully investigate this question in order to obtain more definitive data to demonstrate the bioavailability of these products and to correlate bioavailability in vivo with the dissolution rate of digoxin tablets in vitro. Therefore, any person who submits an abbreviated new drug application for digoxin products for oral use shall, within the times specified in the new § 130.51, submit to the Food and Drug Administration additional data in the form of records and reports, pursuant to section 505(j) of the act, which show adequate evidence of the product's bioavailability. A review of these data will facilitate a determination of whether there is a ground for withdrawing approval of the drug in question under section 505(e) of the act. Failure to submit these required records and reports is in itself a violation of the act, justifying withdrawal of approval of the application.

Digoxin products for parenteral use are new drugs subject to the requirements of the Drug Efficacy Study Implementation notice (DESI 8627) published in the FEDERAL REGISTER of July 27, 1972 (37 FR 15024). The conditions for marketing digoxin products for parenteral use are described in the DESI notice and include a requirement for the submission of data to show the biologic availability of the drug in the formulation which is marketed.

Digoxin tablets formulated so that the quantity of digoxin dissolved

at one hour, when tested by the method in the USP, is greater than 95 percent of the assayed amount of digoxin or so that the quantity of digoxin dissolved at 15 minutes is greater than 90 percent of the assayed amount of digoxin are new drugs which may not be marketed without an approved new drug application. Persons intending to market such drugs are required to submit full new drug applications as provided for in § 130.4 (21 CFR 130.4). The application shall include, but not be limited to, clinical studies establishing significantly greater bioavailability than digoxin tablets meeting compendial requirements and dosage recommendations based on clinical studies establishing the safe and effective use of the more bioavailable digoxin product. Marketing of these digoxin products will be allowed only under a proprietary or trade name, established name, and labeling which differs from that used for digoxin tablets that meet all of the requirements in USP XVIII and that are formulated so that the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or that the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin.

The Food and Drug Administration is familiar with two in vitro methods ("paddle-water," "paddle-acid"), in addition to that described in the USP, developed to measure digoxin tablet dissolution. These three methods result in data which show significant differences in dissolution in comparative tests on some formulations. Definitive bioavailability data to compare the relative value of each of these methods to predict bioavailability of the few formulations where the

methods show significant differences in dissolution rate are not now available. Until such data are available it is not possible to rule out the usefulness of each method in particular situations or to define the limitations of any method. Once such data is available it is anticipated more stringent dissolution rate requirements will be set. The Commissioner requests that manufacturers who conduct research utilizing the "paddle-water" and "paddle-acid" methods, particularly in comparison with the method in the USP, submit any data obtained using these methods to the Food and Drug Administration pursuant to section 505(j) of the act.

Available evidence shows that digoxin tablets which have a dissolution rate below the compendial requirement (i.e., 55 percent at one hour) when tested by the in vitro method in USP XVIII are not adequately bioavailable when tested by in vivo methods. Correlative in vivo and in vitro data are not now available to predict with certainty the minimum dissolution rate at which biologic availability will be demonstrated. Manufacturers whose digoxin tablets do not now meet the compendial requirements for dissolution may reformulate their product to achieve a dissolution at any rate above the dissolution requirements of the USP, but not more than 95 percent dissolution at one hour or more than 90 percent dissolution at 15 minutes. The Food and Drug Administration recommends that these manufacturers reformulate their products to achieve dissolution of 70 to 90 percent at one hour by all three methods. This recommendation is based on data compiled by the Food and Drug Administration which indicates that when in vitro tests uniformly show dissolution at 70 to 90 percent at one hour by all three methods there is good probability to predict that in vivo tests

will demonstrate that the product is bioavailable. To assist manufacturers who do not have the capability to determine dissolution by all three methods, the Food and Drug Administration is prepared, on request, to test samples of reformulated tablets by all three methods and to supply the results of these analyses to the manufacturer.

