REPORT OF THE COMPTROLLER GENERAL OF THE UNITED STATES

Recalls Of Large Volume Parenterals (Liquid Drugs Administered Intravenously Or By Other Non-oral Means)

Food and Drug Administration
Center for Disease Control
Department of Health, Education, and Welfare

Between July 1, 1965, and November 10, 1975, there were recalls of 608 chemical large volume parenteral products involving over 43 million individual containers which had been distributed. Between January 1, 1970, and November 10, 1975, there were 17 recalls of biological large volume parenteral products.

Most of these recalls were due to contamination, resulting in most cases from manufacturing problems. The Food and Drug Administration is developing regulations to improve quality controls in the manufacturing of large volume parenterals.

MWD-76-67

907296

MARCH 12, 1976

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

B-164031(2)

The Honorable Gaylord Nelson
United States Senate

Dear Senator Nelson:

In response to your October 16, 1973, request, this is our report on recalls of large volume parenteral drug products between July 1, 1965, and November 10, 1975. The Food and Drug Administration of the Department of Health, Education, and Welfare monitors the manufacturer's effectiveness in recalling drug products from the market.

As requested by your office, we obtained formal written comments from the Department on matters in the report. We also obtained comments from Abbott Laboratories, Cutter Laboratories, and Travenol Laboratories, three major manufacturers of chemical large volume parenterals discussed in this report. In accordance with instructions from your office, we asked them for expedited comments. Generally, they did not consider the time allowed for their comments adequate to submit comprehensive responses to the matters discussed in this report.

We invite your attention to the fact that this report contains recommendations to the Secretary of Health, Education, and Welfare. As you know, section 236 of the Legislative Reorganization Act of 1970 requires the head of a Federal agency to submit a written statement on actions he has taken on recommendations to the House and Senate Committees on Government Operations not later than 60 days after the date of the report, and the House and Senate Committees on Appropriations with the agency's first request for appropriations made more than 60 days after the date of the report. We will be in touch with your office in the near future to arrange for copies of the report to be sent to the Secretary and to the four Committees to set in motion the requirements of section 236.

Sincerely yours,

Comptroller General
of the United States

Contents

ABBREVIATIONS

CDC	Center for Disease Control
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
GAO	General Accounting Office
GMPs	good manufacturing practices
GRAS	generally recognized as safe
HEW	Department of Health, Education, and Welfare
LVP	Large Volume Parenteral
USP	The United States Pharmacopeial Convention, Inc.

COMPTROLLER GENERAL'S REPORT
TO THE HONORABLE GAYLORD NELSON
UNITED STATES SENATE

RECALLS OF LARGE VOLUME PARENTERALS (LIQUID DRUGS ADMINISTERED INTRAVENOUSLY OR BY OTHER NON-ORAL MEANS)
Food and Drug Administration
Center for Disease Control
Department of Health, Education, and Welfare

D I G E S T

Large volume parenterals are chemical or biological liquid drugs, packaged in 100 milliliter or larger single dose containers, including intravenous solutions, peritoneal dialysis solutions, and irrigating solutions.

According to a 1974 Food and Drug Administration estimate, there are about 100 million administrations of large volume parenterals to people in the United States annually. (See pp. 1 to 5.)

Between July 1, 1965, and November 10, 1975, manufacturers recalled 608 chemical large volume parenteral products. Most of these recalls were due to manufacturing problems generally associated with product contamination and involved over 43 million containers of large volume parenterals which had been distributed. Fifty-four deaths and 410 injuries were associated with contaminated chemical large volume parenterals which were recalled. FDA officials cautioned that these are reports of deaths and injuries associated with the use of the products as opposed to deaths and injuries proven to be caused by them.

Between January 1, 1970, and November 10, 1975, there were 17 instances of recalls involving biological large volume parenterals, mostly due to either product contamination or adverse reactions associated with the products. Six deaths and 11 injuries were associated with biological large volume parenterals which were recalled. (See p. 6.) According to Food and Drug Administration and Center for Disease Control officials, patients administered these products are usually in severe physical condition, therefore, it is

difficult to unequivocally attribute their death or injury to a particular cause.

Many recalls of large volume parenterals were attributed to manufacturing problems. The Secretary of Health, Education, and Welfare has issued regulations providing criteria for determining whether drugs have been manufactured, processed, packed, or held in accordance with good manufacturing practices. (See p. 1.)

The Food and Drug Administration, however, does not believe these regulations are adequate for large volume parenterals and has begun developing good manufacturing practice regulations specifically for large volume parenterals. (See p. 23.)

Because these regulations are essential to insure the integrity and safety of these products, the Secretary should direct the Food and Drug Administration to give high priority to issuing the good manufacturing practice regulations for large volume parenteral products. (See p. 35.)

The Center for Disease Control, responsible for investigating, collecting, analyzing, and distributing data related to disease conditions, could, in carrying out its responsibilities, better assist the Food and Drug Administration's efforts to regulate large volume parenterals if the Center had a better understanding of the data needed for regulatory purposes.

The Center and the Food and Drug Administration have a broad informal understanding regarding each agency's investigational responsibilities, but a formal interagency agreement, taking into consideration the priorities, missions, and areas of responsibility of each agency, might better insure that data developed by each agency will be mutually beneficial in carrying out their respective responsibilities. (See p. 26.)

The Secretary should direct the Commissioner, Food and Drug Administration, and the Director, Center for Disease Control, to evaluate the need to establish such a formal interagency agreement. (See p. 35.)

HEW concurred in GAO's recommendations. (See p. 36.)

GAO also obtained comments from three major manufacturers of chemical large volume parenterals discussed in this report. Two of the manufacturers did not consider the time allowed for their comments adequate to submit comprehensive responses to the matters discussed in this report. (See app. V, VI, and VII.)

CHAPTER 1

INTRODUCTION

On October 16, 1973, Senator Gaylord Nelson requested that we

--develop statistical data on large volume parenterals (LVPs), including the number of LVP products recalled since fiscal year 1966, deaths and injuries associated with contaminated recalled products, and the cause of the recalls;

--review and develop data on the Food and Drug Administration's (FDA's) regulatory activities over LVPs;

--identify the Center for Disease Control's (CDC's) role in the regulation of LVPs; and

--develop information concerning FDA's contract with the United States Pharmacopeial Convention, Inc. (USP), to study problems regarding LVPs.

FDA, which administers the Federal Food, Drug, and Cosmetic Act (FD&C Act) as amended (21 U.S.C. 301 et seq.) and the drug provisions of the Public Health Service Act as amended (42 U.S.C. 262), has defined an LVP as a liquid drug, either chemical or biological in nature, packaged in a single dose container with a capacity of 100 milliliters or more, and intended to be administered to humans or animals. LVPs include intravenous solutions intended for injection into a vein, peritoneal dialysis solutions used for internal detoxification of the blood, and irrigating solutions used to cleanse open wounds. According to a 1974 FDA estimate, there are about 100 million administrations of LVPs to people in the United States annually.

FDA, a part of the Department of Health, Education, and Welfare (HEW), is responsible for insuring that both chemical and biological drugs in interstate commerce are safe and effective. The FD&C Act prohibits the introduction in interstate commerce of drugs which are adulterated or misbranded. The act defines an adulterated drug as, among other things, one which has not been produced in conformity with good manufacturing practices (GMPs). The Secretary, HEW, issued regulations (21 C.F.R. 210.211) providing criteria for determining whether drugs have been manufactured, processed, packed, or held in accordance with GMPs. A drug is misbranded if its labeling or packaging is false or misleading.

A drug is also deemed to be adulterated and misbranded if it does not conform to standards provided for it in either the "United States Pharmacopeia," a publication of USP, or the "National Formulary," published by the American Pharmaceutical Association, unless such nonconformity is stated on its label. These compendia 1/ are formally recognized under the FD&C Act as the official source of standards for drug identity, strength, quality, and purity. A drug listed in them is referred to as an "official" drug. FDA is responsible for enforcing the compendia drug standards.

A drug not listed in the compendia is deemed adulterated if its strength differs from, or its purity or quality falls below, that which it is purported or represented to possess.

The FD&C Act also requires a drug manufacturer to:

--Register its manufacturing establishments and products with FDA.

--File new drug applications with FDA and obtain FDA's approval of the application before introducing new drugs into interstate commerce. Applications must demonstrate the drug's safety and efficacy.

--Be inspected once every 2 years. Inspections include a review of plant manufacturing conditions, production procedures and controls, and complaint files.

A primary objective of the required biennial inspections is to determine whether drug manufacturers are following GMPs. As part of some inspections, samples of a product are drawn at various stages of processing. Generally, the decision to collect samples is judgmental, partly based on the need to develop evidence concerning GMP violations.

During fiscal years 1966 through 1974, FDA made 161 inspections of 18 chemical LVP manufacturing facilities. Samples were collected during 76 of the inspections. (See app. II.)

Biological LVPs are also subject to the provisions of the Public Health Service Act, which require that biological drug products be safe, pure, and potent and that they and their manufacturers be licensed. Chemical drugs are not regulated by the Public Health Service Act.

1/Effective January 2, 1975, the "Pharmacopeia" and the "National Formulary" were unified by the purchase of the "Formulary" by USP.

Before 1938 an approved new drug application was not required to market a drug. According to an FDA official, many LVP products were marketed before 1938 and are generally recognized as safe (GRAS) based on a satisfactory history of usage rather than actual data of clinical studies demonstrating safety and efficacy.

When violative drug products are found, FDA can initiate one or more of the following legal actions through the Department of Justice. 1/

--Prosecute individuals violating the FD&C Act or the Public Health Service Act.

