REPORT TO THE CONGRESS

Public Hazards From Unsatisfactory Medical Diagnostic Products

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

BY THE COMPTROLLER GENERAL OF THE UNITED STATES

MWD-75-52

APRIL 30, 1975

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

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

This is our report discussing public hazards from unsatisfactory medical diagnostic products. The Food and Drug Administration, Department of Health, Education, and Welfare, is responsible for administering the activities discussed in this report.

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).

We are sending copies of this report 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

BMDDP	Bureau of Medical Devices and Diagnostic Products
CDC	Center for Disease Control
DOD	Department of Defense
DPSC	Defense Personnel Support Center
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office

GMPs	good manufacturing practices
GOT	glutamic oxalacetic transaminase
HEW	Department of Health, Education, and Welfare
PHS Act	Public Health Service Act
USPC	United States Pharmacopeial Convention

COMPTROLLER GENERAL'S
REPORT TO THE CONGRESS

PUBLIC HAZARDS FROM UNSATISFACTORY MEDICAL DIAGNOSTIC PRODUCTS
Food and Drug Administration
Department of Health, Education, and Welfare

D I G E S T

WHY THE REVIEW WAS MADE

Diagnostic products help to determine the presence or absence of a disease or medical condition. Unreliable diagnostic products could pose a serious hazard to the public health.

GAO, aware of congressional interest in consumer protection, made this review to see how effective Federal controls are in insuring the reliability of diagnostic products.

FINDINGS AND CONCLUSIONS

Diagnostic products are chemical or biological in origin. There are two types of diagnostic products--those taken internally (in vivo) and those used to analyze specimens taken from the body (in vitro).

In vivo diagnostic products are considered drugs and regulated accordingly. Chemical drugs are regulated under the Federal Food, Drug, and Cosmetic Act, which requires drugs in interstate commerce to be safe and effective.

Biological drugs shipped interstate are controlled under the same act and under section 351 of the Public Health Service Act, which requires that these products be licensed to insure they are safe, pure, and potent.

Chemical drugs are not regulated by the Public Health Service Act. The Food and Drug Administration, Department of Health, Education, and Welfare (HEW), administers the Food, Drug, and Cosmetic Act and the drug provisions of the Public Health Service Act.

According to the Administration, in vitro diagnostics may be classified as either drugs or medical devices. The Food, Drug, and Cosmetic Act prohibits sale in interstate commerce of drugs and medical devices that are adulterated or misbranded. However, medical devices, unlike drugs, are not required to be proven safe and effective before marketing.

In vitro diagnostic products are reagents (chemical or biological substances), kits, or instruments used to examine specimens for the presence or absence of a disease or condition. Reagents may be sold either in bulk form or

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in test kits.

HEW's Center for Disease Control, which is responsible for administering the Clinical Laboratories Improvement Act, has played an important role in monitoring diagnostic products.

Although the Center lacks regulatory authority over in vitro diagnostics, it evaluates in vitro biological diagnostic products under premarket and market testing programs.

Under its premarket program, the Center tests samples of each product lot submitted voluntarily by a manufacturer before marketing, and, under its market program, it tests products purchased from the marketplace.

Unreliable diagnostics on the market

- Unreliable in vitro diagnostics are being sold in the United States and exported to foreign countries. Center officials estimate that 25 percent of all diagnostic test results are unreliable and that erroneous diagnostic tests result in, among other things, unnecessary medical treatment, withholding necessary medical treatment, and lost income, costing the U.S. economy $25 billion annually.

The Center for Disease Control, at GAO's request, tested 44 marketed in vitro diagnostic products to determine whether laboratory test results using the products would aid a physician in diagnosis. The Center judged that 32 of the products were unsatisfactory for diagnostic use.

In addition, during fiscal year 1974, the Center tested about 2,000 other in vitro diagnostic product samples; 450 of them did not meet its standards. (See pp. 6 to 21.)

Food and Drug Administration's regulatory activities have been ineffective

Although the Administration has regulatory responsibility for in vitro diagnostic products, its regulation of these products has been ineffective. Until about 2 years ago, the Administration did not have a formal program to control in vitro diagnostic products.

However, because of the increasing use of these products and the need to better assure their effectiveness and reliability, the Administration in March 1973 issued regulations for their control.

The regulations provide for voluntary registration of in vitro diagnostic manufacturers and a listing of their products and for establishing performance and labeling standards. In addition, the Administration plans to establish manufacturing criteria under which in vitro diagnostics must be manufactured. (See p. 24.)

As of September 1974, however,

about 18 months after issuance of the regulations, the Administration's control over in vitro diagnostics had not been effectively implemented. Manufacturers generally had not registered; the Administration had established neither performance standards, manufacturing criteria, nor an adequate surveillance program. (See pp. 25 to 29.)

Requirements for exported products inconsistent

Exportation of biological and chemical in vitro diagnostic products is regulated under the Public Health Service and Food, Drug, and Cosmetic Acts, respectively; however, the export provisions of these acts are inconsistent. Under the Public Health Service Act, exported in vitro biological diagnostics must meet U.S. standards of safety, purity, and potency.

In contrast, under the Food, Drug, and Cosmetic Act, exported chemical in vitro diagnostics are required only to

--adhere to the specifications of the foreign purchaser,

--comply with the laws of the destination country, and

--be labeled to show they are intended for export.

Since many countries do not have standards governing the reliability of in vitro diagnostics, the export provision of the Food, Drug, and Cosmetic Act does not assure that misbranded and/or adulterated chemical in vitro diagnostic products are not exported. (See pp. 29 and 30.)

Foreign countries not always notified of U.S. recalls

The Administration believes it has a moral obligation to notify foreign countries of domestic recalls of in vitro diagnostic products and has established procedures to do so.

However, GAO's review of recalled in vitro diagnostic products which had been distributed internationally from January 1971 through February 1974 showed that in 23 of 35 instances FDA had not notified the foreign countries involved. Consequently, products recalled in the United States could continue to be marketed and used elsewhere. (See pp. 47 and 48.)

Need for clarifying the Administration's authority over biological in vitro diagnostics

Legislation concerning the regulation of in vitro biological diagnostics is not clear, and not all in vitro biologicals are regulated in the same way.

The Administration believes it has discretionary authority to license an in vitro biological diagnostic under the Public Health Service Act or

control it under the regulatory program established for in vitro diagnostics.

The Administration, under the Public Health Service Act, licenses some in vitro biological diagnostic products. However, it has not licensed about 2,000 other such products. Judicial decisions which have interpreted the Administration's authority to license in vitro biological diagnostics have not clearly defined the Administration's authority regarding these products. (See ch. 4.)

Need to improve problem-product reporting system

To effectively regulate in vitro diagnostics, the Administration must systematically obtain information concerning problems with such products. Administration efforts to obtain such information from professional organizations and from foreign countries who use U.S.-produced in vitro diagnostics have not been adequate.

In some cases, organizations wanting to report information to the Administration through a problem-product reporting system have been discouraged from doing so.

In addition, the Center for Disease Control has information concerning problems with in vitro diagnostic products but generally does not provide such information to the Administration. Because the Center does not have regulatory authority over in vitro diagnostic products, GAO believes the Center should routinely furnish such information to the Administration. (See pp. 43 and 44.)

When the Administration has learned of problems concerning in vitro diagnostics, it has not always taken adequate investigational action.

GAO reviewed 128 complaints submitted to the Administration and found that investigational action was not taken to determine the validity of the complaint and the need for regulatory action on 94 of them, including instances of potentially unreliable products. (See pp. 41 to 43.)

RECOMMENDATIONS

The Secretary of HEW should direct the Commissioner of the Food and Drug Administration to take immediate measures to strengthen the Administration's program for controlling in vitro diagnostics. Specifically, the Administration should:

--Hasten development of product class standards.

--Establish criteria under which in vitro diagnostics must be manufactured.

--Establish an adequate surveillance program, including (1) product testing, to determine compliance with labeling and performance standards, and (2) periodic

inspections of manufacturing plants.

--Expand operation of the problem-product reporting system to develop additional sources of information on problem in vitro diagnostics.

--Establish, where feasible, communication with foreign countries to develop information on regulatory actions and complaints of foreign countries concerning U.S.-produced in vitro diagnostic products.

--Take prompt regulatory action when appropriate, concerning products (1) which performed unsatisfactorily in the Center for Disease Control's tests and (2) against which complaints were otherwise reported.

--Strengthen the Administration's program of notifying foreign users of U.S.-produced in vitro diagnostic products which have been recalled.

--Evaluate the need for additional resources to effectively carry out objectives of the in vitro diagnostic program and, if warranted, allocate additional resources to the program.

The Secretary should require the Director of the Center for Disease Control to routinely provide the Administration with information concerning problem in vitro diagnostics identified by the Center in its testing. (See pp. 51 and 52.)

AGENCY ACTIONS AND UNRESOLVED ISSUES

HEW generally agreed with GAO's recommendations and said several actions had been or would be taken to implement them. (See pp. 52 to 54.)

MATTERS FOR CONSIDERATION BY THE CONGRESS

Several legislative proposals were introduced in the 93d Congress to provide the Administration with additional authority to regulate in vitro diagnostic products. These proposals would have

--required mandatory registration of all manufacturers;

--required periodic inspections of in vitro diagnostic manufacturers;

--given the Administration access to manufacturers' quality control, complaint, and other records needed to determine compliance with the Food, Drug, and Cosmetic Act;

--allowed the Administration to detain products suspected of being violative;

--authorized the Administration to require firms to recall all violative products; and

--prevented export of in vitro diagnostic products not meeting U.S. standards.

GAO recommends that the Congress enact similar legislation.

In addition, the Congress may wish to clarify its intention as to whether products of biological origin should be controlled under the Food, Drug, and Cosmetic Act or whether they should be licensed in accordance with the Public Health Service Act. (See pp. 54 and 55.)

CHAPTER 1

INTRODUCTION

Today more than ever, doctors are relying on laboratory tests to help diagnose, treat, or control medical conditions and diseases. An inaccurate diagnosis may result in injury to an individual's health; death; or, at a minimum, needless medical expense. Unreliable diagnostic products contribute to inaccurate laboratory test results.

Products used to perform diagnostic tests are chemical or biological in origin. There are two types of diagnostic products--those taken internally (in vivo) and those used to analyze specimens taken from the body (in vitro).

In vivo diagnostic products are considered drugs and are regulated accordingly. Chemical drugs are regulated under the Federal Food, Drug, and Cosmetic (FD&C) Act, as amended (21 U.S. C. 301). Biological drugs are subject to both the FD&C Act and section 351 of the Public Health Service (PHS) Act, as amended (42 U.S.C. 262). The FD&C Act requires that a drug be safe and effective before it is introduced in interstate commerce. The PHS Act requires that biological drugs shipped interstate be licensed to insure they are safe, pure, and potent as well as safe and effective under the FD&C Act. Chemical drugs are not regulated by the PHS Act. The Food and Drug Administration (FDA), Department of Health, Education, and Welfare (HEW), administers the FD&C Act and the drug provisions of the PHS Act.

We have issued a number of reports concerning FDA's regulatory activities involving drugs. (See app. I.) These reports discussed, among other matters, (1) FDA's monitoring of adverse drug reactions, (2) the need to insure that vaccines are effective, (3) problems in obtaining compliance with Federal good manufacturing practices for drugs, and (4) the need for additional Federal regulatory authority to protect the consumer from harmful drugs.

This report discusses FDA's regulation of in vitro diagnostics which, according to FDA, may be classified as either drugs or medical devices. The FD&C Act prohibits the sale in interstate commerce of medical devices that are adulterated or misbranded but, unlike drugs, does not require that

medical devices be proven safe and effective before marketing.

According to industry reports, laboratories in the United States perform about 3 billion in vitro diagnostic tests a year. Industry experts estimate that clinical laboratory services involving these tests cost the consumer about $1.3 billion in 1970 and they expect the cost to increase to $2.8 billion by 1980.

Government and industry experts estimate that manufacturers produce about 100,000 different in vitro diagnostic products. Total sales of in vitro diagnostic products in 1973 were estimated at about $400 million.