The references set forth in the preamble together with the following additional supportive data and background information have been assembled and are on display in the office of the Hearing Clerk, Food and Drug Administration, Room 6-86, 5600 Fishers Lane, Rockville, MD 20852:

1. Doherty, J. E., W. H. Perkins and G. K. Mitchell, "Tritiated Digoxin Studies in Human Subjects," Archives of Internal Medicine, 108:531, 1961.

2. Levy, G., "Effect of Dosage Form on Drug Absorption a Frequent Variable in Clinical Pharmacology," Archives of International Pharmacodynamics, 152, No. 1-2:59-68, 1964.

3. Jelliffe, R. W., "A Mathematical Analysis of Digitalis Kinetics in Patients with Normal and Reduced Renal Function," Mathematical Biosciences, 1:305-325, 1967.

4. Doherty, J. E., W. H. Perkins and W. J. Flanigan, "The Distribution and Concentration of Tritiated Digoxin in Human Tissues," Annals of Internal Medicine, 66, No. 1:116, 1967.

5. Butler, V. P. and J. P. Chen, "Digoxin Specific Antibodies," Proceedings of the National Academy of Sciences, 57:71, 1967.

6. Smith, T. W. and E. Haber, "Measurement of Clinical Blood Levels of Digoxin by Radioimmunoassay," The Journal of Clinical Investigation, 48:78A, 1969.

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The two methods for in vitro dissolution tests referred to in the preamble, namely the "paddle-water" and the "paddle-acid" methods, are set forth in § 130.51(h).

Therefore, pursuant to provisions of the Federal Food, Drug, and Cosmetic Act (secs. 201(p), 501(b), 502, 505, 701(a); 52 Stat. 1041-1042, 1049-1053, 1055; 21 U.S.C. 321(p), 351(b), 352, 355, 371(a)) and under authority delegated to the Commissioner (21 CFR 2.120), Part 130 of Title 21 of the Code of Federal Regulations is amended by adding a new § 130.51 as follows:

§ 130.51 Digoxin products for oral use; conditions for marketing.

(a) Studies have shown evidence of clinically significant differences in bioavailability in different batches of certain marketed digoxin products for oral use from single manufacturers as well as in batches of these products produced by different manufacturers. These differences were observed despite the fact that the products met compendial specifications. Other studies have shown that there is a sufficient correlation between bioavailability in vivo and the dissolution rate of digoxin tablets in vitro to make the dissolution test an important addition to the compendial standards. Because of the potential for serious risk to cardiac patients using digoxin products which may vary in bioavailability, the Commissioner of Food and Drugs has determined that immediate action must be taken to assure the uniformity of all digoxin products for oral use. The Commissioner is of the opinion that digoxin products for oral use are new drugs within the meaning of section 201(p) of the Federal Food, Drug, and Cosmetic Act for which approved new drug applications are required. The Commissioner has determined that, because of questions raised regarding the bioavailability of digoxin products for oral use, there is sufficient evidence to invoke

the authority under section 505(j) of the act to fully investigate this question and to facilitate a determination of whether there is a ground for withdrawal of approval of the drug product under section 505(e) of the act. Marketing of these products may be continued only under the following conditions:

(1) Digoxin products for oral use, other than tablets: Any person marketing digoxin products for oral use, other than tablets, shall submit to the Food and Drug Administration on or before (insert date 30 days after the date of publication in the FEDERAL REGISTER), an abbreviated new drug application for these products. Any such drug product then on the market which is not the subject of an application submitted for the drug product shall be subject to regulatory procedures under section 505 of the act. In addition to the information specified in § 130.4(f), the application shall contain:

(i) A full list of the articles used as components of the digoxin product, specifications for components, detailed identification and analytical procedures used to assure that the components meet established specifications of identity, strength, quality, and purity and a complete description of the manufacturing process.

(ii) The source of the digoxin used in the formulation including the name and address of the supplier.

(iii) A statement that stability studies will be conducted to establish a suitable expiration date for the digoxin product in the form in which it is distributed.