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

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

In addition, FDA may request a manufacturer to voluntarily detain or recall a product. A voluntary detention or recall is an action taken by a manufacturer, at FDA's request or at its own initiative, to detain or remove from the market a product suspected or known to be defective. A manufacturer is not required to notify FDA of recalls it initiates. Because FDA does not have detention or recall authority, it cannot enforce such actions; they must be negotiated between industry and FDA. A manufacturer assumes full responsibility for removing a recalled product from the market. FDA's role is to monitor the manufacturer's effectiveness in removing the product.

CDC, another HEW agency, has responsibility under authority of the Public Health Service Act (42 U.S.C. 241) for providing leadership and direction to programs and activities designed to improve the public health by preventing or controlling diseases. Although CDC has no regulatory authority over LVP products, as part of its overall responsibility it collaborates with FDA in areas of mutual program interest regarding LVPs.

1/Our report entitled "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) discusses FDA's need for additional authority to more effectively carry out its responsibilities under the FD&C Act.

LVP MANUFACTURERS

According to data FDA supplied to us in February 1974, there were 361 chemical LVP products being marketed. The four major manufacturers of these products are

--Abbott Laboratories, North Chicago, Illinois;

--Travenol Laboratories, Deerfield, Illinois;

--Cutter Laboratories, Berkeley, California; and

--McGaw Laboratories, Division of American Hospital Supply Corporation, Glendale, California.

A fifth firm, Pharmacia Laboratories, Inc., Piscataway, New Jersey, began manufacturing and distributing chemical LVP products in April 1974.

The following table summarizes the number of chemical LVP products produced by each manufacturer.

	Number of products			Number listed in	
Manufacturer	GRAS	New drugs	Total	"Pharmacopeia"	"National Formulary"
Abbott	58	15	73	25	3
Travenol	62	35	97	55	4
Cutter	69	19	88	35	1
McGaw	81	18	99	35	a/5
Pharmacia	-	4	4	-	-
Total	270	91	361	150	13

a/One of these five drugs is also listed in the "Pharmacopeia."

According to FDA, there are two biological LVP products on the market--Normal Serum Albumin and Plasma Protein Fraction. There are 17 manufacturers--including Abbott, Travenol, and Cutter--licensed to produce either or both of the biological products.

PROCEDURES FOLLOWED IN THE MANUFACTURE OF CHEMICAL LVPS

Following are the basic procedures generally followed in the manufacture of chemical LVP drug products.

1. Materials, including chemicals, containers, closures, and packaging and labeling materials, are sampled and inspected for conformance to specifications.

2. Chemical ingredients are mixed with distilled water in a tank.

3. The mixed batch is filtered while being transferred from the mix tank to a filling machine.

4. The batch is filled into previously washed containers. The containers are closed, sealed, and a vacuum is drawn in the case of those LVPs packaged in glass containers. Samples are periodically selected to be checked for the volume of fill, tightness of closure, degree of vacuum, etc. The filled containers are then placed in an autoclave (sterilizer).

5. LVPs are sterilized in their final container by heat. After sterilization, the containers are gradually cooled and a sample is drawn to test for sterility and pyrogens (bacterial substances that can cause fever).

6. The entire batch is then inspected visually for particulate matter and packaged for shipping.

CHAPTER 2

RECALLS OF LVPS

From July 1, 1965, through November 10, 1975, manufacturers recalled 608 1/ chemical LVP products. 2/ Most of the recalls were due to manufacturing problems--generally associated with product contamination--and involved over 43 million individual containers of LVPs which had been distributed. (See app. III.) Between January 1, 1970, and November 10, 1975, there were 17 recalls involving biological LVPs, mostly due to either product contamination or adverse reactions associated with the products. (Information concerning recalls of biological LVPs before January 1970 was not readily available.) Fifty-four deaths and 410 injuries were associated with recalled chemical LVPs and 6 deaths and 11 injuries were associated with recalled biological LVPs.

CHEMICAL LVP RECALLS

Of the 608 chemical LVP products recalled during the 10-year period July 1965-November 1975, 451 were recalled at FDA's request. The following table shows the number of chemical LVP products recalled by each firm and the initiator of the recalls.

Manufacturer	Number of products recalled	Recall initiated by FDA	Recall initiated by Manufacturer
Abbott	221	106	115
Travenol	38	27	11
Cutter	216	190	26
McGaw	131	128	3
Pharmachem (note a)	1	-	1
Sherman (note b)	1	-	1
Total	608	451	157

a/Pharmachem, Inc., stopped producing LVPs in 1971.

b/Sherman Laboratories stopped producing LVPs in 1969.

1/Includes some products recalled more than once for different reasons.

2/In this report, the term "product" includes all package sizes and lot numbers produced by a firm having the same formulation.

FDA records indicated that 459 of the 608 chemical LVPs were recalled because they were contaminated with unwholesome or undesirable elements which made the products a potential health risk. Sixteen products were recalled because they contained sorbitol (a molecular variation of sugar) or a high concentration of dextrose, which were associated with adverse reactions. (The products recalled had been marketed without approved new drug applications and have been withdrawn from the market. These products are further discussed on pp. 19 to 21.) The remaining products were recalled because of improper labeling, product discoloration, variations from formula, inadequate research data, leaking containers, and serious deviations from GMPs.

According to FDA and CDC records, hospitals reported that 54 deaths and 410 injuries were associated with the use of 366 of the 459 chemical LVPs recalled because of contamination. There were no deaths or injuries reported for the remaining 93 recalled contaminated products.

Death and injury data by product manufacturer and date of recall are shown below.

Manufacturer	Recall date	Number of Deaths	Injuries	Products recalled
Abbott	6- 7-69	-	33	70
Abbott	3-22-71	50	362	105
Travenol	6-22-73	-	2	1
Cutter	3-15-73	4	9	189
Sherman	9- 5-67	-	4	1
Total		54	410	366

FDA officials told us that available information does not provide a basis for precisely determining the number of deaths and injuries caused by LVP contaminations and they have found it impossible to draw a direct cause-effect relationship between any given death or injury and a specific product or hospital practice.

FDA officials said it is often difficult to determine the causes of LVP contamination. There are many potential sources of contamination at both the manufacturer and hospital levels. For example, contamination at the manufacturer level can occur as a result of bottle cracks, defective container closures, or faulty maintenance of sterilization equipment. Contamination at the hospital level can occur during changes of LVP containers and administration sets, addition of medications to the LVP, or other handling of the LVPs.

At best, according to FDA officials, strong circumstantial evidence that product contamination at the manufacturer level caused a death or injury is provided in a limited number of cases where the same unusual organism found in a patient was found in the remains of the product which had been given to the patient. However, FDA officials said that in such cases a possibility exists that product contamination and/or patient injury may have resulted from improper hospital practices.

Therefore, FDA officials cautioned that figures on deaths and injuries found in FDA and CDC records reflect reports of injuries or deaths associated with the use of an LVP as opposed to injuries or deaths proven to be caused by an LVP.

The following information, covering the period July 1965-November 1975, concerns recalls of contaminated chemical LVP products which involved reported deaths or injuries.

Abbott

In 1971 and 1969 Abbott recalled contaminated chemical LVP products that involved reported deaths or injuries. Abbott's products were manufactured at its North Chicago, Illinois, and Rocky Mount, North Carolina, plants.

On March 22, 1971, at FDA's request, Abbott recalled 105 LVP products marketed in containers with screw-cap closures which were contaminated with bacteria. This recall resulted in an immediate halt in production of Abbott LVPs packaged in containers with screw-cap closures.

A hospital official's advice to a CDC official in October 1970 of five cases of septicemia (blood poisoning) associated with the use of Abbott LVP products was the initial indication that a problem existed. In November 1970 a second hospital reported to CDC septicemia cases associated with the use of Abbott LVP products. Subsequently, several other hospitals made similar reports to CDC.

CDC advised FDA of the reported septicemia cases. In January 1971 FDA examined the sterility testing procedures and control records at Abbott's Illinois and North Carolina plants and found no deficiencies in the sterility testing of either LVPs or LVP administration sets or indications that any contaminated lots of LVPs and administration sets had been distributed.

Between December 1970 and March 1971, CDC conducted investigations to determine the cause of the septicemia cases.

On March 1, 1971, CDC informed FDA that it found several instances where the cap of an LVP container was contaminated with multiple organisms. However, CDC and FDA believed that before the septicemia incidents could be attributed to the contaminated caps, it had to be shown that organisms in the caps were released into the drug. Therefore, CDC conducted further studies attempting to relate the contaminated caps to the problem by investigating the circumstances permitting migration of organisms from the caps to the solution. CDC's studies showed that the organisms migrated with high frequency from caps to the solutions during simple manipulation of the cap.

On March 12, 1971, CDC, FDA, various top-level HEW, and Abbott officials met to discuss CDC's findings. The FDA and HEW representatives concluded that steps should be taken to protect the public. A decision was made to embargo all Abbott LVPs except those required for emergency needs and to recommend precautionary measures to users of Abbott LVPs.

Accordingly, on March 13, 1971, FDA and CDC each issued formal public statements outlining the national scope of the problem and special procedures to be followed to minimize the risk of contamination from Abbott LVPs. The statements announced that Abbott would replace the products as rapidly as possible, but because they were essential for patient care they could not be withdrawn before replacements were available. FDA and CDC were uncertain as to whether all hospitals could immediately obtain replacements.