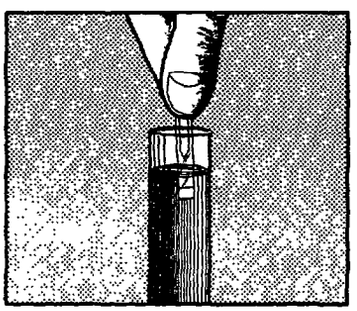
In vitro diagnostic products are reagents (chemical or biological substances), kits, or instruments which are used to examine a specimen for the presence or absence of a disease or condition. Reagents may be sold either in bulk form or in test kits. Technicians use commercial reagents sold in bulk form in conjunction with their own methods and equipment. Test kits contain complete instructions for performing the test and may contain equipment to be used with the reagents.

The term "in vitro diagnostic products", as discussed in this report, refers to all such products ranging from test kits as simple as dipsticks (see p. 3) to reagents used in conjunction with sophisticated testing methods and equipment (see p. 4).

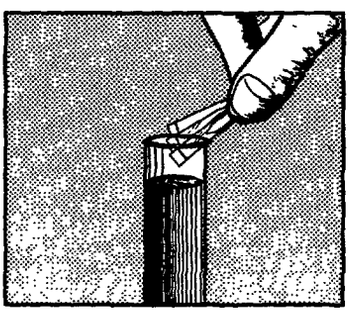
Until recently FDA did not have a formal program to regulate in vitro diagnostic products. Pursuant to the FD&C and PHS Acts, FDA issued regulations in March 1973 to control in vitro diagnostics. These regulations provide for labeling and performance standards which in vitro diagnostic products must meet. According to HEW's Assistant General Counsel, Food and Drug Division, FDA regulations do not classify in vitro diagnostics as either drugs or devices to avoid possible litigation over the definition of such products. If an in vitro diagnostic product fails to comply with these standards, FDA intends to classify it as either a drug or device and subject it to the applicable statutory requirements. FDA's Bureau of Medical Devices and Diagnostic

Products (BMDDP)[1] is primarily responsible for administering FDA activities for regulating in vitro diagnostic products. FDA's Bureau of Biologics administers the regulation of in vitro biological diagnostic products.

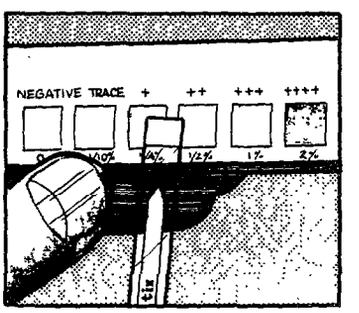
DIRECTIONS–Must be followed exactly



1. Dip reagent end of strip in urine specimen for two seconds and remove.(As an alternate method, wet reagent area of strip for 2 seconds by passing through urine stream.)

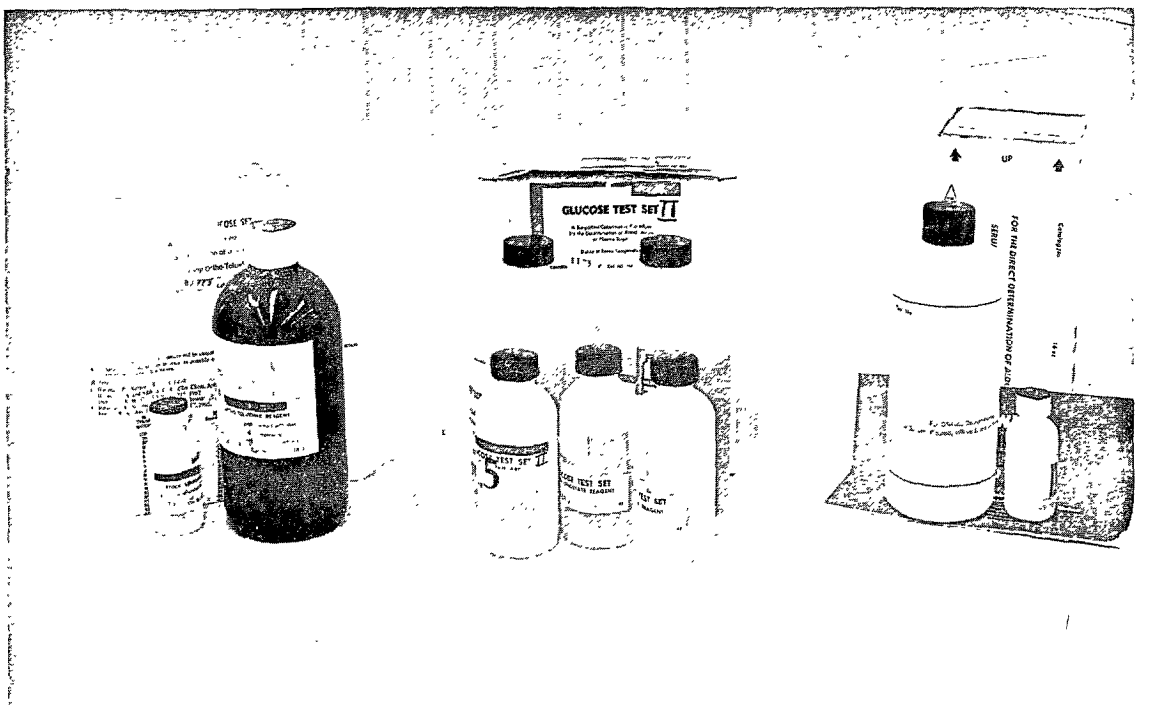


2. Tap edge of strip against side of urine container or sink to remove excess urine.



3. *Exactly 30 seconds* after removing from urine, compare *reagent side* of strip to the closest matching color block. Original color of reagent area is light blue; disregard color changes that occur after 30 seconds.)

[1]BMDDP was created in February 1974. Before then FDA's Bureau of Drugs was responsible for in vitro diagnostic products.



Above--Bilirubin test kits. (See p. 9.)
Below--Glucose test kits. (See p. 8.)
Both are used in laboratories with technical laboratory equipment.

HEW's Center for Disease Control (CDC), responsible for administering the Clinical Laboratories Improvement Act of 1967 (42 U.S.C. 263a), has played a significant role in monitoring diagnostic products used in clinical laboratories.

Because accurate test results demand reliable diagnostic products, CDC has developed performance standards for about 2,000 in vitro microbiological (a subclass of biological) diagnostic products and has established programs for premarket and market testing of these products. Under its premarket testing program, CDC tests samples of each product lot submitted voluntarily by the manufacturer before it is marketed. Under its market testing program, CDC tests products purchased from the marketplace. Although CDC evaluates in vitro diagnostics, it does not have regulatory authority over these products. (CDC's testing programs are further discussed on pp. 18 to 21.)

CDC does not have a formal program for testing chemical in vitro diagnostics but has occasionally tested such products.

CHAPTER 2

PROBLEMS WITH IN VITRO DIAGNOSTIC PRODUCTS

Although FDA has regulatory responsibility for in vitro diagnostic products, its regulation of these products has been ineffective. Unreliable in vitro diagnostic products are being marketed in the United States. A CDC official estimated that 25 percent (about 750 million) of all diagnostic test results are unreliable and that erroneous diagnostic tests result in, among other things, unnecessary medical treatment, withholding necessary medical treatment, and lost income costing the economy about $25 billion annually.

Although CDC is not authorized to regulate in vitro diagnostic products, it has evaluated commercially produced diagnostic products, primarily biological diagnostics, since 1956. Therefore, we requested CDC's assistance in evaluating chemical in vitro diagnostic kits.

RESULTS OF CDC TESTING FOR GAO

At our request, CDC tested 44 in vitro diagnostic kits purchased in July 1973. These kits are commonly used in seven clinical laboratory tests which help physicians diagnose several diseases and medical conditions. The results of CDC's testing were provided to us in its December 1973 report entitled "Diagnostic Products in the Clinical Laboratory, A Preliminary Survey of Selected 'Kits' and Reagent Sets for Clinical Chemical Analyses." CDC concluded that 32, or about 73 percent, of the 44 kits were unsatisfactory for diagnostic use.

Criteria used in CDC's evaluation

The evaluated kits were selected from a large number of kits on the market. The selection was based primarily on the frequency with which test results were used in making medical decisions and the seriousness of those decisions. Also, the kits selected represented varied methodologic approaches which could be expected to produce differences in test results.

To evaluate the 44 kits, CDC first developed measurement standards. The standards, or reference methods, utilize

reliable analytical techniques extensively used in other laboratories. Each kit was used in accordance with the manufacturer's instructions and was evaluated on its performance. The results were compared to CDC's reference method and evaluated on the basis of the following factors:

1. Bias--Represents the deviation from the value obtained by CDC using its reference method.

2. Precision--Represents the reliability with which the test results can be reproduced (even though they may be consistently biased).

3. Interference--Represents the extent of deviation from CDC's reference method by which drugs or naturally occurring chemicals interfere with the test results.

4. Recovery--Measures the procedure's ability to accurately determine the amount of a pure chemical under consideration when quantities of the chemical have been added to the solution being analyzed.

5. Instructions--Represents a scaled estimate of the accuracy, clarity, and usefulness of the instructions in the test kit.

CDC evaluated each product to determine if laboratory tests results would "* * * aid the physician in diagnosis, or be of very little or no value--or even misleading * * *." CDC concluded that its test results of the 44 in vitro diagnostics were applicable to the reliability of only the specific kits tested and were sufficient to conclude that many of these kits provided results which were unsatisfactory for clinical use. However, because of the small number of kits tested, the study results are not projectable to the same products produced by the manufacturer.

Product test results

A tabulation of all 44 product test results is contained in appendix II. The following table shows CDC test results for each product class tested.

Product class tested	Number of kits tested	Test results	
		Satisfactory	Unsatisfactory
Glucose	8	4	4
Cholesterol	7	1	6
Bilirubin	7	1	6
Sodium	3	1	2
Calcium	5	1	4
Glutamic oxal-acetic trans-aminase (GOT)	10	3	7
Thyroxine	4	1	3
Total	44	12	32

CDC's test results for each product class and the possible medical significance of laboratory tests using such products are summarized below.

Glucose

Glucose, a tissue nutrient necessary for life, is a vital component of human blood. In some diseases the blood glucose concentration is altered and a laboratory determination is necessary to help the physician diagnose and control the disease. For example, glucose determinations are used to diagnose diabetes, a serious disease which in its extreme form can be fatal.

About 93 million blood glucose determinations are made annually at an estimated cost of about $140 million. Accurate results are important because the healthy patient who is misclassified as having an abnormally high glucose level, even temporarily, may be subjected to additional testing, an extended hospital stay, special diets, and drugs in addition to personal inconvenience and psychological trauma. On the other hand, the patient with a high glucose level

who is misdiagnosed as a result of laboratory error will have treatment postponed or perhaps be incorrectly treated.

Also, inaccurate determinations of glucose levels in the blood of a diabetic will adversely effect treatment. A severe diabetic receives insulin, a very potent drug which is usually self-administered. Incorrect analysis may lead to insufficient treatment or an overdose of insulin which can decrease blood glucose to life-threatening levels.

CDC evaluated eight blood glucose test kits; four were unsatisfactory. To be useful, these kits must be able to reliably demonstrate high, low, or normal glucose concentrations in the blood. The four unsatisfactory kits failed to accurately measure these concentrations consistently and reliably and their use could have resulted in clinically erroneous conclusions.

Bilirubin

Bilirubin is a waste product of blood. Red blood cells are broken down in the body when the cells reach a certain age--about 120 days--and the hemoglobin (the oxygen-carrying component of the blood) is released to be eventually broken down into bilirubin, which is carried in the blood plasma. As the blood circulates through the liver, most bilirubin is removed and excreted as part of the bile. The bile in turn is excreted into the intestines via the gall bladder and thus removed from the body. Bilirubin concentrations in the blood increase when (1) the liver fails to excrete bilirubin as fast as it is formed or (2) the red cells are broken down at excessive rates.