(iv) A statement that the product label will contain a suitable expiration date. In the absence of any stability test data, this expiration date shall be no longer than one year after the batch is manufactured. If the expiration date is greater than one year, supporting stability data shall be included in the application.

(v) Labeling that is in compliance with all requirements of the act and regulations promulgated thereunder, the pertinent parts of which are as indicated in paragraph (e) of this section.

(vi) A statement that the applicant will initiate recall of all stocks of the drug product outstanding when so requested by the Food and Drug Administration.

(vii) A statement that the applicant intends to conduct in vivo bioavailability tests and that the applicant, under the records and reports provisions of section 505(j) of the act, will:

(a) Within 30 days after the submission of the application, submit to the Food and Drug Administration the protocol which the applicant proposes to follow in conducting these in vivo bioavailability tests. The protocol shall contain all of the essential elements set forth in paragraph (d) of this section. The tests shall not be initiated prior to receiving notification from the Food and Drug Administration that the bioavailability protocol has been reviewed and either approved or its deficiencies delineated.

(b) Within 180 days after receiving notification from the Food and Drug Administration that the bioavailability protocol has been reviewed, submit to the Food and Drug Administration the results of the in vivo bioavailability tests.

(2) Digoxin tablets: Any person marketing digoxin tablets, in addition to complying with all of the requirements of paragraph (a)(1) of this section, shall include in their abbreviated new drug application:

(i) A statement that the applicant will establish procedures to test each lot of digoxin tablets prior to releasing the batch for distribution to assure that the batch meets all of The United States Pharmacopeia (USP XVIII) requirements for digoxin tablets including, but not limited to, potency, content uniformity, and dissolution and that the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or that the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin.

(ii) A statement that finished product specifications shall be established to include provisions to assure that the range of average one-hour dissolution values among batches of digoxin tablets does not exceed 20 percent.

(3) Before releasing for distribution any batch of digoxin tablets manufactured after (insert date of publication in the FEDERAL REGISTER), the manufacturer shall:

(i) Test a sample of the batch to assure that the batch meets all of the requirements of The United States Pharmacopeia (USP XVIII) including, but not limited to, potency, content uniformity, and dissolution and that the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or that the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin.

(ii) Submit a sample of the batch to the Food and Drug Administration according to the procedures set forth in paragraph (g) of this section. Results of tests conducted on the batch by or for the manufacturer and the batch production record shall accompany the sample.

(iii) Withhold the batch from distribution until he is notified by the Food and Drug Administration that the sample was tested and found to meet all of the requirements in The United States Pharmacopeia (USP XVIII) for potency, content uniformity, and dissolution and that the quantity of digoxin dissolved at one hour is not more than 95 percent of the assayed amount of digoxin or that the quantity of digoxin dissolved at 15 minutes is not more than 90 percent of the assayed amount of digoxin.

(iv) Submit a sample of each batch of digoxin tablets as provided for in paragraphs (a)(3)(ii) of this section until he is notified by the Food and Drug Administration that he is released from the certification program. This notification will be made on the basis of sample test results, inspectional findings regarding compliance with current good manufacturing practice, and compliance with all other requirements of this section and any other directives issued by the Food and Drug Administration as a condition for release from the certification program.

(4) Any manufacturer who has distributed any batch of digoxin tablets which does not meet the compendial requirement for dissolution, when tested by the method in The United States Pharmacopeia (USP XVIII), shall initiate recall of the subject batch when so requested by the Food and Drug Administration.

(b) Failure of an applicant to submit the protocol and/or the results of the in vivo bioavailability tests showing adequate evidence of the product's bioavailability within the times specified in paragraph (a)(1)(vii) of this section and/or to comply with all of the certificiation requirements of paragraph (a)(3) of this section shall be justification for withdrawal of approval of the application under section 505(e) of the act.