On March 19, 1971, the CDC Director informed FDA's Associate Commissioner for Compliance that CDC had received reports of about 300 septicemia cases involving Abbott LVPs and expressed concern that the March 13 public statements had not had a significant impact on the problem. The Director said that he was convinced there was a sufficient supply of products available from Abbott's competitors and that it was necessary to stop the use of all Abbott solutions. After a meeting of CDC, FDA, and HEW officials, on March 22, 1971, FDA issued a press release recommending that all hospitals and other health care facilities begin an orderly, expeditious shift from the use of Abbott LVPs to other LVP products and requested Abbott to recall its products. Abbott complied with FDA's request.

An FDA inspection of Abbott's Rocky Mount, North Carolina, plant conducted during March 19 and April 1, 1971, disclosed "objectionable" building and equipment conditions and personnel, production, and quality control practices which could have contributed to microbial contamination of products. FDA's inspection reports noted that:

--Lubricant used on chain conveyors was dripping on filled and capped bottles before sterilization.

--Water used to cool filled sterilized bottles was found by the firm to have a greater bacterial count than the manufacturer's established limit, which was a maximum of 20 bacteria per milliliter. On at least 25 occasions since June 1, 1970, bacterial counts were over 50 per milliliter.

--Filled sterilized bottles were processed through a rinser-blower unit and rinsed with municipal water without receiving bactericidal treatment at the plant. Hot air used to dry rinsed bottles was unfiltered; the air intake was covered with a black, powdery, dirtlike substance; and according to the firm, the air supply system had never been cleaned.

--Product samples for sterility analysis were collected by the firm from trays immediately after sterilization but prior to being subjected to a number of subsequent production steps.

An FDA inspection of Abbott's North Chicago, Illinois, plant conducted March 19 to April 13, 1971, disclosed 147 questionable conditions and practices which caused Abbott to be required to halt its production of LVPs packaged in containers with screw-cap closures at that plant.

In June 1971 FDA allowed Abbott to resume commercial sale and distribution of its LVPs after Abbott switched to a rubber-stopper-type closure system and FDA

--developed manufacturing and testing protocols to be followed by Abbott,

--reviewed proposed manufacturing facility changes involving production and control procedures,

--inspected Abbott facilities to assure acceptable operation, and

--collected and examined product samples from new trial production to verify sterility.

According to CDC data, 25 hospitals reported 412 cases of septicemia associated with the use of Abbott LVP products; 50 of these cases involved deaths.

On May 29, 1973, a Federal grand jury indicted Abbott and five of its senior officials for interstate shipment of LVPs that were "unsterile and dangerous to the public health." The indictment charged the drugs were adulterated because they contained live bacteria and were not produced under conditions consistent with GMPs.

The Eastern District Court of North Carolina dismissed the indictment on December 17, 1973, on the grounds of prejudicial pretrial publicity by FDA and the Justice Department. The Government appealed the district court's decision and on October 2, 1974, the Court of Appeals of the Fourth Circuit reversed the lower court. While the court of appeals found that there had been prejudicial pretrial publicity, it held that voire dire examination of prospective jurors could guarantee a fair trial. Abbott petitioned the court of appeals for a rehearing, which was denied on November 5, 1974. Abbott requested review of the matter by the Supreme Court. However, on March 24, 1975, the Supreme Court let stand the decision by the Fourth Circuit Court of Appeals.

The trial of the case began before the district court on July 21, 1975. On August 5 and 12, 1975, all counts of the indictments against the individual Abbott officials and the firm were dismissed on motion of the Government. Also on August 12, the firm entered a plea of nolo contendere to one charge of conspiracy to ship contaminated LVPs in interstate commerce, a misdemeanor (18 U.S.C. 371). The firm was fined $1,000 and court costs.

Abbott's earlier recall in June 1969, involving 70 LVP products, was initiated by the manufacturer. Abbott had experienced the following problems with LVPs produced at its North Chicago plant from November 1968 through February 1969.

--An increase in the incidence of hairline cracks in the neck of glass bottles used for LVPs. Under certain conditions the crack could open sufficiently to permit an interchange between the atmosphere and the contents of a bottle which could result in product contamination.

--An increase in the incidence of production problems, such as damaged caps and improper threading due to wear of a capping machine.

On April 25, 1969, FDA became aware that a problem existed with LVPs manufactured at Abbott's North Chicago, Illinois, plant when an FDA inspector noticed Abbott personnel visually examining LVPs for contamination at a warehouse in Oregon.

On May 7 FDA contacted Abbott requesting an explanation for the visual inspection. Abbott informed FDA that small flaws had been detected in the necks of the glass containers used for LVPs manufactured between November 1968 and February 1969 and that the flaws could compromise the product's sterility.

At a May 9 meeting Abbott told FDA that it had (1) replaced the problem capping machine, (2) increased its inspection of glass bottles for hairline cracks and other defects, and (3) increased the number of quality control samples taken.

On May 10 Abbott restricted further distribution of the affected LVPs and told hospitals, nursing homes, and drug stores to temporarily quarantine LVPs already distributed until it could provide more information.

An FDA plant inspection from May 12 to June 3 revealed a number of deviations from GMPs which had not been previously reported. Some of the deviations cited in FDA's inspection report were:

--Use of recirculated bacteriologically contaminated washing solution.

--Sporadic and infrequent inspection of bottle capper.

--Processing line too fast to allow for adequate in-process inspection and proper handling of glass containers.

--No defect specifications for incoming or inprocess glass.

--Failure to rotate inspectors frequently enough to maintain effective inspection.

On June 3 FDA advised Abbott of the deficiencies.

On June 7 Abbott notified hospitals, nursing homes, and drug stores that it was recalling the quarantined LVPs.

Abbott received reports of several incidents of patients experiencing adverse reactions after being administered the LVPs in question. According to FDA investigations, 12 of 33 reported adverse reactions were "definitely or probably" related to contamination of the LVP product.

FDA's Chicago district office believed the June inspection provided information which would adequately demonstrate that LVPs at the North Chicago plant were being packaged in

defective bottles. Accordingly, in mid-June 1969 FDA instructed its Chicago district office to prepare a recommendation for an injunction against Abbott. The recommendation for an injunction for violations of adulteration and misbranding provisions of the FD&C Act was submitted to FDA headquarters on July 9.

By letter dated June 27, 1969, Abbott informed FDA that the following actions were being taken to correct the deficiencies.

--An electronic glass inspection device was being installed in the glass supplier's production process.

--Incoming glass containers were being preinspected before delivery.

--Proper glass-handling practices were being emphasized to minimize breakage and exposure.

Although Abbott indicated it had initiated corrective action, it also stated that it did not believe any of the drugs produced during the period in question failed to meet applicable standards or violated GMPs.

While the recommendation for an injunction was being prepared, the Chicago district office recommended on July 2 that, because of GMP deviations, FDA seize Abbott's 5-percent dextrose quarter strength saline solutions produced during FDA's inspection. Although FDA headquarters did not concur in the proposed seizure, on July 11 FDA summoned Abbott to a hearing which took place on September 3 and 8, 1969. Section 305 of the FD&C Act provides a person an opportunity for a hearing before a violation of the act is reported to a U.S. attorney for institution of a criminal proceeding.

The hearing focused on the charge by FDA's Chicago district office that solutions were being produced in defective glassware at Abbott's North Chicago plant. The evidence was reexamined by an FDA employee with expertise in glassware examination. His opinion was that most of the defects were not critical. An FDA memorandum of February 2, 1971, discussing the chronology of events, stated that this removed any objective evidence supporting the claim that Abbott was using defective containers.

The case was then reduced to a question of whether Abbott's glassware purchase system and inspection procedures met the material control requirements under FDA's GMP regulations. An FDA memorandum of February 2, 1971, stated that the Chicago district office believed that there was insufficient

evidence to establish that Abbott's procedures were not meeting GMPs. Abbott repeatedly claimed to set industry standards in this area, and FDA did not have sufficient evidence to refute this. No further action was taken in the case.

Abbott Laboratories advised us that the data presented on Abbott recalls of LVPs contained inaccuracies and omissions. (See app. V.) Most of the omissions or inaccuracies alleged by Abbott concerned matters contained in FDA or CDC records which were the source for information contained in this report.

Travenol

On June 22, 1973, Travenol recalled one lot of its 5-percent Dextrose Injection LVP solution packaged in plastic containers. This lot was manufactured in May 1973 at Travenol's Kingstree, South Carolina, plant. Of the 690 cases in this lot, only 6 had been distributed--all to 1 hospital where patients experienced pyrogenic (fever) reactions. Travenol told us that it destroyed the undistributed cases.

On May 31, 1973, a hospital patient experienced a pyrogenic reaction during infusion of Travenol's 5-percent Dextrose Injection solution packaged in plastic containers. A second patient administered the solution suffered an identical reaction on June 5.

On June 6 the hospital administrator contacted a Travenol sales representative concerning the pyrogenic reactions. On the same day, the representative visited the hospital, reviewed information related to the reactions, and instructed the hospital to destroy the remaining stock except for samples he took to be tested.

Travenol subsequently tested the suspected solution on rabbits and found that it produced pyrogenic reactions. By letter dated July 6, 1973, Travenol notified FDA of both the adverse reactions and its June 22 recall.