The most common use of bilirubin determinations is in diagnosing liver disease. For example, a liver damaged by hepatitis cannot remove bilirubin, which may accumulate in the blood to such an extent as to color the patient's skin yellow (jaundice). A decreasing bilirubin level may indicate a turning point in the disease, whereas increasing levels may indicate a more serious condition. In 1973 about 60,000 cases of hepatitis were reported in the United States. However, CDC officials said that only about 10 percent of the cases are reported. They estimate that there are about 600,000 cases of hepatitis annually.

Rapid red cell breakdown is commonly caused by incompatability of the blood of a newborn baby with that of its mother. If red cells are destroyed rapidly, bilirubin may accumulate in levels sufficient to produce permanent brain damage in the child. About 21,500 babies suffer each year from mother-child blood-type incompatibilities.

Guided by laboratory results of bilirubin determinations, the pediatrician can evaluate the rate of bilirubin production and decide whether to replace the child's blood, a dangerous procedure. In many instances, a transfusion may be unnecessary because the destruction of red cells reaches a maximum and declines. Inaccuracies in the bilirubin determination may lead to inappropriate medical decisions which, in turn, could cause complications, such as mental retardation or even death, as well as unnecessary expense.

An estimated $64 million is spent annually on about 43 million bilirubin determinations. CDC evaluated seven kits used for blood bilirubin determinations; six were unsatisfactory. A CDC official said these six kits produced erroneous results which could lead a physician to misdiagnose a patient's immediate problem and, therefore, handle the patient's medical care inappropriately.

Cholesterol

Cholesterol is a fatlike material widely distributed throughout the body. It is believed that as people age cholesterol tends to be deposited on the blood vessel walls, contributing to arteriosclerosis. Persons with arteriosclerosis may subsequently develop coronary heart disease. Estimates of coronary heart disease among the U.S. population run as high as 5 percent (over 10 million people). Elevated blood cholesterol levels may alert the physician to the need for appropriate therapy to help prevent the development of coronary heart disease.

Falsely low determinations of blood cholesterol may indicate a healthy patient and delay treatment which might prevent a heart attack. Falsely elevated determinations may lead to additional medical procedures and possibly subject the patient to unnecessary special dietary or drug regimens.

Approximately 50 million cholesterol determinations are made annually, costing the consumer about $75 million. CDC evaluated seven blood cholesterol kits; six were unsatisfactory. CDC concluded that the instructions accompanying these kits were often grossly inadequate and that, as a group, the procedures prescribed for using the kits represented serious deviations from approved scientific methods for cholesterol tests.

Sodium

Sodium plays a principal role in both water and acid-base balance in the human body. Sodium determinations must be extremely accurate to be of maximum use to the physician.

In acutely ill patients, small errors in sodium determination may lead to incorrect treatment with serious consequences. Surgery and its complications frequently leave the patient's regulation of fluids and salts entirely in the hands of the physician and nursing staff. Precise laboratory monitoring of sodium levels is vital for maintaining life over long periods with intravenous fluid therapy. Excessive administration of sodium, for example, may lead to cardiac and lung complications, and patients can actually drown in their own fluids that fill the lung. Also incorrect treatment may lead to a complex maladjustment of total body fluid and chemical balance, which may be difficult to interpret and treat and may be quite expensive to the patient through extended hospital stay and additional testing.

In hospitals that handle acutely ill or surgical patients, sodium determinations are among the 10 most frequently performed tests. An estimated 39 million such determinations are made annually, costing about $58 million. CDC tested three sodium test kits; only one was satisfactory. The other two kits decisively failed to show accurate readings and, according to a CDC official, could lead the physician to follow an erroneous course of treatment.

Calcium

Calcium, an important mineral constituent of bone, is essential for many critical body functions. The level of calcium in blood plasma is regulated by a number of factors,

including the activity of the parathyroid gland in the neck. High calcium levels may result from parathyroid tumors or bone cancer. Low levels are found in diseases involving deficiency of parathyroid hormone or vitamin D.

The most critical use of the calcium determination is in the diagnosis of parathyroid activity. The calcium determination must be especially accurate in diagnosing hyperparathyroidism (excessive secretion of parathyroid hormone), an insidious disease imitating a number of other diseases. It is chiefly identified by elevated calcium levels in the blood as well as altered calcium and phosphorus excretion in the urine. A surgeon's reliance upon a falsely elevated test result could lead to unnecessary surgical removal of normal parathyroid glands or might necessitate the patient receiving injections of parathyroid hormone for the rest of his life.

There are over 200,000 cases of hyperparathyroid disease in the United States. Approximately 38 million calcium tests are done each year, costing about $57 million. CDC tested five calcium kits; four were unsatisfactory. None of the four kits met all of CDC's criteria for bias, precision, interference, and recovery. In addition, CDC concluded that the instructions accompanying all five kits were inadequate.

GOT

GOT is an enzyme which controls the transfer of protein and represents an important metabolic path in supplying energy to the cells of such vital tissues as heart muscle and liver. Normally only small amounts of GOT are present in the blood. In diseases causing a breakdown of cells containing large amounts of GOT, the enzyme may leak into the blood and its excess indicates a disease.

GOT levels increase in two common diseases, heart attack and hepatitis (liver disease). After a heart attack caused by constriction or blockage of the coronary arteries, a portion of the heart muscle loses its blood supply and dies. The dying tissue cells disintegrate and their contents, including GOT, enter the bloodstream. Typically, the GOT level reaches a peak and then declines in about a week, a pattern highly suggestive of a heart attack. There are about 1.4 million heart attacks each year in the United States.

The GOT levels in the blood of a hepatitis patient are usually much higher than the levels seen in heart disease and may remain elevated for a longer time. GOT blood level determinations are useful to the physician who may prescribe drugs potentially toxic to the liver. Toxicity levels can be monitored by periodic GOT determinations.

An estimated $71 million is spent annually on about 47 million GOT determinations. CDC tested 10 kits marketed for use in GOT determinations; 7 were unsatisfactory. CDC concluded that some kits lacked precision and gave misleading interpretations.

Thyroxine

Thyroxine is an iodine-containing hormone produced by the thyroid gland whose function is to regulate the body's energy production and consumption. Certain diseases interfere with this function. A deficiency of this hormone slows down the body metabolism and an excess speeds it up dangerously. Diseases interfering with metabolism are often seriously debilitating with multiple and often confusing symptoms. In their initial stages these diseases may be difficult to diagnose.

An estimated 7 million thyroxine determinations are made annually, costing about $56 million. CDC evaluated four kits used to test thyroxine; three were unsatisfactory. CDC's study indicated that some of these kits were not measuring thyroxine and that laboratory determinations based on their results would, in some cases, provide totally erroneous information.

Manufacturer's comments on CDC's test results

In December 1973 CDC provided the test results of the 44 in vitro diagnostic kits to the 30 manufacturers of these products for their review and comment. Only five manufacturers provided comments. However, only one of the five expressed disagreement with CDC's evaluation. This manufacturer's comments and CDC's response are summarized below.

--The manufacturer contended that CDC's study could hardly be considered indicative of the true performance of some of the kits in the field as good laboratory practices dictate that the results of a product should not be used for diagnosis unless it has been used in conjunction with other diagnostic techniques and laboratory personnel have become familiar with it.

In responding to the manufacturer, CDC stated that the degree of familiarity achieved by CDC personnel during its study was considerably greater than that achieved by many users of the kit and similar products before the results were used for diagnosis.

--The manufacturer stated that although the CDC study cautioned that interpretations of the findings could not be extrapolated, the study extrapolates by determining if the product would aid the physician.

CDC said that the cautionary statement concerning extrapolations referred to the small number of products examined out of the thousands of such products on the market. The kits sampled could not possibly be representative of the entire field.

--The manufacturer took exception to the use of a statistical analysis on the basis of what it considered an inadequate data base. The manufacturer stated that the validity of any statistical analysis depends on the use of a truly representative sample. Small data pools can almost never be considered accurate.

CDC stated that in its testing of the manufacturer's product it used the results of about 36 separate analyses and concluded that the data collected was representative of the performance capability of the product tested.

--The manufacturer contended that its product was not fairly evaluated since it was tested at a concentration beyond which the product labeling claimed to perform. It also said the interference identified in CDC's test results for this product was due to bias between the kit and the reference method, not interference with other substances.

CDC responded that the product was tested according to CDC's guidelines and that no conclusions were drawn using data from samples with concentrations beyond which the product labeling claimed to perform. In addition, CDC stated that, although the inherent variability between the kit and the reference method precludes exact assessment of the degree of interference, the mean effect of two commonly interfering substances exceeded CDC's acceptability limits.

CDC TESTING OF SICKLE CELL ANEMIA PRODUCTS

In September 1973 CDC published its evaluation of products used to test for sickle cell anemia. This evaluation was done because numerous sickle cell detection programs, many federally funded, had been instituted in recent years.

Sickle cell anemia is a genetically transmitted condition, occurring mostly in blacks, in which red blood cells are rapidly destroyed. Individuals with one normal and one sickling gene are generally healthy but have the sickling trait which can be detected by testing their blood. These individuals carry the disease. There are more than 2 million carriers of sickle cell in the United States. Sickle cell anemia kills half its victims before they reach the age of 20.

Accurate diagnosis is important because of the variety and severity of symptoms which must be treated during a sudden intensification of the disease. In addition, it provides a basis for genetic counseling, in which individuals are informed of the probabilities of producing children with sickle cell anemia. If two carriers produce children, the chances are one in four that the child will have sickle cell anemia and two in four that the child will be a carrier.

CDC evaluated seven commercial test kits used to diagnose sickle cell anemia. It concluded that their accuracy varied greatly and incorrect diagnosis can often be expected. CDC considered five kits to be unsatisfactory.

Kits similar to the ones CDC considered unsatisfactory were used in a 1972 New York City Health Services Administration sickle cell anemia screening program in which about 109,000 people were tested. The test results were used as a basis for genetic counseling. CDC's evaluation of one kit similar to that used in the program showed that it gave 15.5-percent false negative results.

As a result of CDC's evaluation, the New York City Health Services Administration has changed its sickle cell screening program. The current program requires more precise testing before genetic counseling is performed.

OTHER STUDIES OF IN VITRO DIAGNOSTIC PRODUCTS

We reviewed other studies of in vitro diagnostic products which identified numerous unsatisfactory products. These studies were similar to CDC's in that they evaluated the products' bias, precision, interference, recovery, and instructions. (See p. 7.) Several products found unsatisfactory in these studies were the same products CDC found unsatisfactory in testing performed at our request. For example, a study of 12 kits used to measure cholesterol found 10 kits unacceptable. Two of the 10 had also provided unsatisfactory results in CDC's testing.

The table on page 17 identifies products found unsatisfactory by both CDC and independent studies.

Other studies found many unsatisfactory in vitro diagnostic products that CDC had not tested for us. These studies identified problems with products used to test for pregnancy, rheumatoid arthritis, and sickle cell anemia as well as products used to diagnose other diseases and conditions.

The studies indicate that information on the unacceptability of certain in vitro diagnostics has been available for many years and that such unsatisfactory products have been a continual problem.

Products CDC found unsatisfactory (as coded in app. II)	Other studies which found the same products unsatisfactory		
	Study (note a)	Year reported	Study conclusions
Cholesterol - Chol-2 and Chol-3	A	1968	Provided unacceptable results
Cholesterol - Chol-2	B	1968	Exceeded acceptable limits of error
Glucose - Gl-1	C	1969	Kit's precision was considered unacceptable
Glucose - Gl-1	D	1969	Fell significantly short of meeting criteria for acceptability
Calcium - Ca-3 and Ca-4	E	1970	Results obtained from kits could lead to errors in clinical interpretations
Sodium - Na-1	F	1971	Performance of kit unsatisfactory for sodium determinations
Thyroxine - T_4-4	G	1972	Although better than other available kits, it was less than satisfactory

[a]See appendix III for study acknowledgments.

CDC'S MICROBIOLOGICAL PRODUCT TESTING PROGRAMS

CDC tests in vitro microbiological diagnostic products under its market and voluntary premarket testing programs. Under both programs, products are evaluated to determine if they meet CDC's established criteria. Although CDC has identified unsatisfactory products, it has no regulatory authority over in vitro diagnostic products and generally has not referred products considered unsatisfactory to FDA for regulatory action. (This is further discussed in ch. 5.)