(c) Any product reformulation or change in manufacturing process will require the submission of a supplement to the approved abbreviated new drug application containing adequate data to demonstrate the bioavailability of the reformulated product. Food and Drug Administration approval of the supplement is required before the reformulated product is marketed. The Food and Drug Administration recommends that, where digoxin tablets are reformulated, manufacturers reformulate their ————————————

product to achieve dissolution of 70 to 90 percent at one hour when tested by all three methods (i.e., the USP method, and the "paddle-water" and "paddle-acid" methods) described in paragraph (h) of this section.

(d) The protocol for the in vivo bioavailability tests required in paragraphs (a) and (c) of this section shall employ a three-way crossover design using the digoxin test product; a reference digoxin tablet supplied, on request, by the Food and Drug Administration; and bulk digoxin USP in an oral solution. Appropriate venous blood and urinary samples are to be collected and analyzed. The method shall be capable of detecting the difference between the reference tablet and the reference oral solution. Bioavailability of the test product shall be demonstrated if a mean absorption of at least 75 percent of the combined mean of the two reference standards is observed. Assistance in developing a protocol for a particular dosage formulation may be obtained by contacting the Food and Drug Administration, Bureau of Drugs (HFD-220), 5600 Fishers Lane, Rockville, MD 20852.

(e) Parts of the digoxin product labeling indicated below shall be substantially as follows:

CARDIAC (DIGITALIS) GLYCOSIDES LABELING
GUIDELINE (ADULT)

DESCRIPTION

The cardiac (or digitalis) glycosides are a closely related group of drugs having in common specific and powerful effects on the myocardium. These drugs are found in a number of plants. The term "digitalis" is used to designate the whole

group. Typically, the glycosides are composed of three portions, a steroid nucleus, a lactone ring, and a sugar (hence "glycosides").

(This section should include a chemical and physical description of digoxin and the same quantitative ingredient information as that required on the label.)

ACTION

The digitalis glycosides have qualitatively the same therapeutic effect on the heart. They (1) increase the force of myocardial contraction, (2) increase the refractory period of the atrioventricular (A-V) node, and (3) to a lesser degree, affect the sinoatrial (S-A) node and conduction system via the parasympathetic and sympathetic nervous systems.

Gastrointestinal absorption of digoxin is a passive process. Absorption of digoxin from tablets is 50-75 percent. Digoxin is only 20-25 percent bound to plasma proteins and is predominantly excreted by the kidneys unmetabolized unless there is significant renal failure. Renal excretion of digoxin is proportional to glomerular filtration rate and is largely independent of urine flow. Digoxin is not effectively removed from the body by dialysis, exchange transfusions or during cardiopulmonary bypass presumably because of

tissue binding. In subjects with normal renal function digoxin is excreted exponentially with an average half-life of 36 hours resulting in the loss of 35-40 percent of the body stores daily.

Serum levels and pharmacokinetics are essentially unchanged by massive weight loss suggesting that lean body mass should be used in dosage calculations. The peak blood level from oral dosing with tablets occurs 1-3 hours after administration. The onset of therapeutic action of digoxin after oral tablets is 1-2 hours with the peak therapeutic effect occurring 6-8 hours after dosing.

INDICATIONS

1. "Congestive heart failure," all degrees, is the primary indication. The increased cardiac output results in diuresis and general amelioration of the disturbances characteristic of right (venous congestion, edema) and left (dyspnea, orthopnea, cardiac asthma) heart failure.

Digitalis, generally, is most effective in "low output" failure and less effective in "high output" (bronchopulmonary insufficiency, infection, hyperthyroidism) heart failure.

Digitalis should be continued after failure is abolished unless some known precipitating factor is corrected.

2. "Atrial fibrillation"—especially when the ventricular rate is elevated. Digitalis rapidly reduces ventricular rates and eliminates the pulse deficit. Palpitation, precordial distress or weakness are relieved and any concommitant congestive failure ameliorated.

Digitalis is continued in doses necessary to maintain the desired ventricular rate and other clinical effects.