In a letter to Travenol dated July 17, 1973, FDA discussed "significant adverse conditions" noted in FDA's inspection of Travenol's Kingstree, South Carolina, plant during May 7-11, 1973. The inspection findings had also been discussed with plant officials at the conclusion of the inspection. In its letter FDA pointed out that the engineering design for the plant's water-handling storage systems was inadequate and consequently that the quality of the water used in manufacturing LVPs was poor. Examination of microbiological test data showed that the bacterial count in raw

water, deionized water, sterilizer cooling water, and distilled water was high. FDA also advised Travenol that the plant's laboratory sterility test faciliies were inadequately controlled. FDA requested a report, within 30 days, of the firm's plans to bring the plant into compliance with the FD&C Act.

On August 13-15, 1973, FDA performed a followup inspection of the Kingstree plant. According to its report, deficiencies similar to those reported in the May 1973 inspection as well as inadequate cleaning procedures for filling equipment were found.

FDA's November 8, 1973, summary of the recall noted that Travenol quality control personnel attributed the pyrogen problem to improper "clean up" of the Kingstree plant. According to the summary, Travenol planned no changes in its control procedures. Travenol advised us, however, that modifications and improvements had been made to this plant as a result of FDA inspections of May and August 1973. In addition, Travenol said that further improvements were being considered, but it decided in November 1973 to discontinue manufacturing LVPs at the Kingstree plant.

Cutter

On March 15, 1973, Cutter recalled one lot of its 5-percent Dextrose in Lactated Ringer's Injection solution (an intravenous solution which contains 5-percent sugar by weight, plus salts which are commonly found in blood plasma) produced at its Chattanooga, Tennessee, plant because of product contamination. On March 20, after contamination was found in additional lots, all 5-percent Dextrose in Lactated Ringer's Injection solution produced at the Chattanooga plant since September 13, 1972, were recalled. On April 5, at FDA's request, Cutter expanded its earlier recalls to include all parenteral solutions manufactured at that plant before March 14, 1973.

Hospitals reported four deaths and nine injuries associated with Cutter's recalled LVPs. The first report was received by CDC from a Milwaukee, Wisconsin, hospital on February 23, 1973.

Cutter had previously experienced bacterial contamination problems with LVPs produced at the Chattanooga plant. On September 28, 1972, Cutter discontinued production and distribution of irrigating solutions at its Chattanooga plant because it had been experiencing an increased rate of bacterial contamination during sterility retests on irrigating solutions in bottles with screw-cap closures.

On October 3, 1972, Cutter advised FDA of the problem and on October 11 Cutter notified FDA that it planned to recall its irrigating solutions marketed in containers with screw-cap closures. On October 14 Cutter initiated the recall; however, it continued to produce LVP products marketed in other than screw-cap closures.

FDA inspected the Chattanooga plant during October 4-19, 1972. FDA found deficiencies in the sterilizer's plumbing and related drainage systems which allowed contaminated drain water to be back-siphoned and mixed with recirculating water used in the sterilization cooling cycle. In addition, incoming city water and recycled water used for cooling the sterilized bottles (poststerilization cycle) were not being microbiologically controlled. A major problem was that Cutter did not know the quality of its incoming or recycled water.

FDA determined that the entire LVP product line at the Chattanooga plant was produced under identical conditions and, therefore, was constantly exposed to potential microbiological contamination during the poststerilization cycle, and the manufacture of LVPs under such conditions resulted in significant deviations from GMPs. At the conclusion of the inspection FDA advised Cutter of the deficiencies.

FDA reinspected the Chattanooga plant on November 8 and 9, 1972. Some of the deviations from GMPs found during the previous inspection were again noted, as well as other deviations, and Cutter was advised of the deficiencies and the need to correct them.

In a November 22 telephone conversation with FDA officials, Cutter representatives stated that the firm's management believed the objectionable conditions had been corrected to the point that test-run production with screw-cap closures could begin. Further, the firm believed that production, under existing conditions, of products having closures other than screw caps would not create a public health hazard. FDA advised Cutter of the seriousness of continuing production under existing conditions and suggested it halt production until suitable changes had been made. Cutter, however, continued producing LVPs. Accordingly, FDA informed Cutter that a followup inspection of the Chattanooga plant would begin on November 27, 1972.

FDA inspected the Chattanooga plant between November 27 and December 1. The results indicated the problem of back-siphonage had been eliminated, but specifications had not been established to control the microbiological quality of either the incoming city water or the water being recirculated and used to spray-cool filled sterilized bottles. In

addition, pipes used to circulate water were not being sanitized following nightly shutdowns and preliminary tests of water used for spray cooling showed a bacteria build up.

In a December 6, 1972, meeting with FDA, Cutter discussed the actions it was taking in an attempt to resume production of irrigating solutions marketed in screw-cap closures which had been halted on September 28, 1972. Because there was no industrywide standard and FDA's current GMPs contained no specific guidelines on water quality, Cutter asked FDA what criteria the firm should use in evaluating the quality of the water used to cool filled sterilized bottles. Although FDA did not indicate what microbiological specifications would be acceptable, it advised Cutter that the water must be sterile and offered a number of proposals for assuring that the quality of the water used throughout the cooling cycle would be acceptable. FDA stated, however, that no distribution of irrigating solutions in containers with screw-cap closures should be made until the firm had conducted sufficient tests to assure FDA the solutions were being manufactured in accordance with GMPs.

By letter dated December 18, Cutter advised FDA of corrective actions it had taken or planned to take.

From February 19-22, 1973, FDA conducted a followup inspection. At the conclusion of this inspection FDA again cited Cutter's manufacturing procedures as being deficient and in violation of GMPs. FDA found that Cutter had not established any control over the microbiological quality of either the distilled water used in processing or the incoming and recirculated water used in the spray-cooling cycle. Therefore, LVPs produced at that time remained susceptible to contamination.

Subsequently, CDC advised FDA of reported septicemia cases involving hospital patients who received Cutter's LVPs. Pursuant to this information, FDA conducted another inspection of Cutter's Chattanooga plant. The inspection started March 14 and ended March 28, 1973. According to CDC, as of September 13, 1972, Cutter began using a new time-temperature-pressure sterilization cycle in producing 5-percent Dextrose in Lactated Ringer's Injection solution. The new process subjected the bottle-and-bung (bottle and cap) assembly to greater pressure gradients, particularly during the water-spray-cooling cycle.

FDA's March 1973 inspection of the Chattanooga plant disclosed that the new sterilization process had not been proven effective and that the plant still had not established a microbiological standard to control the quality of the spray-cooling water. According to CDC these findings, plus

reports that cracks appeared in bottles, suggested that small amounts of contaminated water were entering the solution either through minute cracks in the bottle or along the bottle-bung interface. Accordingly, FDA officials concluded that there were no assurances that LVPs produced at the plant were safe.

On March 15, 1973, Cutter recalled one lot of its 5-percent Dextrose in Lactated Ringer's Injection solution, and on March 20, 1973, in response to FDA's request, Cutter recalled all of the 5-percent Dextrose in Lactated Ringer's Injection solution produced at its Chattanooga plant after September 13, 1972.

In a phone conversation with Cutter on March 30, 1973, FDA suggested that production and distribution of all products manufactured at the Chattanooga plant be immediately discontinued and that any distributed products be recalled. However, Cutter requested an opportunity to discuss the matter.

On April 2 FDA met with Cutter and recommended that the March 20 recall be expanded to include all LVPs produced before March 14, 1973. Cutter proposed that the recall be limited to products manufactured before December 28, 1972, because Cutter said at that time it began testing the quality of incoming city water. FDA found the proposal untenable because Cutter had not established standards so that the test results could be effectively used, and investigations attributed patient injuries to 5-percent Dextrose in Lactated Ringer's Injection solution produced after December 28, 1972. In a telegram to Cutter on April 3, 1973, FDA concluded:

> "From the record of plant production and control deficiencies, most of which have been brought to your attention on several occasions during inspections of the Chattanooga plant, including inspections in February and March 1973, it is clear to us that a recall limited to drugs produced prior to December 28, 1972, will not serve as an adequate step toward protection of the public health. We think that the record is clear, as discussed in considerable detail in the Cutter Labs/FDA conference on April 2, that all production of the Chattanooga plant to date has been under conditions which make impossible any assurance that the drugs are safe for use as required under the Food, Drug, and Cosmetic Act. We believe that the evidence of poor manufacturing practice which has existed, and to a significant extent continues to exist, gives us no recourse other than to reject your proposal as being inadequate."

The suggested recall followed on April 5, 1973, at which time Cutter's Chattanooga plant terminated production. During the next 18 months the firm made widespread manufacturing improvements and restructured the physical plant. In October 1974 FDA informed Cutter that it had no objection to the resumption of manufacture and distribution of LVPs at the Chattanooga plant, as FDA's September 1974 inspection showed deficiencies at the Chattanooga plant had been adequately corrected.

Sherman

On September 1, 1967, Sherman recalled all its Lactated Ringer's Injection solution in 1,000 milliliter containers. The recall occurred after two hospitals experienced four injuries associated with the product's use and an analysis of the solution revealed positive pyrogen contamination. On September 5, 1967, Sherman notified FDA of the recall and the related injuries.

FDA had inspected Sherman's Detroit, Michigan, plant in March 1967. The inspection report stated that some of the firm's manufacturing practices and quality control procedures were inadequate in that:

--Accepted raw materials were being stored in a quarantine area.

--Returned goods were not routinely assayed before being incorporated into a new batch.

--An employee filling ampules of 50-percent dextrose in water got far ahead of the employee sealing the ampules, which could possibly result in contamination.

FDA's June 1969 inspection of the Detroit plant showed that Sherman improved its manufacturing facilities, procedures, controls, and methods to the point where the firm generally appeared to be operating in compliance with GMPs.