Instead CDC reports unsatisfactory test results to the manufacturers and relies on their voluntary cooperation not to market products not meeting CDC criteria. However, CDC has no mechanism for assuring that unsatisfactory products are not marketed.

Following is a summary of CDC's market and voluntary premarket program test results of in vitro microbiological diagnostic products for fiscal years 1972-73.

	Premarket program	Market program
1972:		
Samples tested	957	250
Percent unsatisfactory	19	53
1973:		
Samples tested	1,433	178
Percent unsatisfactory	23	55
1974:		
Samples tested	2,068	66
Percent unsatisfactory	22	42

Under the voluntary premarket program, a manufacturer choosing to participate submits for CDC's evaluation samples of currently marketed in vitro microbiological diagnostic products. The manufacturer determines the degree of participation in this program. For example, the manufacturer may submit samples of all lots of products it manufactures or samples of selected lots. CDC officials said the results of the voluntary testing program are not forwarded to FDA because CDC officials believe it would jeopardize manufacturer participation. Manufacturers have sent various products to CDC, including products used to test for rabies, polio, mumps, and venereal disease.

Under its market testing program, CDC purchases in vitro microbiological diagnostics on the market and evaluates them using CDC specifications. CDC's policy is to forward the results of its market testing program to FDA only when FDA requests information on the specific product tested. However, FDA is not notified of what CDC is testing. Under the market testing program, CDC evaluates products it suspects are unreliable. Examples of two product classes CDC evaluated are those used to test for cryptococcus and salmonella.

Cryptococcus

Cryptococcus is a fungus that most commonly affects the central nervous system. Cryptococcosis--the disease caused by the fungus--can cause severe chronic infection of the brain. The patient progressively loses weight and may finally die of central respiratory failure. Systemic cryptococcosis is almost always fatal unless treated. With therapy, the fatality rate is about 25 percent.

The true incidence of cryptococcosis is unknown because in many States it is not a reportable disease and, even where it is reportable, it may go undiagnosed because it is not often suspected. However, it has been estimated that there are about 300 new cases each year. In 1969, the latest year for which CDC statistics were available, 117 deaths were attributed to cryptococcosis.

CDC stated that the most sensitive and specific diagnostic test available for cryptococcosis is a latex agglutination test which identifies the cryptococcus fungus (antigen) circulating in the serum sample. This product was available from only one manufacturer. In 1973 CDC evaluated 24 cryptococcal test kits and found 14 (58 percent) "completely unsatisfactory." CDC informed the manufacturer on September 6, 1973, that:

> "The serious nature of cryptococcal meningitis the reliance placed by some physicians on serological test results, and the serious consequence of failure to treat or of unnecessary treatment, require that immediate action be taken to assure that no further use of this product will occur until proper quality control procedures are put into operation."

CDC supplied this information to FDA, which subsequently requested that the manufacturer notify its consignees of the problems associated with the cryptococcal test kits. The manufacturer sent a letter to its consignees concerning the product and on September 21, 1973, informed FDA that it had voluntarily stopped all further kit shipments.

Salmonella

Salmonella is a bacteria which often causes food poisoning. Salmonellosis is the infection caused by the bacteria. A previous GAO report entitled "Salmonella in Raw Meat and Poultry: An Assessment of the Problem" dated July 22, 1974 (B-164031(2)), said that some authorities consider salmonellosis to be one of the most important communicable disease problems of bacterial origin in the United States. About 1,300 types of salmonella can cause salmonellosis. Twelve types account for about 78 percent of all documented human infections. An estimated 2 million cases of human salmonellosis occur annually resulting in medical payments and lost working days costing at least $300 million.

Salmonellosis symptoms include headache, vomiting, diarrhea, abdominal pain, and fever. Severe salmonellosis may even cause death.

During the period 1971-73, CDC purchased and evaluated 391 products used in the typing of the salmonella bacteria. These products are used to investigate the cause of salmonellosis epidemics and represented most of such salmonella diagnostic products on the market during that time. Of the products tested, 194, or about 50 percent, were unsatisfactory. CDC did not provide these test results to FDA since FDA did not specifically request them.

FDA ACTIONS AGAINST UNSATISFACTORY IN VITRO DIAGNOSTICS

When adulterated or misbranded in vitro diagnostic products are found, FDA can classify them as either drugs or devices and initiate one or more of the following legal actions through the Department of Justice.

--Prosecute individuals violating the FD&C Act.

--Enjoin an individual or firm to perform or not perform some act.

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

In addition, FDA may request the firm to voluntary recall a product. A voluntary recall is an action taken by a firm, at FDA's request or at its own initiative, to remove from the market a product suspected or known to be defective. Because there is no law requiring such removal, FDA cannot enforce recalls; they are a matter of negotiation between industry and FDA. When a firm does not recall a product at FDA's request, FDA may initiate one of the above legal actions.

During the 3 years ended February 1974, FDA had seized one in vitro diagnostic product but had not initiated an injunction or prosecution action against any in vitro diagnostic manufacturer. According to HEW's Assistant General Counsel, Food and Drug Division, FDA has never initiated a prosecution action against an in vitro diagnostic manufacturer. FDA instead relied primarily on voluntary recalls to remove unsatisfactory products from the market.

During January 1, 1971, through February 28, 1974, there were 32 voluntary recalls of in vitro diagnostic products. The products involved in these actions included products used to test for gonorrhea, pregnancy, hepatitis, and calcium levels. Of these recalls, seven were initiated at FDA's request for such reasons as product unreliability or ineffectiveness. The manufacturers initiated the remaining 25 recalls because of such problems as superpotency, false test results, and incorrect expiration dates.

FDA actions on products CDC tested for GAO

We discussed with FDA the results of CDC's testing done at our request. An FDA official informed us that in July 1974 FDA initiated field inspections of each manufacturer of a product which CDC found unsatisfactory in its testing for us. The objective of the inspections was to:

--Obtain from the manufacturers data used to support all labeling claims made by products.

--Review the quality control procedures followed by the manufacturers to insure that the products would perform as labeled.

--Review the manufacturers' study used to support each product's expiration date, which is required on all such products as of September 1974.

--Review the adequacy of the manufacturers' shipping methods.

--Determine if the manufacturers made any changes in their products or labeling as a result of the CDC study.

--Review the manufacturers' complaint files and determine if any complaints had been received regarding the products' performance or labeling.

--Obtain a copy of each product's labeling and advertising material.

As of September 1974 these inspections were still in process.

CHAPTER 3

REGULATION OF IN VITRO DIAGNOSTIC PRODUCTS

Before March 1973 FDA did not have a formal program to control in vitro diagnostic products. However, the rapid development of in vitro diagnostic products combined with the increasing use of and reliance on the results from such products by physicians, hospital personnel, and clinical laboratories indicated to FDA that these products needed closer scrutiny because of the possibility of inaccurate and unreliable test results. Therefore, on March 15, 1973, FDA issued final regulations for their control.

However, as of September 1974, about 18 months after issuance of the regulations, FDA's program for controlling in vitro diagnostics had not been effectively implemented.

FDA'S PROGRAM

FDA's March 15, 1973, regulations set forth the conditions an in vitro diagnostic product must meet if it is not to violate the provisions of the FD&C and/or the PHS Acts pertaining to drugs or devices. (See pp. 1 to 3.) These regulations provide for:

--Voluntary registration of in vitro diagnostic manufacturers and a listing of their products.

--Labeling standards for all in vitro diagnostic products.

--Performance standards for similar-type products (called product class standards) to control products which cannot be adequately controlled by labeling standards alone.

--Criteria for manufacturing in vitro diagnostic products.

In addition, FDA plans to initiate surveillance activities, including plant inspections, to determine whether products are meeting applicable standards and whether production methods and controls are suitable.

Voluntary registration

Because FDA does not regulate in vitro diagnostics as drugs, it lacks specific authority to require mandatory registration of in vitro diagnostic manufacturers and a listing of their products. Therefore, FDA's program provides for voluntary registration. The development of a complete list of manufacturers and their products for FDA's use in regulating the in vitro diagnostics industry depends on all manufacturers' cooperation. According to an FDA official, incomplete identification of all in vitro diagnostic manufacturers and their products will hamper FDA's efforts to insure that products currently marketed and new products to be marketed are properly labeled and meet applicable performance standards.

On March 7, 1973, FDA issued regulations providing that manufacturers of drugs already registered as such submit to FDA a list of drugs and in vitro diagnostic products they manufacture. FDA requested that the first list be submitted during June 1973. In addition, on March 15, 1973, it issued regulations providing for voluntary registration of in vitro diagnostic manufacturers by April 15, 1973. FDA publicized these requests in various trade journals and at industry briefings.

Despite these efforts, according to a Bureau of Medical Devices and Diagnostic Products official, the voluntary program has not been successful. As of May 1974 only 155 of the estimated 600 to 1,000 firms had registered, indicating on their registration forms that they produce a total of about 13,000 products (about 13 percent of the estimated 100,000 such products). Therefore, FDA does not have the complete list of in vitro diagnostic manufacturers or their products which is necessary to effectively regulate such products.

Labeling

The labeling standards, which FDA considers its primary method of controlling in vitro diagnostics, require product labels to contain such information as

--product contents;

--directions for use;

--performance characteristics, such as accuracy, precision, and sensitivity;

--means by which users can determine whether the product meets its appropriate standards at time of use, such as using expiration dates on labels; and

--warnings concerning its use.

The labeling standards were to become effective on March 15, 1974. However, from December 1973 through February 1974, 9 manufacturers and 2 manufacturers' associations representing over 200 manufacturers petitioned FDA requesting that the effective date be extended.

The extension was requested because of:

--The many products needing new labels.

--Material shortages and printing timelags for new packages and labels.

--The need for research and testing before new labels could be written.

--The longer periods FDA had granted for compliance with labeling requirements for other products.

--The number of small businesses involved which were unfamiliar with FDA's regulatory activities and lacked in-house expertise to bring about compliance with FDA requirements.

--Problems with interpreting the regulations.

The petitions requested extensions of from 3 months to 1 year. Some petitions requested extensions for only one class of product, some covered several product classes, and others requested extensions for all in vitro diagnostics. Of the petitions requesting extensions for more than

one product class, most indicated that compliance with the labeling standards for some of the products would be achieved by March 15, 1974. One manufacturers' association stated that compliance would be achieved by that date for a substantial and important segment of in vitro diagnostic products.

On the basis of the petitions and conversations with manufacturers' representatives, FDA determined that most manufacturers had tried to comply but were unable to relabel all their products by March 15, 1974. Therefore, FDA extended the effective date to September 15, 1974.

Product class standards

The March 15, 1973, regulations stated that FDA will propose performance standards for classes of similar products--called product class standards--to reduce or eliminate unreasonable risk of illness or injury when there are no other practical means of protecting the public.

The product class standards would describe

--performance requirements necessary for a class of products to assure the accuracy and reliability of results,

--procedures and methods to test products to assure their capability for performing satisfactorily, and

--any special information needed on the labels.

Although FDA intends for the labeling standards to provide more immediate controls, product class standards will be established for those products which cannot be adequately controlled through labeling standards alone. An advisory committee of experts has been established to advise FDA on such matters as the priorities for establishing product class standards and the adequacy and reasonableness of proposed standards.

In November 1973, after considering the advisory committee's recommendation, FDA identified the 10 top-priority product classes for which product class standards were to

be established. FDA has estimated that its first two product class standards, which are used for glucose determinations and calibrators used in clinical chemistry tests, will be issued in April and June 1975, respectively. As of September 1974 FDA had not established target dates for issuing standards for the remaining eight top-priority product classes of in vitro diagnostic products nor determined which product classes would need standards.

BMDDP officials estimated that there will be a need for about 100 such standards. One official estimated that it would take about 10 years to establish standards for those classes of products which present an unreasonable risk of illness or injury to the public.

Manufacturing practices

The March 15, 1973, regulations provide that, in addition to meeting applicable standards, in vitro diagnostic products must be produced in accordance with good manufacturing practices (GMPs) concerning production methods and controls. GMPs already exist for the production of drugs (21 C.F.R. 133). However, FDA has not established GMPs specifically applicable to the manufacture of in vitro diagnostic products. The March 1973 regulations provide that drug GMPs should also serve as guidelines to manufacturers of in vitro diagnostic products.