3. "Atrial flutter" digitalis slows the heart and regular sinus rhythm may appear. Frequently the flutter is converted to atrial fibrillation with a slow ventricular rate. Stopping digitalis at this point may be followed by restoration of sinus rhythm, especially if the flutter was of the paroxysmal type. It is preferable, however, to continue digitalis if failure ensues or if atrial flutter is a frequent occurrence.

4. "Paroxysmal atrial tachycardia" digitalis may be used, especially if it is resistant to lesser measures. Depending on the urgency, a more rapid acting parenteral preparation may be preferable to initiate digitalization, although if failure has ensued or paroxysms recur frequently, digitalis is maintained by oral administration.

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Digitalis is not indicated in sinus tachycardia or premature systoles in the absence of heart failure.

"Cardiogenic shock"—the value of digitalis is not established, but the drug is often employed, especially when the condition is accompanied by pulmonary edema. Digitalis seems to adversely affect shock due to infections.

CONTRAINDICATIONS

The presence of toxic effects (See "Overdosage") induced by any digitalis preparation is an absolute contraindication to all of the glycosides.

Allergy, though rare, does occur. It may not extend to all preparations and another may be tried.

Ventricular Fibrillation.

Ventricular tachycardia, unless congestive failure supervenes after a protracted episode not itself due to digitalis.

WARNINGS

Many of the arrhythmias for which digitalis is advised are identical with those reflecting digitalis intoxication. If the possibility of digitalis intoxication cannot be excluded, cardiac glycosides should be temporarily withheld if permitted by the clinical situation.

The patient with congestive heart failure may complain of nausea and vomiting. These symptoms may also be indications of digitalis intoxication. A clinical determination of the cause of these symptoms must be attempted before further drug administration.

Patients with renal insufficiency are apt to be unusually sensitive to digoxin. See Action Section for mechanism.

PRECAUTIONS

"Potassium depletion" sensitizes the myocardium to digitalis and toxicity is apt to develop even with usual dosage. Hypokalemia also tends to reduce the positive inotropic effect of digitalis.

Potassium wastage may result from diuretic, corticosteroid, hemodialysis and other therapy. It is apt to accompany malnutrition, old age and long-standing congestive heart failure.

"Acute myocardial infarction," severe pulmonary disease, or far advanced heart failure are apt to be more sensitive to digitalis and more prone to disturbances of rhythm.

"Calcium" affects contractility and excitability of the heart in a manner similar to that of digitalis. Calcium may produce serious arrhythmias in digitalized patients.

"Myxedema"—Digitalis requirements are less because excretion rate is decreased and blood levels are significantly higher.

"Incomplete AV block," especially patients subject to Stokes Adams attacks, may develop advanced or complete heart block. Heart failure in these patients can usually be controlled by other measures and by increasing the heart rate.

"Chronic constrictive pericarditis," is apt to respond unfavorably.

"Idiopathic hypertrophic subaortic stenosis" must be managed extremely carefully. Unless cardiac failure is severe it is doubtful whether digitalis should be employed.

"Renal insufficiency" delays the excretion of digitalis and dosage must be adjusted accordingly in patients with renal disease.

NOTE: This applies also to potassium administration should it become necessary.

Electrical conversion of arrhythmias may require adjustment of digitalis dosage.

ADVERSE REACTIONS

Gynecomastia, uncommon.

Overdosage or toxic effects. Gastrointestinal--anorexia, nausea, vomiting, diarrhea are the most common early symptioms of overdosages in the adult (but rarely conspicuous in infants). Uncontrolled heart failure may also produce such symptoms. Central Nervous System - headache, weakness, apathy, visual disturbances.

Cardiac Disturbances (Arrhythmias)-- ventricular premature beats is the most common, except in infants and young children.

Paroxysmal and nonparoxysmal nodal rhythms, atrioventricular (inference) dissociation and paroxysmal atrial tachycardia (PAT) with block are also common arrhythmias due to digitalis overdosage.