Other recalls

Cutter initiated a recall of its peritoneal dialysis solutions (five separate products) containing sorbitol on December 29, 1971, after being notified of four cases of reversible comas associated with one of its sorbitol-containing LVPs. As a result of the Cutter case, on January 3, 1972, FDA began investigating similar solutions containing sorbitol.

On March 21, 1972, FDA requested McGaw and Travenol to recall a total of seven sorbitol-containing LVPs. FDA's request stated:

> "On the basis of our investigations including recent reports of injuries related to the use of subject products, we have concluded that the safety of these products has not been established under the conditions of use recommended and suggested in the current labeling and that the products are not generally recognized as safe and effective among appropriately qualified experts. We are therefore requesting that all such products be recalled from the market to the user level. We have determined that such a recall will not jeopardize the lives of patients currently being treated with such solutions since dextrose-containing solutions are readily available. * * *
>
> "The future distribution and use of sorbitol-containing peritoneal dialyzing solutions is therefore required to be in conformance with the new drug procedures promulgated pursuant to * * * the Federal Food, Drug, and Cosmetic Act. * * *"

On February 1, 1973, based on reports of adverse reactions, FDA requested Abbott, Cutter, McGaw, and Travenol to recall a total of four 7-percent dextrose peritoneal dialysis solution products. In its recall request FDA stated:

> "FDA has been advised that solutions for peritoneal dialysis containing 7% or more dextrose have been associated with significant adverse reactions due to rapid dehydration. We regard this as a potential threat to consumer safety.
>
> "In addition, FDA has concluded that there is no justification for commercially prepared solutions containing more than 4.25% dextrose for peritoneal dialysis."

According to FDA, the firms began marketing 7-percent dextrose peritoneal dialysis products as follows:

Cutter	1959
Travenol	1960
McGaw	1964
Abbott	1972

These LVPs had been marketed without approved new drug applications. FDA, however, explained that the FD&C Act

does not require clearance of all drugs as a prerequisite to marketing but only for a "new drug," defined by the FD&C Act as a drug whose composition is such that qualified experts would not generally recognize it as being safe and effective.

FDA officials told us that because peritoneal dialysis solutions had been formulated by hospitals for many years before the drug industry began marketing them, their general safety was established on the basis of their usage history. FDA did not make a determination that the products were generally recognized as safe or that a new drug application was needed nor was FDA requested to do so by the firms.

Regarding the removal of these products from the market, FDA advised us that because of the information associating the solutions with adverse reactions, FDA informed the manufacturing firms that the products were considered "new drugs" and would require an approved new drug application before marketing could be resumed. No new drug applications have been filed and such products are no longer being marketed.

BIOLOGICAL LVP RECALLS

FDA records show that from January 1, 1970, to November 10, 1975, there were 17 recalls involving either or both biological LVPs--Normal Serum Albumin or Plasma Protein Fraction--which were marketed by 6 manufacturers. The following table shows the number of recalls for each firm.

Manufacturer	Number of recalls
Abbott Laboratories	4
Armour Pharmaceutical Co.	6
Dow Chemical Co.	1
Hyland, Division of Travenol Laboratories	3
Lederle Laboratories	1
Merck, Sharp, & Dohme	2
Total	17

Most of the recalls were due to pyrogenic or other types of patient reaction to the products. FDA officials advised us that pyrogens cannot be completely eliminated from blood-derivative products such as biological LVPs without destroying the products. Therefore, according to FDA, some pyrogens can be expected to be found in biological LVPs and many of the adverse reactions may have occurred in patients especially sensitive to pyrogens; thus some of the recalls were initiated as a precautionary measure.

Data developed by CDC indicates 6 deaths and 11 injuries were associated with the biological LVPs recalled due to contamination. These deaths and injuries were related to Normal Serum Albumin recalled by Lederle. However, FDA and CDC officials said that because patients administered Normal Serum Albumin are usually in severe physical condition, it is difficult to unequivocally attribute their death or injury to a particular cause.

CDC received its first notification of deaths and injuries associated with Lederle's Normal Serum Albumin product from a Baltimore, Maryland, hospital on August 2, 1973. On August 14, 1973, Lederle recalled selected batches of its Normal Serum Albumin and on September 26 it expanded the recall to include all its outstanding Normal Serum Albumin.

CHAPTER 3

EFFORTS TO IMPROVE GMP REGULATIONS

GMP regulations for drugs cover such areas as (1) maintaining formula and batch production control records and procedures, (2) establishing test procedures to insure that drug components and the finished product conform to appropriate standards of identity, strength, quality, and purity, and (3) keeping distribution records of each drug batch to facilitate its recall, if necessary.

FDA, however, does not believe that its drug GMPs are adequate for LVPs as many of the LVP recalls discussed earlier were attributed to manufacturing problems. Accordingly, FDA plans to supplement its drug GMPs with additional regulations applying more directly to the manufacture of LVPs.

In this regard, FDA initiated in April 1973 an evaluation of LVP manufacturing practices to identify areas needing improvement and to develop GMP regulations for LVPs. FDA invited industry participation in this effort.

During May and June 1973, FDA inspected all plants producing chemical LVPs, which involved 4 manufacturers and their 10 plants. Plant inspections were made to

--determine practices which could be regarded as manufacturing or quality control inadequacies within the framework of current GMPs,

--provide FDA with more comprehensive technical knowledge regarding theories and concepts of GMPs for LVPs, and

--identify areas of production and quality control which should be changed, modified, or further studied to possibly establish new standards of GMPs.

During July and August 1973, FDA evaluated the information obtained during the plant inspections, reviewed literature concerning heat sterilization, and contacted recognized LVP experts. In addition, some FDA headquarters officials responsible for developing the GMPs visited four plants to obtain first-hand familiarity with the complexities of the industry.

On the basis of its evaluation of the manufacture of LVPs, FDA identified certain elements of the manufacturing

process that required special attention to insure products of microbiological integrity. These included:

--Design, maintenance, and cleaning of equipment: Some firms did not have established cleaning and maintenance schedules for major pieces of equipment. There was also a demonstrated need to construct plumbing without direct connections from manufacturing equipment or lines to sewers and to remove all unused dead-end lines in distilled water systems to eliminate the accumulation of bacteria and pyrogens which could feed into the system and contaminate passing fluid.

--Quality controls for distilled water, dry chemical raw materials, and containers and closures used in the production and packaging of LVPs: All raw materials must be pyrogen-free and manufacturers should be aware of the microbial attributes of each raw material.

--Standards for particulate and/or bacterial contamination from the plant environment, such as air and personnel: Air used in the process of filling empty bottles should be filtered and employees performing certain production operations should be required to wear specific sterile garb.

--Sterilization procedures: So that all individual LVP products comprising a lot receive the same sterilization treatment, a lot should be defined as an autoclave load and receive a lot number. However, some firms did not number the finished product containers to identify the autoclave load in which the lot or batch was sterilized. There was also a need to (1) limit the time lapse between manufacture of a batch and completion of its sterilization cycle to limit microbial growth in containers, (2) develop an adequate sterilization cycle, and (3) require prescribed levels of chlorine in autoclave cooling water to minimize bacteria.

--Uniform sampling procedures: Not all firms were testing the microbial count of unsterilized filled containers from every batch immediately before sterilization. Also, among the various firms there were substantial differences both in the conditions under which finished product sterility testing was performed and the procedures for pyrogen testing, as well as the interpretation of these results.

FDA has developed a proposed supplement to its drug GMP regulations which it submitted to LVP manufacturers at the end of January 1974 for comment. As of February 1, 1976, the proposed supplement to the GMP regulations was being processed by FDA for publication in the "Federal Register" for public comment.

CHAPTER 4

CDC'S ROLE CONCERNING LVPS AND ITS INTERACTION WITH FDA

CDC does not have authority to regulate LVPs or other drugs and, accordingly, does not perform regulatory functions regarding them. As part of its overall responsibility under the Public Health Service Act (42 U.S.C. 241) to prevent and control diseases, CDC investigates, collects, analyzes, and distributes data related to disease conditions. According to FDA, investigational data developed by CDC has, in some cases, helped FDA in its regulatory activities involving contaminated LVPs. However, CDC's investigational data is not always adequate for FDA use in initiating regulatory action.

CDC and FDA have a broad informal understanding regarding each agency's investigational responsibilities, but do not have a formal interagency agreement for collaborating on investigations. A formal interagency agreement would better insure that the data developed by them would be mutually beneficial in carrying out their responsibilities.

CDC'S RESPONSIBILITIES AND ACTIVITIES

Under authority of the Public Health Service Act, the Secretary, HEW, has delegated to CDC the responsibility of providing leadership and direction to programs and activities designed to improve the public health by preventing or controlling diseases, improving laboratory performance, and assuring safe and healthful working conditions for all working people.

A primary responsibility of CDC is to aid State and local health departments and hospitals in controlling health problems, including those associated with LVPs. CDC investigates such problems and informs the hospital, health department, and FDA of its findings.

CDC is also responsible for

--maintaining surveillance over communicable diseases and certain preventable conditions of national importance,

--investigating special disease problems and recommending control measures,

--collaborating with FDA and other Federal agencies in areas of mutual program interest,

--collecting, analyzing, and publishing morbidity and mortality data, and

--providing consultation and technical assistance on epidemiological matters.

A major source for CDC's detection of disease is the National Nosocomial Infections 1/ Study--a nationwide cooperative surveillance network. CDC officials advised us that CDC developed the network in 1969 in cooperation with State and territorial epidemiologists. The network includes public health offices, State health departments, and about 70 hospitals who voluntarily report health hazards and infectious diseases to CDC. CDC reviews the data for marked changes in the rate or character of infections to determine whether an investigation is warranted.