GMPs provide criteria for determining whether adequate methods, facilities, and controls are used in all phases of drug manufacture and distribution. FDA uses these criteria in inspections of equipment, finished and unfinished materials, containers, manufacturing records, and laboratory controls. Such inspections constitute FDA's basic tool for determining if products under its regulatory jurisdiction comply with the law. They allow FDA to identify manufacturing practices that could result in unsatisfactory products and obtain evidence to support legal actions when violations are found.

FDA believes that controls exercised over the manufacture of in vitro diagnostic products are at least as critical as those which must be imposed on the manufacture of drugs. However, in May 1973, because FDA was unfamiliar

with methods used in manufacturing in vitro diagnostics, it initiated inspections of several in vitro diagnostic manufacturers to identify those concepts of the drug GMPs which would serve as a basis for developing GMPs for in vitro diagnostic products. However, as of September 1974, FDA had not established GMPs for manufacturing of in vitro diagnostic products.

Surveillance activities

To determine if in vitro diagnostic products on the market meet applicable standards, FDA plans to initiate a comprehensive surveillance program consisting of plant inspections to determine compliance with GMPs and testing of products on the market. A BMDDP official said that FDA also needs to establish a laboratory for systematically testing diagnostic products on the market and for developing product class standards. However, he said that, because manpower allocations to the surveillance program have been limited, FDA's initial surveillance will be limited to reviewing product labels which are to be obtained from manufacturers. FDA does not intend to review the product's performance, but merely examine the labels for completeness of information.

In addition, FDA intends to contract for certain laboratory testing of products to obtain information for developing product class standards and evaluating product complaints. However, these contracts would not provide for systematic market testing of products to determine if an in vitro diagnostic product meets applicable labeling and product class standards.

Accordingly, as of September 1974, FDA had not implemented an effective program to monitor the manufacturing and marketing of in vitro diagnostic products to assure their effectiveness and reliability.

INCONSISTENCIES IN THE REQUIREMENTS FOR EXPORTED IN VITRO DIAGNOSTICS

The United States is one of the world's leading suppliers of in vitro diagnostic products. The exportation of biological and chemical in vitro diagnostic products

is regulated under the PHS and FD&C Acts, respectively; however, the export provisions of these acts are inconsistent. Under the PHS Act exported biological products, including in vitro biological diagnostics, must meet U.S. standards of safety, purity, and potency.

In contrast, under the FD&C Act exported chemical in vitro diagnostics are required only to (1) adhere to the specifications of the foreign purchaser, (2) comply with the laws of the destination country, and (3) be labeled to show they are intended for export. Since many countries do not have standards governing the reliability of in vitro diagnostics, the export provision of the FD&C Act does not assure that misbranded and/or adulterated chemical in vitro diagnostic products are not exported.

There is a need for consistency in the law concerning exportation of in vitro diagnostic products. Legislation was introduced in the 93d Congress to amend the FD&C Act to prohibit the exportation of in vitro diagnostics not meeting U.S. standards. This is further discussed on pages 32 and 33.

PROPOSED LEGISLATION

Three bills were introduced in the 93d Congress to amend the FD&C Act to strengthen FDA's program for controlling in vitro diagnostics. The bills were:

--S. 2368 and H.R. 9984, which would have provided FDA with a clear legislative mandate to regulate in vitro diagnostic products, and

--S. 3012, which would have provided FDA with authority regarding detention and recall of suspected products and access to manufacturers' records.

Legislative mandate to regulate in vitro diagnostic products

S. 2368 and H.R. 9984 would give FDA a clear legislative mandate consistent with its current program for controlling in vitro diagnostic products. These bills defined in vitro diagnostics as devices, thereby eliminating the need for

FDA to define an in vitro diagnostic product as a drug or a device for regulatory purposes.

The bills would require FDA to classify all in vitro diagnostic products according to the type of regulation necessary to adequately protect the public. The three categories into which products would be grouped are those which:

--Could adequately be controlled by general labeling requirements.

--Require performance standards to prevent unreasonable risk of injury or illness.

--Require premarket scientific evaluation before being marketed to assure the products' safety and effectiveness and to prevent unreasonable risk of injury or illness.

In addition, the bills would:

--Require mandatory registration of in vitro diagnostic manufacturers and their products.

--Require FDA to inspect the plants of manufacturers of in vitro diagnostic products at least once every 2 years.

--Authorize FDA to conduct premarket scientific evaluations of in vitro diagnostic products to identify unreliable products before they reach the consumer.

--Require the manufacturer of a new in vitro diagnostic product to obtain advice from FDA before a product is marketed as to whether it would be subject to premarket evaluation, performance standards, and/or general labeling requirements.

--Authorize FDA to require a manufacturer to repair, replace, or refund the value of an in vitro diagnostic product which either creates a substantial health hazard or fails to comply with an established standard.

Access to records, detention, and recall authority

S. 3012 would give FDA:

--Access to quality control records, including all records pertaining to product composition, processing, and complaints.

--Access to records relevant to determining compliance with the FD&C Act and orders issued pursuant to it.

--Authority to detain any article believed to be misbranded or adulterated for up to 20 days pending regulatory action.

FDA has stated that the lack of authority to detain such products has impeded effective enforcement of consumer protection laws and has resulted in the sale of defective products.

A previous GAO report, "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), recommended that FDA be authorized to detain products, recall violative products, and obtain access to records.

Although authority for access to records and detention of products in the proposed legislation would have applied to all products and their manufacturers covered by the FD&C Act, the proposed recall authority would have been limited to medical devices and in vitro diagnostic products only. To effectively remove violative products from the market, it is important that FDA have authority to recall all such products subject to its control.

Controls over exports

S. 2368 would prohibit exportation of in vitro diagnostics not meeting U.S. standards, except if the Secretary, HEW, determines such exportation is in the interest of public health and safety and has the approval of the country to which such products are intended for export.

This provision would have amended the FD&C Act which permits the export of in vitro diagnostic products not meeting U.S. standards as discussed earlier in this chapter.

CHAPTER 4

NEED FOR CLARIFYING FDA'S AUTHORITY OVER BIOLOGICAL IN VITRO DIAGNOSTICS

Legislation concerning the regulation of in vitro biological diagnostics is not clear, and not all in vitro biologicals are regulated in the same way. FDA believes it has discretionary authority as to how it may regulate in vitro biological diagnostics.

Section 351(a) of the PHS Act provides that the Secretary, HEW, license biological products and their manufacturers before the products may be transported in interstate commerce. Before the products can be licensed, HEW requires them (1) to meet standards designed to insure their safety, purity, and potency under the PHS Act and (2) to be safe and effective under the FD&C Act. A manufacturer may not sell a licensed product until it has conducted tests to determine that it meets applicable standards.

FDA's policy provides that in vitro biological diagnostics are to be controlled in accordance with the regulatory program established for in vitro diagnostic products in March 1973. However, in some cases, FDA has required such products to also be licensed under the PHS Act. As a result, some in vitro biologicals are licensed, while others are not. For example, FDA has licensed in vitro biological diagnostics used in determining blood types and in vitro microbiological (a subclass of biological) diagnostics used to diagnose Haemophilus influenza and hepatitis. However, about 2,000 other in vitro microbiologicals used in diagnosing polio, rabies, measles, cryptococcosis, and other diseases have not been licensed.

FDA'S RATIONALE FOR ITS DISCRETIONARY USE OF LICENSING AUTHORITY

The Director of FDA's Bureau of Biologics told us that, because of resource and personnel constraints, only those biological in vitro diagnostics which FDA deems to be a

critical national health hazard or those used in determining the safety of other licensed biological products are considered for licensing. The Bureau of Biologics is responsible for regulatory activities involving biological products.

HEW's Assistant General Counsel, Food and Drug Division, advised us that, although section 351(a) allows FDA to license in vitro microbiologicals under the PHS Act, the licensing requirements are discretionary by virtue of section 351(g) of the PHS Act. Paragraph (g) provides that nothing in the PHS Act shall be construed as in any way affecting, modifying, repealing, or superseding provisions of the FD&C Act. The HEW Assistant General Counsel contends that paragraph (g) provides an inherent exemption which gives FDA the option not to license certain biologicals; therefore, FDA plans to control these products primarily through the regulatory program it established for in vitro diagnostics.

JUDICIAL INTERPRETATIONS OF THE PHS ACT

Some doubt exists as to whether the Congress intended to cover in vitro microbiologicals in the PHS Act, since in vitro microbiological diagnostics were unknown, presumably nonexistent, until about 30 years after the enactment of the act in 1902.

The legislative history of the act indicates that it was to regulate in vivo substances only. The Congress, therefore, did not consider covering certain biologicals, including in vitro microbiological diagnostic products. Whether this absence of congressional consideration precludes coverage of such products under the PHS Act was addressed by the Blank case (U.S. Court of Appeals, Fifth Circuit in Blank v. United States, 400 F. 2d 302 (5th Cir. 1968)).

The Blank case held that products known as citrated whole human blood and packed human red blood cells were not biological products within the meaning of section 351 and therefore were not subject to regulation or control thereunder.

At the time of the Blank case, a "biological product" was defined under the PHS Act as any:

> "***virus, therapeutic serum, toxin, antitoxin, or analogous product, or arsphenamine or its derivatives (or any other trivalent organic arsenic compound), applicable to the prevention, treatment, or cure of diseases or injuries of man***."

The rationale of the Blank decision was that when the PHS Act was enacted the products and processes involved in blood transfusion were unknown and therefore not within congressional intent. Thus, if the product is not specifically identified in the act, it is not subject to its provisions. The court also considered and rejected the contention that citrated whole human and packed human red blood cells were "analogous" to any of the enumerated biological substances of section 351(a).

The Blank case is one of the few decisions interpreting section 351(a). It is the only case that has considered whether a particular biological product not contemplated by the Congress at the time of enactment can be regulated under the PHS Act. Critics of the Blank case have contended that the court's interpretation of the statute would be broadened if a test case were brought today.

As a result of the Blank decision, emergency legislation was enacted in 1970 to amend section 351(a) of the PHS Act to include vaccines, blood, blood components and derivatives, and allergenic biological substances.

The legislative history of the 1970 amendment reveals that HEW believed the products and processes involved in blood transfusions could be regulated under the PHS Act on the basis of a prior case (United States v. Steinschreiber, 218 F. Supp. 426 (S.D.N.Y. 1962), 219 F. Supp. 373 (S.D.N.Y. 1963), aff'd per curiam, 326 F. 2d 759 (2nd Cir. 1964)). The adverse decision in the Blank case, however, was not appealed to the Supreme Court because HEW apparently did not become aware of the decision until after the time for asking review had expired.

The Steinschreiber case held that normal human plasma was a product analogous to (and interchangeable with) a therapeutic serum and therefore within the scope of section 351(a) but did not deal with the issue of whether the absence of congressional intent concerning a particular biological product precludes its regulation under the PHS Act. The Blank case differed from the Steinschreiber case because it dealt with the question of congressional intent. Because the Blank decision is the more definitive interpretation of the statute, it necessarily reflects the present status of the law, although technically it is the view of only the fifth circuit court.

However, should a manufacturer decide to challenge FDA's authority to regulate in vitro microbiological diagnostic products under the PHS Act, recent court decisions indicate that the reasoning set forth in the Blank case might be rejected. Courts currently take a more liberal attitude in interpreting Federal public health laws than that taken in the Blank case.

Until further judicial determinations are made, the Blank case holding remains the sole decision on whether in vitro microbiological diagnostic products not contemplated by the Congress can be regulated under the PHS Act.