Conduction Disturbances—excessive slowing of the pulse is a clinical sign of digitalis overdosage. Atrioventricular block of increasing degree, may proceed to complete heart block.

NOTE: The electrocardiogram is fundamental in determining the presence and nature of these toxic disturbances. Digitalis may also induce other changes (as of the ST segment), but these provide no measure of the degree of digitalization.

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TREATMENT OF ARRHYTHMIAS PRODUCED BY OVERDOSAGES

Digitalis is discontinued until after all signs of toxicity are abolished. This may be all that is necessary if toxic manifestations are not severe and appear after the time for peak effect of the drug.

Potassium salts are commonly used. Potassium chloride in divided doses totaling 4 to 6 gm. for adults (See Pediatric Information for children) provided renal function is adequate.

When correction of the arrhythmia is urgent, potassium is administered intravenously in a solution of 5 percent dextrose in water, a total of 40–100 mEq. (40 mEq. per 500 ml.) at the rate of 40 mEq. per hour unless limited by pain due to local irritation.

Additional amounts may be given if the arrhythmia is uncontrolled and the potassium well tolerated.

Electrocardiographic monitoring is indicated to avoid potassium toxicity, e.g. peaking of T waves.

CAUTION

Potassium should not be used and may be dangerous for severe or complete heart block due to digitalis and not related to any tachycardia.

Chelating agents to bind calcium may also be used to counteract the arrhythmia effect of digitalis toxicity, hypokalemia and of elevated serum calcium which may also precipitate digitalis toxicity.

Four grams (0.8 percent solution) of the disodium salt of EDTA is dissolved in 500 ml. of 5 percent dextrose in water (50 mg. per ml.) and administered over a period of 2 hours unless the arrhythmia is controlled before the infusion is completed.

A continuous electrocardiogram should be observed so that the infusion may be promptly stopped when the desired effect is achieved.

Other counteracting agents are: ~~Quinidine,~~ ——— Quinidine procainamide, and beta adrenergic blocking agents.

DOSAGE AND ADMINISTRATION

Oral digitalis is administered slowly or rapidly as required until the desired therapeutic effect is obtained without symptoms of overdosage. The amount can be predicted approximately from the weight of the patient with allowances made for excretion during the time taken to induce digitalization.

Subsequent maintenance dosage is also determined tentatively by the amount necessary to sustain the desired therapeutic effect.

Recommended dosages are practical average figures which may require considerable modification as dictated by individual sensitivity or associated conditions. (See Warning Precautions.)

The average digitalizing dose with digoxin tablets is 1.25-1.5 milligrams. Digitalization may be accomplished by several approaches. A dose of 1.0 milligram orally usually produces a digitalis effect in 1-2 hours and becomes maximal in 6-8 hours. Additional doses of 0.25 or 0.5 milligram may be given at 6-8 hour intervals to full digitalization.

The usual daily oral maintenance dose is 0.25-0.5 milligram. For previously undigitalized patients, institution of daily maintenance therapy without a loading dose results in development of steady-state plateau concentrations in about seven days in patients with normal renal function. By giving 0.75 milligram digoxin daily in divided doses the desired therapeutic affect may be achieved in a previously undigitalized patient with normal renal function in 4-5 days.

It cannot be overemphasized that the values given are averages and substantial individual variation can be expected.

(If pediatric dosage is available the labeling sections above should be expanded to include the following information.)

PEDIATRIC INFORMATION

WARNINGS

Newborn infants during first month of life have a sharply defined tolerance to digitalis. Impaired renal function must also be carefully taken into consideration.

"Premature and immature infants" are particularly sensitive and further reduction of dosage may be necessary.

Congestive failure accompanying acute "glomerulonephritis" requires extreme care in digitalization. A relatievly low total dose administered in divided doses and concomitant use of reserpine or other antihypertensive agents has been recommended. Constant ECG monitoring is essential and digitalis discontinued as soon as possible.

IDIOPATHIC HYPERTROPHIC SUBAORTIC STENOSIS

See Adult Precautions.