CDC collaborates with other agencies in conducting investigations and has the technical expertise to gather statistical data and perform the epidemiological investigations. If the investigation indicates a contaminated drug product may be the cause of a health hazard, CDC may assist FDA by investigating and testing the suspect product.

LACK OF FORMAL INTERAGENCY AGREEMENTS

Although it is FDA's policy to initiate and enter into formal interagency agreements with other governmental bodies whenever exchanges of knowledge and information will strengthen programs of mutual concern and interest, no formal interagency agreements for FDA/CDC collaboration of investigation efforts have been established. CDC and FDA have a broad informal understanding regarding investigational responsibilities.

FDA officials stated that its informal understanding provides for CDC to submit to FDA, on a continuous basis, reports on three basic types of epidemiological data--information on nosocomial infections, enteric (intestinal) diseases, and viral infections. However, because CDC's data is not product related it is of limited use to FDA.

1/Nosocomial infections are infections acquired during hospitalization.

CDC officials expressed the opinion that formal interagency agreements between FDA and CDC are needed to further establish and clarify FDA's and CDC's basic priorities, missions, and areas of responsibility and to insure that data developed by each agency will be mutually beneficial in carrying out their respective responsibilities.

In contrast to CDC's view, FDA officials believe the informal understanding with CDC regarding investigational responsibilities is satisfactory. They stated that because of the complexities of FDA's broad realm of authority, which includes foods, drugs, cosmetics, and medical devices, it would be difficult to enter into formal interagency agreements requiring greater specificity.

We discussed with FDA officials certain concerns expressed by CDC officials. For example, one CDC official was concerned that FDA did not use samples collected by CDC in the 1971 Abbott recall.

The FDA officials said several areas of misunderstanding have existed between the two agencies and that some CDC officials do not understand the type of information FDA needs to undertake regulatory action. The FD&C Act requires that official USP procedures be used for testing the characteristics of drug products listed in the "Pharmacopeia." According to FDA officials, CDC's examinations of Abbott's products in 1971 were not made in accordance with official USP sampling and testing procedures. One FDA official said that although CDC's techniques may be satisfactory or possibly superior to those specified by the USP, the samples were not used to support FDA's regulatory action because USP procedures must be used in the final analysis.

FDA officials said CDC may misunderstand the degree of importance FDA attaches to CDC epidemiological and analytical work. FDA officials told us that CDC's epidemiological evaluations are considered as part of FDA's overall evaluation of a need for regulatory action. For example, CDC's information was useful as a basis for FDA's request that Cutter initiate its 1973 recall of 5-percent Dextrose in Lactated Ringer's Injection solutions. (See pp. 18 and 19.)

CHAPTER 5

FDA CONTRACT WITH USP TO STUDY LVP PROBLEMS

On April 10, 1972, FDA awarded a cost-reimbursement contract to USP to identify problems in the manufacture or administration of LVPs and to make recommendations to increase the safety of LVPs. Originally FDA's contract with USP covered the period May 1, 1972, through April 30, 1973, and had an estimated cost of $100,000. On April 30, 1973, the contract's expiration date was extended to May 31, 1973, with no change to its estimated cost. On June 29, 1973, the estimated cost of the contract was increased to $236,000 and extended until May 31, 1974. On June 7, 1974, the contract was further increased to $366,000 and extended to May 31, 1975.

USP STUDY APPROACH

Under the contract, USP established the National Coordinating Committee on Large Volume Parenterals to identify and evaluate problems relating to the manufacture and use of LVPs. The committee is made up of representatives from the following 13 organizations:

FDA
USP
National Formulary
CDC
National Association of Boards of Pharmacy
Joint Commission on the Accreditation of Hospitals
American Hospital Association
American Society of Hospital Pharmacists
National Association for Practical Nurse Education and Service
American Medical Association
American Nurses Association
Parenteral Drug Association
Representatives of Abbott, Cutter, McGaw, and Travenol

The scope of the National Coordinating Committee's activities was limited to LVP problems having clinical significance and the potential for at least a partial solution. Initially the committee compiled a list of 167 problems it considered significant. To augment its efforts, the committee subcontracted with the University of Mississippi to:

--Conduct a literature review and prepare a bibliography concerning reported problems with LVPs.

--Study the LVP practices of a national sample of 26 hospitals to identify key problems. As part of the study, registered pharmacists with advanced training in hospital pharmacy observed the steps in the preparation and administration of LVPs in each hospital and interviewed personnel directly involved in the hospital's LVP programs.

The University of Mississippi study, completed in August 1973, identified several problems which appeared to arise from several sources, including inadequacies in (1) the education and training of personnel in hospital policies and procedures; (2) hospital communications, inventory controls, and distribution systems; (3) the design and construction of commercially available equipment and devices; (4) the interpretation of stability information as it applies to intravenous solution admixtures; (5) labeling practices; (6) the working environment of the nurse; and (7) the packaging of LVPs by the manufacturer.

Based upon the results of the University of Mississippi study, the National Coordinating Committee increased its list of LVP problems to 179. Subsequently, the committee reviewed its composite list and identified 50 problems deserving priority attention. Most of these problems relate to the following general areas:

--In-hospital LVP usage including administration, compounding, maintaining product sterility, and education of personnel.

--Manufacture of LVPs including GMPs and product sterility.

--Regulation including detection of LVP contamination and recall activity.

IN-HOSPITAL USAGE PROBLEMS

In-hospital LVP usage was the source for about 70 percent of the 50 priority LVP problems identified by the committee. In-hospital usage problems included (1) opening LVPs in unsterile air, (2) unqualified personnel administering and compounding LVPs, and (3) LVP administration sets being allowed to remain in use too long.

The problem of opening LVPs in unsterile air was the subject of an article entitled "Bacterial Contamination of Intravenous Fluids Opened in Unsterile Air," which appeared in the April 1971 issue of the "American Journal of Hospital Pharmacy." The article, which was included in the

bibliography developed under the University of Mississippi study, discussed a study of five areas of a large hospital in which intravenous solutions were readied for administration. These areas included two internal medicine wards, two locations in the pharmacy, and one surgical ward. According to the article, the results of the study showed a relationship between the incidence of LVP contamination and the contamination of the air in which the solutions were opened. The study raised serious questions concerning the safety of opening in contaminated air intravenous fluids packaged under a partial vacuum.

Regarding the unsterile air problem the committee concluded that

--airborne contamination can be introduced into LVPs through air vents in product containers upon opening and during reduction of liquid volume upon administration and

--although it is impossible with currently available techniques to prevent airborne contamination in hospitals, levels of bacteria in the air vary markedly in different areas of the hospital and appear to be related primarily to the presence and activity of people within those areas.

The National Coordinating Committee recommended to organizations such as the American Medical Association, the American Society of Hospital Pharmacists, and CDC that studies be performed to determine the risk of contamination through air vents and that until such studies are completed, air vents in LVP containers should be equipped with high-efficiency filters.

The University of Mississippi, under its contract with the committee, sent a questionnaire to a sample of hospitals regarding qualifications of hospital personnel who compound (the addition of an ingredient to an LVP solution) and administer LVPs. The results of the questionnaire showed that pharmacists were not involved in compounding in 75 percent of the 133 hospitals that responded to the questionnaire. The committee noted that since compounding requires specialized pharmaceutical skills and knowledge, which most nurses and physicians do not possess, the pharmacist should accept the responsibility for compounding LVPs.

The National Coordinating Committee recommended to organizations such as the American Hospital Association, the American Medical Association, the Joint Commission on the Accreditation of Hospitals, and the American Nurses Association that, whenever resources and funding allow, compounding of

LVPs should be performed under the supervision of a qualified pharmacist. The committee also recommended that

--a committee of experts be established to compile procedures for compounding LVPs and

--in-hospital teams be formed to encourage functional specialization for compounding and administering LVPs.

The committee was also concerned that LVP administration sets for some types of fluids remaining in use over 24 hours and other fluids for over 12 hours increased risk of LVP-associated disease. It referred to CDC studies which demonstrated that LVP administration sets in use for greater than 48 hours have a significantly greater risk of contamination than sets in use for less than 48 hours. Accordingly, the committee recommended that hospitals establish guidelines stipulating that administration sets be changed every 24 hours or every 12 hours, according to the type of fluids involved.

MANUFACTURING PROBLEMS

The manufacturing process was the source for about 20 percent of the 50 problems the National Coordinating Committee identified as requiring priority attention.

The committee expressed concern with manufacturing problems relating to the lack of adequate quality control standards and procedures including questionable sampling techniques, sterilization monitoring, and container and closure designs. It pointed out that

> "* * * several nationwide epidemics associated with the administration of contaminated large volume parenteral solutions have emphasized inadequacies in current methods of end product testing, the need for their improvement, as well as the need for monitoring the sterility of the manufacturing process * * *."

The committee recommended to FDA, CDC, USP, the Parenteral Drug Association, and the major manufacturers of LVPs that

--measures be taken to improve sterility monitoring, including establishment of an ad hoc committee consisting of representatives from industry, regulatory agencies, and others to review and propose improved sampling schemes and testing methods and

--standards be developed for containers and container closures.

REGULATION PROBLEMS

About 10 percent of the priority problems identified by the committee dealt with regulation of LVPs. The committee was concerned with the adequacy of FDA's rules, regulations, and procedures in the areas of surveillance and recall. It cited recalls of LVPs due to contamination as an indication of the need for sounder surveillance and more expeditious recall activities. The committee also found that most hospitals did not have an adequate system to monitor infection rates.