Although FDA generally intends to regulate in vitro biological diagnostic products in accordance with the March 1973 regulations, the Congress expressed its desire that biological products, if they are to be regulated at all, be formally regulated under the PHS Act. An example of this preference is found in the 1970 House report 91-1035, "Biological Product Licensing" (91st Cong., 2d sess.). The report discusses the need to amend section 351 of the PHS Act to clarify congressional intent regarding licensing of biological products. It also discusses HEW's decision to regulate biological products as drugs under the FD&C Act as a result of the Blank case. That report stated:

> "As an interim measure, and certainly not the ideal solution to the problem, the Secretary has amended the good manufacturing practice regulations for drugs under the Federal Food, Drug, and Cosmetic Act to incorporate by reference the standards for manufacturing,

processing, packaging, and holding these biological products that were issued under section 351 for the Public Health Service Act. The committee clearly recognizes, and wishes to emphasize, that this approach is purely an interim measure. It has led to considerable objections and unfortunate misunderstandings on the part of many concerned with the processing, sale, and shipment of these products. Unless remedied by legislation such a procedure may lead to additional litigation and further confusion. To forestall such complications it is important that the authority of the Secretary be, (sic) clarified***."

There is a need for legislation to clarify FDA's authority with respect to regulating biological diagnostics, especially regarding the applicability of the PHS Act to in vitro products.

CONTROL OF BIOLOGICAL DIAGNOSTICS FOR ANIMAL USE

In contrast to FDA's control over in vitro biological diagnostics for human use, the Department of Agriculture requires the licensing of all in vitro biological diagnostics for animal use, including all microbiologicals.

Under the Virus-Serum-Toxin Act of 1913 (21 U.S.C. 151-158), all veterinary biologics sold or shipped interstate must be prepared under a U.S. license issued by the Secretary of Agriculture. The licensing requirements for veterinary biologicals are similar to those prescribed by the PHS Act.

In addition, the Department of Agriculture believes that such products sold intrastate should also be brought under Federal regulations. The Department believes that products purportedly prepared only for intrastate shipment can, and often do, either intentionally or inadvertently, find their way into interstate or foreign commerce and that it is essential in the public interest that these products be federally controlled.

CHAPTER 5

NEED TO IMPROVE INFORMATION GATHERING AND DISSEMINATION

To effectively regulate in vitro diagnostics, FDA must systematically obtain information concerning problems with such products. FDA has not obtained all available information on problem products and, when it has received information, it has not always taken prompt, appropriate action.

Specifically FDA has not:

--Broadened the information base of its reporting system to provide for participation of all interested organizations.

--Been able to obtain information available at CDC relating to unsatisfactory in vitro diagnostics.

--Obtained information concerning complaints by importers of U.S.-manufactured in vitro diagnostics nor adequately monitored the regulatory actions by other countries concerning these products.

In addition, contrary to its stated policy, FDA has not consistently notified foreign countries of domestic recalls when it was aware of in vitro diagnostic products being recalled. Consequently, products recalled in the United States are possibly still being marketed and used in other countries.

NEED TO EXPAND SYSTEM FOR COLLECTING DATA ON PROBLEM PRODUCTS

In 1968 the Defense Personnel Support Center (DPSC) agreed to give FDA copies of complaints made by Department of Defense (DOD) users of in vitro diagnostic products. DPSC, an activity of the Defense Supply Agency, is responsible for buying and stocking drug items, including in vitro diagnostics for DOD. In fulfilling this responsibility, DPSC monitors the production and quality control of manufacturers supplying drug items to DOD. In addition, DPSC may also conduct its own laboratory examinations of products it purchases to insure they meet contract

specifications. From July 1972 through December 1973 DPSC had forwarded to FDA 25 complaints made by DOD users of in vitro diagnostic products.

In an effort to obtain additional information on problems with in vitro diagnostic products, in March 1973 FDA implemented a pilot diagnostic problem-product reporting system. Selected laboratory personnel were requested to report any problems encountered in using commercially available diagnostic products. Through this system, FDA hopes to

--learn about problems facing users of diagnostic products and

--identify problem patterns involving either particular products or their manufacturers.

The system is operated under a contract with the United States Pharmacopeial Convention (USPC), a nongovernmental organization which sets standards for drug products. Under the contract, USPC is responsible for forwarding copies of complaints to FDA and to the products' manufacturers as well as acknowledging receipt of complaints to the complainants. When the system is fully implemented, USPC will computerize the information received.

Under the pilot phase of this system, about 400 medical technologists, all members of the American Society for Medical Technology, were requested to submit information on their experiences with in vitro diagnostic products. Because medical technologists use these products and become familiar with them, FDA believed that they could make an important contribution by reporting problems with laboratory products, thus extending FDA's surveillance over these products.

FDA officials have concluded that the pilot phase has been successful. Since the system's inception, in March 1973, to December 1973 FDA received reports concerning 103 problems with in vitro diagnostic products. (FDA's disposition of these reports is discussed on p. 41.)

FDA, however, has not accepted offers from two other professional associations--the American Association of

Clinical Chemists and the College of American Pathologists --to contribute information to FDA's problem-product reporting system. An American Association of Clinical Chemists official said his association asked to participate in September 1973 and reaffirmed its request in March 1974. He explained that, because chemists comprise the association's membership, it would provide FDA with a different viewpoint from that of medical technologists concerning the suitability of diagnostic products.

A College of American Pathologists official said his organization also asked to participate in the system. He believed that, since the college's membership consists of pathologists who tend to be laboratory directors, it would provide additional information on the reliability of in vitro diagnostic products.

According to BMDDP officials, other professional organizations were not allowed to participate in the problem-product reporting system because FDA lacked the necessary staff to handle even the complaints presently being received. Because of staffing limitations, the pilot phase, originally scheduled to end in October 1973, was extended until June 1974 and only nominal expansion of the system has been allowed in fiscal year 1975. FDA had planned to expand the system to include 12,000 laboratory personnel; however, the system has been expanded to include only 1,600 additional American Society for Medical Technology members in fiscal year 1975.

The need for a feedback system is basic to any control program; however, although FDA has been aware of other sources of information on diagnostic products, it has not been aggressive in obtaining such information. A broad based information-reporting system would enhance FDA's effectiveness in regulating in vitro diagnostic products.

Disposition of complaints reported to FDA

According to DPSC records from July 1973 to December 1973, DPSC submitted 25 complaints concerning in vitro diagnostic products to FDA. In addition, FDA received 103 complaints through its problem-product reporting system from March 1973, the system's inception, to December 1973.

Although FDA has reviewed the complaints it received, it has not always taken investigational action on them. Some of the complaints, in our view, involve significant problems. FDA's disposition of these 128 complaints, as of September 1974, follows.

Disposition	Number of complaints
Investigational action taken	32
Investigation in process	2
No investigational action taken	94
Total	128

For the 32 complaints on which FDA has taken investigational action, it determined through discussions with the manufacturers, inspections of the manufacturing plants, or other means that (1) the problems had been corrected or would be corrected when the new labeling regulations were implemented, (2) the products had been voluntarily recalled or replaced, or (3) no significant problem existed.

The two complaints which FDA was investigating were reported in July 1973. These complaints involved a diagnostic product for cholesterol determinations which was possibly defective and a diagnostic product to measure prothrombin (blood coagulation) time which had inadequate instructions for storage and use. FDA inspected one manufacturer's plant and plans to inspect the other. As of September 1974, 14 months after the complaints were received, FDA had not completed its investigation.

Regarding the 94 complaints which FDA had not investigated, FDA officials indicated that an investigation was not made in some cases because of insufficient facilities and staff. However, according to these officials, most of the complaints did not warrant further investigation. It appears to us that some of the 94 complaints involved significant problems and further investigations should have been conducted.

For example, in April 1973 FDA received a complaint involving a contaminated product used to culture bacteria. BMDDP officials said they did not investigate the complaint because the specific product lot number was not identified and the specific item against which the complaint was made had been destroyed. However, the user said this was a continual problem, thus indicating that it extended beyond the item in the complaint which, in our opinion, warranted an investigation. In another case, between July and November 1972 four different DOD installations reported that a pregnancy test kit gave inaccurate results. FDA officials stated FDA did not investigate the complaints because it lacked the necessary field staff.

FDA had no record of 15 of the complaints reported by DPSC. FDA officials said that the 15 missing complaints had probably been judged insignificant and had been thrown away. Although DPSC later determined that five of these complaints had no basis, others concerned serious problems. For example, DPSC reported in April 1973 that a DOD medical center complained that a blood-typing serum gave false positive results. DPSC did followup testing of the product and found it unsatisfactory.

In addition, during September 1972 to June 1973 DPSC reported that four different DOD installations complained that a mononucleosis test kit was unacceptable. In August 1973 a medical technologist reported a similar problem under FDA's problem-product reporting system and again FDA did not investigate the problem.

Since these complaints involved potentially unreliable products, FDA should have investigated to determine the complaints' validity and the need for regulatory action against the problem products.

Information available at CDC not provided to FDA

Each year, through its market and voluntary premarket product-testing programs, CDC identifies hundreds of biological in vitro diagnostics judged unsatisfactory because they did not meet CDC specifications. Of the approximately 2,000 product samples tested in the fiscal year 1974 market and

voluntary premarket programs, CDC found about 450 unsatisfactroy, including those used to test for rubella, influenza, venereal disease, and rabies. However, as previously discussed, most of the unsatisfactory test results were not reported to FDA. Since March 1973, when FDA initiated a formal program to control in vitro diagnostic products, the only unsatisfactory test results which CDC has reported to FDA concerned CDC's evaluation of 24 cryptococcal kits. (See pp. 19 to 20.)

Because CDC has no regulatory authority over in vitro diagnostic products, it should provide information concerning problem products to FDA to assure that the problems are investigated and corrected.

Information not obtained on exported products

FDA has no means to systematically obtain complaints concerning problems with U.S.-manufactured in vitro diagnostic products exported to foreign countries. We obtained information concerning the efficacy and reliability of such products from health officials of 19 foreign countries. Their information indicated that during January 1971 through October 1973, 6 foreign countries experienced problems with 59 U.S.-manufactured in vitro diagnostic products. However, FDA in most cases was unaware of these problems. The following were some problems encountered by the six countries:

--Products used for determining pregnancy and for typing blood yielded false observations.

--Products used for the serological test and diagnosis of cholera erroneously indicated the presence of two strains of cholera instead of one.

--Instructions for a GOT test kit (see pp. 12 and 13) did not caution the user that very high levels of GOT can use up the reagent and could cause false test results.

--Products used to diagnose blood diseases were unstable and thus could produce inaccurate results.

In addition, because of the prospects of regulatory actions by two foreign countries over certain U.S.-manufactured in vitro diagnostic products, the manufacturers discontinued exporting them to those countries. Although FDA's Office of International Affairs, Office of the Associate Commissioner for Compliance, is responsible for obtaining information on international compliance activities appropriate to FDA's mission, it was not aware of the problems with these products. These cases are summarized below.

Country A

A health official of Country A said most chemical in vitro diagnostic products imported by Country A were manufactured in the United States and that roughly one-third of the commercial in vitro diagnostic kits and reagents sold in that country for use in clinical chemistry were unsatisfactory. Studies conducted by Country A on a number of in vitro diagnostic kits indicated that many of the kits could frequently yield false information.

As a result of these studies, in February 1973 the cognizant government agency of Country A notified the local distributors of five U.S.-manufactured chemical in vitro diagnostic kits that continued sale of these products would appear to violate the country's drug laws and regulations. All five of these products failed to satisfy Country A's criteria for satisfactory performance. Also, the enclosed instructions and other literature supplied with the products were considered inadequate.

Consequently, the U.S. manufacturers discontinued export of the five kits to Country A. Two of these products were used for determining sodium, two for potassium, and one for calcium. One of the products used for sodium determinations and the product used for calcium determinations were included in CDC's product testing for us and were also found unsatisfactory. However, as of April 1974, 14 months after Country A initiated action against the five products, they were all still on the U.S. market.

The significance of tests for sodium and calcium determinations was discussed on pages 11 and 12. Potassium is essential for several body functions, including metabolism of carbohydrates, maintenance of normal acidity or alkalinity

of body fluids, transmission of nerve impulses, and maintenance of the correct tension between intracellular and extracellular fluids. High blood potassium produces muscular weakness and cardiac disturbances may result, whereas low blood potassium produces generalized weakness and low blood pressure.

Country B

An official from Country B advised us that in 1970 the U.S. manufacturer of chemical occult blood test products sold over the counter discontinued exporting these products to that country because Country B considered the products a health hazard to the users.