"Rheumatic carditis"—such cases, especially when severe, are unusually sensitive to digitalis and prone to disturbances of rhythm. If heart failure develops, digitalization may be tried with relatively low doses; then cautiously increased until a beneficial effect is obtained. If a therapeutic trial does not result in improvement, the drug should be considered ineffective and be discontinued.

NOTE: Digitalis glycosides are an important cause of accidental poisoning in children.

PRECAUTIONS

Dosage must be carefully titrated.

Electrocardiographic monitoring may be necessary to avoid intoxication.

Premonitory signs of toxicity in the newborn are undue slowing of the sinus rate, sinoatrial arrest, and prolongation of PR interval.

OVERDOSAGE EFFECTS

Toxic signs differ from the adult in a number of respects.

Cardiac arrhythmias are the more reliable and frequent signs of toxicity.

Vomiting and diarrhea, neurologic and ophthalmiological disturbances are rare as initial signs.

Premature ventricular systoles are rarely seen; nodal and atrial systoles are more frequent.

Atrial arrhythmias, atrial ectopic rhythms and paroxysmal atrial tachycardia with AV block particularly are more common manifestations of toxicity in children.

Ventricular arrhythmias are rare.

TREATMENT OF TOXIC ARRHYTHMIAS

(See section for adults.) Potassium preparations may be given orally in divided doses totaling 1–2 gm. daily in children. When correction of the arrhythmia is urgent, 5 to 10 mEq. of potassium per hour are given, this amount being dissolved in 100 ml. of 5 percent dextrose in water. Additional amounts of potassium may be given if necessary and well tolerated by the child.

A chelating agent may be tried if other measures fail. EDTA intravenously has been

recommended in a dose of 15 mg./kg./hr. in 5 percent dextrose in water, the total not to exceed 60 mg./kg./day. A continuous electrocardiogram should be observed so that the infusion can be stopped promptly when the desired effect is achieved.

DOSAGE AND ADMINISTRATION

Digitalization must be individualized. Generally, premature and immature infants are particularly sensitive permitting reduced dosage which must be determined by careful titration.

Oral dosage. Newborn (normal), from birth to 1 month, require adult proportions by body weight.

Infants, 1 month to 2 years require approximately 50 percent more by body weight than adult proportions.

Children, 2 years and over require adult proportions by body weight.

(Complete by adding dosage for the specific preparation.)

Long term use of digitalis is indicated in almost all infants who have been digitalized for acute congestive failure unless the cause is transient. Many favor maintaining digitalis until at least 2 years of age in all infants with paroxysmal atrial tachycardia or who show either definite or latent failure.

Many children with severe inoperable congenital defects need digitalis throughout childhood and often for life.

(f) Abbreviated new drug applications shall be submitted to the Food and Drug Administration, Bureau of Drugs, Office of Scientific Evaluation, Generic Drug Staff (HFD-107), 5600 Fishers Lane, Rockville, MD 20852.

(g) All samples of digoxin tablets required by paragraph (a)(3) of this section to be submitted to the Food and Drug Administration shall be handled as follows:

(1) The sample shall consist of 6 subsamples of 1000 tablets each collected at random from throughout the manufacturing run. Each of the 6 subsamples shall be identified with the name of the product, the labeled potency, the date of manufacture, the batch number, and the name and address of the manufacturer.

(2) The sample together with the batch production record and results of all tests conducted by or for the manufacturer to determine the product's identity, strength, quality, and purity, content uniformity and dissolution shall be submitted to the Department of Health, Education, and Welfare, Public Health Service, FDA National Center for Drug Analysis, 1114 Market St., St Louis, MO 63101. The outer wrapper shall be identified "SAMPLE -- DIGOXIN CERTIFICATION."

(h) The Food and Drug Administration is aware of data with two in vitro methods, in addition to that described in The United States Pharmacopeia (USP XVIII), developed to measure digoxin tablets dissolution.