The committee recommended that (1) an expert committee on surveillance systems be developed to make specific proposals to USP, FDA, and representative organizations, (2) FDA's Drug Product Defect Reporting System and CDC's hospital surveillance system be strengthened, and (3) consideration be given to a study of interagency communication channels concerning surveillance and recall. It also recommended a strong educational program for improving in-hospital surveillance and reporting of potentially hazardous situations.

The committee expressed concern with the lack of standards covering the size limits of particulate matter permitted in LVPs. It pointed out that although the major cause for complications associated with LVP therapy may not have been identified, particulate matter has been suspect. The committee recommended that USP establish safe limits of particulate matter size and quantity after careful consideration of the criteria.

IMPLEMENTATION OF COMMITTEE RECOMMENDATIONS

Most of the organizations represented on the National Coordinating Committee have indicated agreement with the recommendations. Accordingly, USP is developing an official standard for test methods for particulate matter to be included in its next official drug compendium, and FDA is considering certain recommendations in light of potential changes to GMP regulations. The National Association for Practical Nurse Education and Service is pursuing implementation by agreeing to publicize new programs and guidelines through educational activities and its association journal.

Other steps being taken to implement the recommendations include establishment of task forces by some organizations to further research and determine feasible solutions to problems and referral of some recommendations to expert panels for further study.

The National Coordinating Committee's future plans include consideration of comments on the recommendations including any necessary refinements and modifications. It also plans to follow the progress on the recommendations' implementation and to disseminate such information.

CHAPTER 6

CONCLUSIONS AND RECOMMENDATIONS

Most LVP recalls were due to manufacturing problems generally associated with product contamination or the presence of pyrogens. Manufacturing practices in some cases did not provide the necessary assurance of product safety and integrity necessitating a recall of all products produced in a plant that demonstrated manufacturing deficiencies. FDA's drug GMPs apparently are not adequate for LVPs. Accordingly, FDA is developing GMPs specifically for LVP products to improve quality control in the manufacturing of these products. The proposed GMPs for LVP products are intended to supplement the drug GMP regulations.

Also, the National Coordinating Committee established by USP has identified problems related to manufacture and use of LVPs and has made recommendations to manufacturers, users, and regulators of these products. FDA is considering the committee's recommendations in its development of supplemental GMPs for LVP products. Because GMPs are essential to insure the integrity and safety of a manufactured product, FDA should expedite the issuance of its supplemental GMPs for LVP products.

Formal interagency agreements would seem needed for more effective coordination between CDC and FDA. The view of some FDA officials that some CDC officials do not understand what data FDA needs to take a regulatory action indicates that the broad, informal understanding between FDA and CDC is inadequate for effective coordination. Formal agreements would insure that data developed by each agency would be mutually beneficial in carrying out their respective responsibilities and thus could minimize duplication of efforts.

RECOMMENDATIONS TO THE SECRETARY, HEW

We recommend that the Secretary, HEW, direct the Commissioner, FDA, to give high priority to issuing the GMPs for LVP products. Also, we recommend that the Secretary direct the Commissioner, FDA, and the Director, CDC, to evaluate the need to establish formal interagency agreements for FDA/CDC interaction, taking into consideration the priorities, missions, and areas of responsibility of each agency, to insure that data developed by each agency will be mutually beneficial in carrying out their respective responsibilities.

AGENCY COMMENTS

HEW agreed with our recommendations. HEW advised us that publication of GMP regulations for LVPs has a high priority within FDA. FDA has prepared a draft of these regulations which it plans to publish upon completion of a thorough agency review.

Also, HEW said it recognizes that FDA and CDC must cooperate closely on matters involving LVPs in order for each agency to effectively carry out its responsibilities. These agencies will jointly determine the appropriate mechanisms for such cooperation and the level of formality required to facilitate effective coordination.

CHAPTER 7

SCOPE OF REVIEW

Our review included:

--Reviewing legislation, regulations, policies, practices, and procedures relating to FDA's and CDC's responsibilities and activities involving LVPs.

--Reviewing a study of LVP problems undertaken by USP, pursuant to its contract with FDA, and interviewing certain members of the study team.

--Reviewing FDA records relating to the regulation of the LVP products discussed in this report.

We also:

--Interviewed FDA officials responsible for the LVP regulatory activities discussed in this report.

--Interviewed FDA and CDC officials as to their roles regarding contaminated LVPs and their procedures for interaction.

APPENDIX I

United States Senate

COMMITTEE ON FINANCE
WASHINGTON, D.C. 20510

October 16, 1973

B-164031(2)

The Honorable Elmer B. Staats
Comptroller General of the United States
U.S. General Accounting Office
441 G Street, N.W.
Washington, D.C. 20548

Dear Mr. Staats:

The Food and Drug Administration is responsible for assuring that only safe and effective drugs, including large volume parentenals (LVPs), reach the public. In the past five to ten years, at least two, and reportedly more, of contaminated LVPs have occurred. These epidemics have involved at least two manufacturers that we know of--Abbott Labs and Cutter Labs.

In March, 1973, an intravenous product manufactured by Cutter Labs was found to be contaminated. At least two patients died after having been treated with the fluids. Both of these incidents resulted in recalls and Federal regulatory action by the Food and Drug Administration.

Because of such incidents, I am interested in learning what the Federal role is as regards the regulation of LVPs. So that I may consider whether legislation is warranted in this area, I would appreciate your assistance in providing me with answers to the following questions.

1. How many (A) FDA-initiated recalls, and (B) voluntary recalls initiated by manufacturers, which have resulted from contaminated LVPs, have occurred in the past 10 years, based on availability of records at FDA?

2. What were the causes of the contamination resulting in the recalls? Do they show a pattern?

3. How many injuries and fatalities are associated with the contaminated incidents? What time periods occurred between reported LVP-connected deaths and recalls, either FDA-ordered or voluntary?

The Honorable Elmer B. Staats October 16, 1973

4. In the cases of LVP-contamination related deaths, how many were related to contamination at the manufacturer level, how many at the hospital use level, (other?)?

5. What is the FDA's regulatory activities over LVPs? How much and often does FDA sample LVP products?

6. How did FDA change its LVP inspection procedures, and any other regulatory activities, after the 1971 Abbott Labs epidemic of contaminated fluids?

7. How many types of LVP drug products are on the market? How many manufacturers are there? (We have been told there are four.)

8. How many LVPs have been classified:

   a) as requiring New Drug Application (NDA) approval?
   b) as "official", and what does that mean as regards regulatory status (FDA says they must comply with a monograph)?
   c) as "gras"?
   d) as switching in and out of "official" status?

9. What is the Center for Disease Control's role in regulation of LVPs? Have there been protocols for CDC and FDA interaction as regards contaminated LVPs, or are they being developed or changed since recent incidents of contamination?

10. What is the United States Pharmacopia doing, pursuant to a contract to examine LVP problems? How far along is their work toward actual recommendations?

Sincerely yours,

GAYLORD NELSON
United States Senator

GN/jrw

CHEMICAL LVP PLANT INSPECTIONS MADE AND INSPECTIONS

DURING WHICH PRODUCT SAMPLES COLLECTED

JULY 1, 1965, TO JUNE 30, 1974

Fiscal year	Abbott Labs		Travenol Labs		Cutter Labs		McGaw		Pharmacia Labs (note a)		Pharmachem Inc. (note b)		Sherman Labs (note c)		Yearly totals	
	Inspections	Samples collected	Inspections	Samples collected	Inspections	Samples collected	Inspections	Samples collected	Inspections	Samples collected	Inspections	Samples collected	Inspections	Samples collected	Inspections	Samples collected
1966	1	1	3	1	2	1	2	2	0	0	0	0	1	1	9	6
1967	1	0	5	0	0	0	1	0	0	0	2	0	1	0	10	0
1968	2	1	10	3	0	0	0	0	0	0	1	0	2	1	15	5
1969	3	2	4	0	5	3	5	5	0	0	3	1	1	0	21	11
1970	2	0	7	4	4	3	4	0	0	0	4	0	0	0	21	7
1971	14	9	5	5	6	6	5	4	0	0	1	0	0	0	31	24
1972	2	1	5	1	1	0	5	2	0	0	0	0	0	0	13	4
1973	3	2	7	3	10	4	3	3	0	0	0	0	0	0	25	12
1974	2	0	5	3	7	2	2	1	2	1	0	0	0	0	18	7
Total	30	16	51	20	35	19	27	17	2	1	11	1	5	2	161	76

a/Pharmacia Labs began distributing LVPs in April 1974.

b/Pharmachem Inc. stopped producing LVPs in 1971.

c/Sherman Labs stopped producing LVPs in 1969.