Occult blood tests identify the presence of blood in urine and feces. These products contain orthotolidine, a possible carcinogen, which apparently can be absorbed through the skin. Because laboratory technicians frequently handled these substances in performing tests, the products were determined to be a possible health hazard. It is essential that proper precautions be taken when any known or suspected carcinogens are used; therefore Country B established a strict regulatory system with respect to such substances, including orthotolidine.

Since the occult blood products did not contain sufficient instructions to assure proper handling, Country B requested the manufacturer of the two products to amend its labeling. Instead, the manufacturer voluntarily removed both products from the country's market in 1970. However, one of these products was still being sold in the United States as of March 1974.

FDA actions on foreign complaints

We provided FDA with the information we received regarding the complaints of foreign health officials as it became available. FDA handled these complaints as follows:

--FDA concluded that the complaint concerning unstable products used in diagnosing blood diseases could not be evaluated because the complainant provided inadequate information.

--FDA advised us that the complaints involving products used for blood typing and pregnancy determinations concerned licensed biologicals. FDA discussed the complaints with the manufacturers and reviewed its records on these products. As of August 1974, FDA was still considering the matter.

--Regarding the complaint concerning a possible carcinogenic substance, FDA stated it contacted the National Institute of Occupational Safety and Health to determine the carcinogenicity of orthotolidine. The Institute is responsible for evaluating the dangers inherent in occupational exposure to carcinogens in the United States. FDA stated that on the basis of the Institute's determination of the carcinogenicity of orthotolidine, it would evaluate the need for regulatory action. As of May 1974, the Institute had not notified FDA as to the hazards of orthotolidine.

--FDA said it had initiated inspections of the manufacturers of the remaining products on which foreign complaints were received. The inspections' purpose was to review (1) the product's labeling, (2) the firms' quality control procedures, and (3) the firms' complaint files.

FOREIGN COUNTRIES NOT ALWAYS NOTIFIED OF U.S. RECALLS

FDA's Director, Office of International Affairs, said FDA believes it has a moral obligation to notify all foreign users of U.S. products that are recalled. The Office is responsible for making such notifications, through the Department of State or the appropriate Embassy, to all foreign countries, except Canada. Office officials said notification should be made every time a public hazard is involved. FDA's Field Compliance Branch, Executive Director of Regional Operations, is responsible for notifying Canadian authorities of recalls involving goods shipped to consignees in that country.

In most cases, FDA did not notify the foreign countries involved of recalled in vitro diagnostics which had been distributed internationally. Of the in vitro diagnostic

products involved in 32 recalls during January 1, 1971, through February 28, 1974, products in 8 of the recalls were distributed in 20 different foreign countries. Because some countries were involved in more than 1 recall, there were 35 instances when FDA should have notified the countries of the recalls. However, FDA had a record of notifying the Department of State or the appropriate Embassy in only 12 instances. FDA officials explained that the appropriate foreign countries were not notified of the remaining 23 instances due to an administrative oversight.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

CONCLUSIONS

Unreliable in vitro diagnostic products are being marketed in the United States and exported to foreign countries. Such products could pose a serious hazard to the public. Although FDA has regulatory responsibility for in vitro diagnostic products, its regulation of these products has not been effective.

Before March 1973 FDA did not have a formal program to control in vitro diagnostics. However, because of the increasing use of these products in diagnosing illness and disease and the need to better insure the effectiveness and reliability of such products, FDA initiated a program for their control. The program provides for voluntary registration of in vitro diagnostic manufacturers and a listing of the products, establishment of product class and labeling standards, and establishment of manufacturing criteria under which in vitro diagnostics must be manufactured.

FDA's program, however, has not been effective. Manufacturers generally have not voluntarily registered, product-class standards and manufacturing criteria have not been established, and an adequate surveillance program has not been instituted. BMDDP officials attributed their inability to effectively accomplish program objectives to inadequate staffing and resources.

FDA's lack of authority in some areas has also hampered its efforts in regulating in vitro diagnostic products. Specifically, because FDA does not regulate in vitro diagnostics as drugs, it does not have authority to obtain access to manufacturers' quality control, complaint, and other relevant records, such as distribution records, needed to determine compliance with the FD&C Act. In addition, FDA lacks authority to detain products suspected of being violative or to require firms to recall violative products.

In addition, FDA has not systematically obtained information concerning the adequacy and reliability of in vitro diagnostic products. Because such information is needed to effectively regulate these products, FDA should make a more concerted effort to obtain all available information from professional organizations and foreign countries concerning problems with in vitro diagnostic products. CDC should be required to routinely furnish FDA with similar information.

When problems concerning in vitro diagnostics have been reported, FDA has not always taken adequate investigational action. Of the 128 complaints submitted to FDA which we reviewed, FDA had not investigated 94 to determine the validity of the complaints and the need for regulatory action. Included in the 94 complaints were several problems involving potentially unreliable products.

In addition, when problem in vitro diagnostic products were recalled, FDA, contrary to its policy, has not consistently notified foreign users. Consequently, products recalled in the United States are possibly still being marketed and used in other countries.

Also legislation concerning the regulation of in vitro biological diagnostics is not clear. FDA believes it is authorized to license in vitro biological diagnostics under the PHS Act and licenses some of them. However, FDA believes that this authority is discretionary and therefore it has not licensed approximately 2,000 other such products. The judicial decisions which have interpreted FDA's authority to license such products have not clearly defined FDA's authority.

Moreover, the exportation of in vitro diagnostic products is regulated under the PHS and FD&C Acts; however, the export provisions of these acts are inconsistent. Consequently, some in vitro biological diagnostics are required to meet U.S. standards before export, while other in vitro biological diagnostics and chemical in vitro diagnostics are not.

There is a need for legislation to clarify FDA's authority concerning regulation of in vitro diagnostics, especially regarding the applicability of the PHS Act to these products.

Several bills were introduced in the 93d Congress to strengthen FDA's program to control in vitro diagnostics. Although the bills would have given FDA some additional authority to control in vitro diagnostics, the methods proposed by the bills are essentially the same as those provided for by FDA's current in vitro diagnostic program. Unless FDA is more aggressive in implementing its current in vitro diagnostic program, the immediate impact such legislation would have on initiating effective controls over these products is questionable.

RECOMMENDATIONS TO THE SECRETARY OF HEW

We recommend that the Secretary direct the Commissioner of FDA to take immediate measures to strengthen FDA's program for controlling in vitro diagnostics. Specifically, FDA should:

--Hasten the development of product class standards.

--Establish criteria under which in vitro diagnostics must be manufactured.

--Establish an adequate surveillance program, including (1) product testing, to determine their compliance with labeling and performance standards, and (2) periodic inspections of manufacturing plants.

--Expand operation of the problem-product reporting system to develop additional sources of information on problem in vitro diagnostic products.

--Establish, where feasible, communication with foreign countries to develop information on regulatory actions and complaints of other countries concerning U.S.-produced in vitro diagnostic products.

--Take prompt regulatory action, where appropriate, concerning (1) products identified by CDC as being unsatisfactory in its testing, (2) products against which complaints were reported under the problem-product reporting system or by DPSC, and (3) U.S.-produced in vitro diagnostics which have been removed from sale in foreign markets or against which complaints were reported to us by foreign users.

--Strengthen FDA's program of notifying foreign users of U.S.-produced in vitro diagnostic products which have been recalled.

--Evaluate the need for additional resources to effectively carry out the objectives of the in vitro diagnostic program and, if warranted, allocate additional resources to the program.

We further recommend that the Secretary require the Director of CDC to routinely provide FDA with information concerning problem in vitro diagnostics identified by CDC in its testing.

AGENCY COMMENTS

HEW generally agreed with our recommendations. (See app. IV.) HEW stated that, during the period covered by our report, the scope of FDA's in vitro diagnostic regulatory program was consistent with the level of resources available and the overall regulatory responsibilities of FDA. It stated that it believes the legislation proposed by the Congress, and mentioned in the report, would enhance the regulation of diagnostic products. HEW's comments on each of our recommendations are summarized below.

Hasten development of product class standards

HEW stated that FDA will develop product class standards as quickly as possible using both in-house resources and assistance of scientific and voluntary standard-setting groups. HEW said the speed with which standards are developed is related to the complexity and number of products involved in each class.

Establish manufacturing criteria

HEW stated that FDA is in the process of developing manufacturing criteria for in vitro diagnostics and that this is part of FDA's program to establish comprehensive GMP regulations for medical device and diagnostic product manufacturing.

Establish an adequate surveillance program

HEW stated that FDA established a surveillance program in November 1974 to determine compliance with labeling requirements for in vitro diagnostic products and to perform limited inspections of manufacturing establishments in cases where a possible health hazard is suspected. As GMP regulations are developed and implemented for device and diagnostic products, the surveillance program will provide for additional scheduled inspections of manufacturing establishments.

Expand problem-product reporting system

HEW stated that, in January 1975, FDA's problem-product reporting system was expanded to include members of the American Medical Technologists and subsequent invitations have been issued to the College of American Pathologists and the American Association of Clinical Chemists. According to HEW, FDA will continue to expand the system as the diagnostic regulatory program develops.

Establish communication with foreign countries

HEW stated that FDA has taken steps to develop a system of communication with foreign countries on regulatory problems. HEW said that such programs depend on the understanding and voluntary cooperation of all countries involved and, therefore, the programs cannot be relied upon as consistent sources of information. FDA will, however, continue to foster its working relationships with foreign countries and encourage broader participation.

Take prompt regulatory action concerning problem products, where appropriate

HEW stated that FDA will continue to evaluate complaints and testing data for in vitro diagnostic products and will recommend further investigative or regulatory action if the circumstances warrant.

Strengthen program to notify foreign user of recalls

HEW stated that FDA has improved the flow of recall reports to foreign countries. The system previously used for this program was evaluated and FDA has taken action to assure accuracy and consistency in the flow of recall data.

Evaluate the need for additional resources

HEW stated that FDA has provided additional resources for in vitro diagnostic regulatory programs consistent with FDA priorities and availability of such resources. According to HEW, a comparison of fiscal year 1974 and 1975 position allocations shows that, out of a total of 80 additional positions allocated throughout FDA in fiscal year 1975, 31 were allocated to the in vitro diagnostic product program.

Require CDC to routinely furnish FDA with needed information

HEW said that FDA and CDC have reached agreement in principle on an interagency agreement which requires CDC to furnish testing results on problem products to FDA on a routine basis. HEW stated the final agreement should be completed by the end of fiscal year 1975.

RECOMMENDATIONS TO THE CONGRESS

We recommend that, to improve FDA's ability to control in vitro diagnostic products, the Congress consider giving FDA a clear legislative mandate for controlling such products. Specifically, we recommend the Congress give FDA clear authority to:

--Require mandatory registration of all manufacturers.

--Require periodic inspections of in vitro diagnostic manufacturers.

--Obtain access to manufacturers' quality control, complaint, and other relevant records, such as distribution records needed to determine compliance with the FD&C Act.

--Detain products suspected of being violative.

--Require firms to recall all violative products under FDA's responsibility.

--Prevent export of in vitro diagnostic products not meeting U.S. standards.

As noted earlier, several bills were introduced in the 93d Congress which, if enacted, would have provided FDA with this additional authority.

In addition, we recommend that the Congress clarify its intention regarding whether products of biological origin should be controlled under the FD&C Act or whether such products should be licensed in accordance with the PHS Act.

CHAPTER 7

SCOPE OF REVIEW

We evaluated activities and plans for regulating in vitro diagnostic products and reviewed agency policies and procedures, pertinent legislation, regulations, and judicial decisions. We also interviewed agency personnel.

We worked primarily at FDA headquarters in Rockville, Maryland; the FDA district office in New York City; and at CDC headquarters in Atlanta, Georgia. We also visited the Veterans' Administration Marketing Center, Hines, Illinois; DPSC, Philadelphia, Pennsylvania; and several medical laboratories in New York City to obtain information on problems experienced with in vitro diagnostics.

To obtain background on the in vitro diagnostics industry, we contacted professional organizations and manufacturers' representatives and reviewed professional literature.

To obtain an assessment of the in vitro diagnostic products marketed, we asked CDC to test in vitro diagnostic products. CDC reported its results to the manufacturers and to FDA.

To obtain information on communications and coordination between FDA and other Federal agencies, we met with officials of CDC, the National Bureau of Standards, the Veterans Administration, DOD, and the Department of Agriculture.

Using a mailing list supplied by FDA, we sent questionnaires to officials in all 50 States, the District of Columbia, Puerto Rico, the Virgin Islands, 7 counties, and 5 cities to obtain information on their efforts to regulate in vitro diagnostic products and on their coordination and communication with FDA. Officials in 43 States, 4 counties, and 1 city responded.

We sought the views of health officials in 35 foreign countries concerning the reliability of U.S.-exported in vitro diagnostic products. In most cases, these views were obtained with the assistance of the International Federation of Clinical Chemistry. Health officials from 19 countries replied.

SELECTED GAO REPORTS CONCERNING

CONSUMER PROTECTION AGAINST POTENTIALLY HARMFUL DRUGS

"Answers to Questions on the Investigational Use of Isoniazid--a Tuberculosis Control Drug" (B-164031(2), Oct. 7, 1971)

"Problems Involving the Effectiveness of Vaccines" (B-164031 (2), Mar. 28, 1972)

"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)

"Problems in Regulating Selected Vaccines" (B-164031(2), Feb. 7, 1973).

"Problems in Obtaining and Enforcing Compliance With Good Manufacturing Practices for Drugs" (B-164031(2), Mar, 29, 1973)

"Supervision Over Investigational Use of Selected Drugs" (B-164031(2), July 23, 1973)

"Assessment of the Food and Drug Administration's Handling of Reports on Adverse Reactions From the Use of Drugs" (B-164031(2), Mar. 7, 1974)

CDC'S TESTING OF IN VITRO DIAGNOSTIC PRODUCTS FOR GAO

Product tested	CDC evaluation as to the products' overall acceptability
Glucose:	
Gl-1	Unsatisfactory
Gl-2	Satisfactory
Gl-3	Unsatisfactory
Gl-4	Satisfactory
Gl-5	Satisfactory
Gl-6	Satisfactory
Gl-7	Unsatisfactory
Gl-8	Unsatisfactory
Bilirubin:	
Bil-1	Unsatisfactory
Bil-2	Satisfactory
Bil-3	Unsatisfactory
Bil-4	Unsatisfactory
Bil-5	Unsatisfactory
Bil-6	Unsatisfactory
Bil-7	Unsatisfactory

APPENDIX II

Cholesterol:	
Chol-1	Unsatisfactory
Chol-2	Unsatisfactory
Chol-3	Unsatisfactory
Chol-4	Unsatisfactory
Chol-5	Unsatisfactory
Chol-6	Satisfactory
Chol-7	Unsatisfactory
Sodium:	
Na-1	Unsatisfactory
Na-2	Satisfactory
Na-3	Unsatisfactory
Calcium:	
Ca-1	Satisfactory
Ca-2	Unsatisfactory
Ca-3	Unsatisfactory
Ca-4	Unsatisfactory
Ca-5	Unsatisfactory
GOT:	
GOT-1	Satisfactory
GOT-2	Unsatisfactory
GOT-3	Unsatisfactory

APPENDIX II

GOT:

GOT-4	Satisfactory
GOT-5	Satisfactory
GOT-6	Unsatisfactory
GOT-7	Unsatisfactory
GOT-8	Unsatisfactory
GOT-9	Unsatisfactory
GOT-10	Unsatisfactory

Thyroxine:

T_4-1	Satisfactory
T_4-2	Unsatisfactory
T_4-3	Unsatisfactory
T_4-4	Unsatisfactory

STUDIES THAT HAVE IDENTIFIED

UNSATISFACTORY IN VITRO DIAGNOSTIC PRODUCTS

Study	Reference
A	Roy N. Barnett, M.D., Ann D. Cash, M.T. (ASCP), and Siegfried P. Junghans, M.D., "Performance of 'Kits' Used for Clinical Chemical Analysis of Cholesterol," The New England Journal of Medicine, vol. 279, no. 18 (1968), pp. 974-979.
B	I.A. Krynski, and J.E. Logan, "Observations on Diagnostic Kits for the Determination of Total Cholesterol," Clinical Biochemistry Journal, Vol. 2 (1968), pp. 105-114.
C	J.E. Logan, L.D. Waddell, and I.A. Krynski, "Observations on Diagnostic Kits for the Determination of Glucose," Clinical Biochemistry Journal, vol. 3, (1970), pp. 129-136.
D	Roy N. Barnett, M.D., and Ann D. Cash, M.T. (ASCP), "Performance of 'Kits' Used for Clinical Chemical Analysis of Glucose," American Journal of Clinical Pathology, vol. 52, no. 4 (1969), pp. 457-465.
E	M.L.E. Sunderland, M.W. Weatherbrun, and J.E. Logan, "Observations On Diagnostic Kits for the Determination of Calcium in Serum," Clinical Biochemistry Journal, vol. 4, (1971), pp. 16-21.
F	Edwaud K. Kim, Leslie D. Waddell and James E. Logan, "Evaluation for Four Reagent Kits and Two Flame Photometers Used to Determine Sodium and Potassium In Serum." Clinical Chemistry, vol. 18, no. 2 (1972), pp. 124-128.
G	Marcia Lee, Norbert W. Tietz, and Charles J. Martinez, "Clinical Evaluation of a Modified 'Oxford T_4-by-Column' Method for Serum Thyroxine," Clinical Chemistry, vol. 18, no. 5, (1972), pp. 422-426.

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

MAR 17 1975

Mr. Gregory J. Ahart
Director, Manpower and
Welfare Division
U.S. General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report to the Congress entitled, "Hazards to the Public From Unsatisfactory Products Used for Medical Diagnosis". They are enclosed.

We appreciate the opportunity to comment on this draft report before its publication.

Sincerely yours,

John D. Young
Assistant Secretary, Comptroller

Enclosure

APPENDIX IV

DEPARTMENT COMMENTS ON THE DRAFT GAO REPORT TO CONGRESS ENTITLED "HAZARDS TO THE PUBLIC FROM UNSATISFACTORY PRODUCTS USED FOR MEDICAL DIAGNOSIS"

We consider that, during the period covered by the report, the scope of the in vitro diagnostics regulatory program was consistent with the level of resources available and the overall regulatory responsibilities of the Food and Drug Administration (FDA). We believe that legislation now pending before the Congress, and mentioned in the report, will enhance the regulation of diagnostic products.

GAO RECOMMENDATION:

The Secretary, HEW, through the Commissioner, FDA, should hasten the development of performance standards for similar type products called product class standards.

DEPARTMENT COMMENT:

We concur. FDA will continue to develop product class standards both with in-house resources and with the assistance of scientific and voluntary standard-setting groups. FDA intends to develop each standard as quickly as possible; however, the speed with which these standards can be developed is related to the complexity and number of products involved in each class. The report itself indicates that there are an estimated 100,000 diagnostic products on the market and that about 100 product class standards will be required.

GAO RECOMMENDATION:

The Secretary, HEW, through the Commissioner, FDA, should establish manufacturing criteria under which in vitro diagnostics must be manufactured.

DEPARTMENT COMMENT:

We concur. FDA is in the process of developing manufacturing criteria for in vitro diagnostics. This is part of the Agency's program to establish comprehensive Good Manufacturing Practice Regulations for medical device and diagnostic product manufacturing.

GAO RECOMMENDATION:

The Secretary, HEW, through the Commissioner, FDA, should establish an adequate surveillance program which includes product testing to determine compliance with labeling and performance standards and periodic inspections of manufacturing plants.

DEPARTMENT COMMENT:

We concur. FDA established a surveillance program in November, 1974, to determine compliance with labeling requirements for in vitro diagnostic products and to perform limited inspections of manufacturing establishments in cases where a possible health hazard is inspected. As Good Manufacturing Practice Regulations are developed and implemented for device and diagnostic products, the surveillance program will provide for additional scheduled inspections of manufacturing establishments.

GAO RECOMMENDATION:

The Secretary, HEW, through the Commissioner, FDA, should expand operation of the problem product reporting system to develop additional sources of information on problem in vitro diagnostic products.

DEPARTMENT COMMENT:

We concur. The original pilot phase of the Product Problem Reporting System was limited to 400 members of the American Society for Medical Technology. Subsequent to the one year pilot phase, results were evaluated and the program expanded to include 2,000 members of that organization. In January, 1975, the program was further expanded to include members of the American Medical Technologists, and subsequent invitations have been issued to the College of American Pathologists and the American Association of Clinical Chemists. FDA will continue to expand this system as the diagnostic regulatory program develops.

GAO RECOMMENDATION:

The Secretary, HEW, through the Commissioner, FDA, should establish, to the extent feasible, lines of communication with foreign countries to develop information on regulatory actions and complaints of other countries concerning U.S. produced in vitro diagnostic products.

DEPARTMENT COMMENT:

We concur. FDA has taken steps to develop a system of communication with foreign countries on regulatory problems. Such programs depend on the understanding and cooperation of all countries involved. These programs are, therefore, voluntary and cannot be relied upon as consistent sources of information. FDA will continue to foster its working relationships with foreign countries and encourage broader participation.

GAO RECOMMENDATION:

The Secretary, HEW, through the Commissioner, FDA, should take prompt regulatory action, where appropriate, concerning products (1) identified by CDC as being unsatisfactory in its testing and (2) against which complaints were otherwise reported.

DEPARTMENT COMMENT:

We concur. FDA has taken and will continue to take appropriate regulatory action against products which are in violation of statutory requirements. FDA will continue to evaluate complaints and testing data for in vitro diagnostic products and will recommend further investigative or regulatory action if the circumstances warrant.

GAO RECOMMENDATION:

The Secretary, HEW, through the Commissioner, FDA, should strengthen FDA's program of notifying foreign users of U.S. produced in vitro diagnostic products which have been recalled.

DEPARTMENT COMMENT:

We concur. FDA has improved the flow of recall reports to foreign countries. The system previously used for this program was evaluated and action has been taken by the Agency to assure accuracy and consistency in the flow of recall data.

GAO RECOMMENDATION:

The Secretary, HEW, through the Commissioner, FDA, should evaluate the need for additional resources to effectively carry out the objectives of the in vitro diagnostic program, and if warranted, allocate additional resources to the program.

DEPARTMENT COMMENT:

We concur. FDA has provided additional resources for this program consistent with the priorities of the Agency and the availability of such resources. Comparison of FY 74 and FY 75 position allocations shows that, out of a total of 80 additional positions allocated throughout FDA in FY 75, 31 were allocated to the diagnostic product program.

GAO RECOMMENDATION:

The Secretary, HEW, should require the Director of CDC to routinely furnish to FDA information concerning problems with in vitro diagnostics identified by CDC in the testing of such products.

DEPARTMENT COMMENT:

We concur. The Food and Drug Administration and the Center for Disease Control have reached agreement in principle on an interagency agreement which requires CDC to furnish testing results on problem products to FDA on a routine basis. The formal agreement should be completed by the end of FY 75.

APPENDIX V

PRINCIPAL HEW OFFICIALS RESPONSIBLE FOR ADMINISTERING ACTIVITIES DISCUSSED IN THIS REPORT

	Tenure of office	
	From	To
SECRETARY OF HEW:		
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 FOR HEALTH:		
Theodore Cooper (acting)	Jan. 1975	Present
Charles C. Edwards	Mar. 1973	Jan. 1975
Richard L. Seggel (acting)	Dec. 1972	Mar. 1973
Merlin K. Duval, Jr.	July 1971	Dec. 1972
Roger O. Egeberg	July 1969	July 1971
Vacant	Feb. 1969	July 1969
Philip R. Lee	Nov. 1965	Feb. 1969
COMMISSIONER, FDA:		
Alexander M. Schmidt	July 1973	Present
Sherwin Gardner (acting)	Mar. 1973	July 1973
Charles C. Edwards	Feb. 1970	Mar. 1973
Herbert L. Ley, Jr.	July 1968	Dec. 1969
James L. Goddard	Jan. 1966	June 1968
DIRECTOR, CDC:		
David J. Sencer	Feb. 1966	Present

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