APPENDIX II

APPENDIX III

CHEMICAL LVP RECALLS

JULY 1, 1965, TO NOVEMBER 10, 1975

Year of recall	Initiator	Reason for recall	Number of: Products recalled	Containers distributed	Containers recovered	Associated deaths and/or injuries
Abbott Laboratories						
1965	Manufacturer	Contamination--defective container cap liners	43	3,513,699	534,652	No known injuries
1967	Manufacturer	Contamination--faulty manufacturing	1	11,046	623	No known injuries
1969	Manufacturer	Contamination--glass containers developed hairline cracks at neck	70	900,000	a/1,500,000	33 injuries
1970	Manufacturer	Product discoloration/low in vitamin C	1	7,518	3,803	No known injuries
1971	FDA	Contamination--inadequate closure design	105	At least 5,586,229	5,586,229	50 deaths 362 injuries
1973	FDA	Adverse reactions	1	1,263	606	No known injuries (note b)
Travenol Laboratories						
1966	Manufacturer	Product low in one electrolyte	1	9,714	1,235	No known injuries
1966	FDA	Disqualified clinical investigator	1	At least 54	54	No known injuries
1967	Manufacturer	Contamination--ineffective closures resulting in leaking containers	5	1,072,126	208,626	No known injuries
1971	Manufacturer	Contamination--an ingredient of the product precipitated	1	18,492	12,410	No known injuries
1972	FDA	Adverse reactions	5	9,440	3,112	No known injuries (note c)
1973	FDA	Adverse reactions	1	821,000	26,121	No known injuries (note b)
1973	Manufacturer	Misbranded	1	4,572	1,841	No known injuries
1973	Manufacturer	Contamination--pyrogenic reactions/ improper equipment cleanup	1	72	60	2 injuries
1973	FDA	Contamination--defective raw material	5	35,640	17,400	No known injuries
1973	Manufacturer	Product contained excessive carbon dioxide	1	245,280	95,145	3 injuries
1974	Manufacturer	Contamination--leaking containers	1	16,548	Not available	No known injuries
1974	FDA	Leaking containers	15	About 5,000,000	d/None	No known injuries
Cutter Laboratories						
1967	Manufacturer	Contamination--improper barometric pressure during processing	2	At least 3,537	3,537	No known injuries
1969	Manufacturer	Contamination--defective coated rubber stoppers	1	6,852	3,589	No known injuries
1970	Manufacturer	Contamination--extraction process of stopper	2	9,468	4,008	No known injuries
1971	Manufacturer	Contamination--glassware had improper sulfur treatment	1	6,768	427	No known injuries
1971	Manufacturer	Label mix-up	1	5,760	4,098	No known injuries
1971	Manufacturer	Adverse reactions	5	37,900	10,915	4 injuries
1972	Manufacturer	Contamination--inadequate production process	10	e/1,796,722	268,944	No known injuries
1973	FDA	Adverse reactions	1	At least 36,854	36,854	No known injuries (note b)
1973	FDA	Contamination--inadequate sterilization cycle and/or improper pressure during processing	189	f/15,440,998	5,559,447	4 deaths 9 injuries
1974	Manufacturer	Label misprint	4	727,600	g/0	No known injuries
McGaw Laboratories						
1972	Manufacturer	Label mix-up	1	18,060	1	No known injuries
1972	FDA	Adverse reactions	2	240,000	19,321	No known injuries (note c)
1973	FDA	Adverse reactions	1	176,250	27,800	No known injuries (note b)
1973	Manufacturer	Contamination--precipitation in product	1	65,800	17,351	No known injuries
1975	FDA	Contamination--mold and particulate matter in product	19	About 1,326,826	Not available	No known injuries
1975	Manufacturer	Label mix-up	1	6,936	h/3,072	No known injuries
1975	FDA	Serious deviations from GMPs	106	At least 6,000,000	Not available	No known injuries
Pharmachem, Incorporated						
1968	Manufacturer	Contamination--particles of packing from container found in product	1	2,213	472	No known injuries
Sherman Laboratories						
1967	Manufacturer	Contamination--pyrogenic reactions/ possible inadequate pyrogen testing	1	1,620	No known	4 injuries
		Total	608	43,162,857		

APPENDIX III

a/A large number of containers returned were of stock manufactured before or after the recall. A detailed accounting was not available.

b/Although no known injuries were associated with the products of Abbott, Travenol, Cutter, and McGaw, there were reports of significant adverse reactions to similar products. See pp. 19 to 21 regarding peritoneal dialysis solutions containing 7-percent dextrose.

c/Although no known injuries were associated with products of Travenol and McGaw, there were injuries associated with similar products produced by another firm and recalled in 1971. There was medical opinion suggesting the problem was a generic one related to the concentration of the solutions. See pp. 19 to 21 regarding products containing sorbitol.

d/Products were not recovered. A "field correction" was performed which consisted of advising customers how to check containers for possible leaks before use.

e/Figure reflects amount distributed for the period between April 1, 1972, and October 4, 1972. Data was not available for bottles distributed before April 1, 1972, also subject to the recall.

f/Figure reflects amount distributed for the period April 1, 1972, to March 14, 1973. The firm distributed 81,399,030 bottles between September 1, 1969, and March 31, 1972, that were also subject to the recall.

g/Products were not removed from trade channels because the labeling misprint did not constitute a significant health hazard. However, the firm notified and advised its accounts of the error.

h/All units checked and all units found mislabeled were destroyed by holder.

APPENDIX IV

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

January 16, 1976

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

Dear Mr. Ahart:

The Secretary asked that I respond to your request for our comments on your draft report entitled, "Recalls of Large Volume Parenterals." The enclosed comments represent the tentative position of the Department and are subject to reevaluation when the final version of this report is received.

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

Sincerely yours,

John Young

John D. Young
Assistant Secretary, Comptroller

Enclosure

APPENDIX IV

DEPARTMENT COMMENTS ON GAO'S REPORT
ENTITLED "RECALLS OF LARGE VOLUME PARENTERALS"

GAO Recommendation

That the Secretary, HEW, direct the Commissioner, FDA, to give high priority to issuing the GMP's for LVP products.

Department Comments

We concur. Publication of the proposed Good Manufacturing Practices Regulations for large volume parenteral products has a high priority within the Food and Drug Administration. FDA has prepared a comprehensive draft of these regulations and will publish them following completion of a thorough Agency review.

GAO Recommendation

That the Secretary direct the Commissioner, FDA, and the Director, CDC, to evaluate the need to establish formal interagency agreements for FDA/CDC interaction, taking into consideration the priorities, missions, and areas of responsibility of each agency, to insure that data developed by each agency will be mutually beneficial in carrying out their respective responsibilities.

Department Comments

We recognize that FDA and CDC must cooperate closely on matters involving LVP's so that each agency can effectively carry out its respective responsibilities. The agencies will jointly determine the appropriate mechanisms for such cooperation and the level of formality required to facilitate effective coordination.

ABBOTT

Laurence R. Lee
Vice President
Secretary and
General Counsel

Abbott Laboratories
Abbott Park
North Chicago, Illinois 60064

January 6, 1976

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

Your Reference: B-164031(2)

Dear Mr. Ahart:

This is in reply to your letter, dated December 23, 1975, seeking our comments on excerpts from your draft of a report to Senator Gaylord Nelson on recalls of large volume parenterals.

Your letter was received on December 29, and requested our comments by no later than January 7, 1976. This is an extremely short time to research all the points covered in your draft and prepare comments on the extremely complicated subject of our recalls of intravenous solutions in 1971 and 1969. Moreover, as the dates indicate, your letter and your deadline for comments fell during the holiday period when many key personnel were on vacation. Further, in view of the numerous obvious inaccuracies and omissions in this draft, a comprehensive response would have required a detailed file search and review by a large number of present and past employees. Your time limitation has made it impossible to conduct such a study.

We must comment, however, on a few of the matters where we have noted the most obvious inaccurate and misleading statements.

REPORTS OF DEATHS AND INJURIES

On page 15, in the last paragraph, the draft states:

"According to CDC data, 25 hospitals reported 412 cases of septicemia associated with the use of Abbott LVP products; 50 of these cases involved deaths."

This report and various elaborations of it received wide publicity. Newspapers and government sources have repeated the figures with no evident regard for the fact that, when examined on a case-to-case basis, the report cannot be substantiated and is totally indefensible. The procedures used to collect the "data" summarized in the report guaranteed that the results would be at best speculation. Much of the "data" were collected by telephone conversations and only rarely was the attending physician consulted. Frequently, non-physicians gave medical judgments that were used as the basis for the report.

When called to account, the CDC and FDA have defended this report by saying that the language of the report merely said that the septicemias were "associated" with the use of Abbott's LVPs, and that 50 of these cases "involved" death. These niceties of language certainly have not been appreciated by the lay public to whom it has been publicized.

Abbott presented a detailed and in-depth analysis, demonstrating the obvious deficiencies and lack of credibility of this report, to the FDA during the Section 305 hearing which took place in early 1972. We presume that the FDA has made available a copy of the transcript of this hearing to the GAO.

ABBOTT'S MANUFACTURING PRACTICES IN 1971

On page 14 of the draft there is reference to

"objectionable" practices in 1971 which could have contributed to microbial contamination of products. The conditions noted on pages 14 and 15 are from FDA inspection reports made after CDC reported finding bacteria under the cap. These conditions were used in an attempt to support the allegation in the criminal case that Abbott had failed to meet "current good manufacturing practice" as required by the Federal Food, Drug and Cosmetic Act. At the trial of the case, before an impartial federal Judge and jury, the government wisely abandoned all of these allegations. Thus, the government did not even attempt to prove that Abbott was in any way not in conformity with current good manufacturing practices at the time of the recall.

We know that the government could find no competent expert who would testify that the observations reflected a failure to meet current good manufacturing practices in 1971. For its part, Abbott reviewed these specifications of "objectionable" conditions with the best experts. There was unanimity that the company did meet current good manufacturing practices in 1971.

On page 12 of the draft, in the second paragraph, there appears the following:

> ". . .In January 1971 FDA made a limited examination of the sterility testing procedures and control records of Abbott's Illinois and North Carolina plants and did not find any deficiencies in the sterility testing of either LVPs or LVP administration sets or indications that any contaminated lots of LVPs and administration sets had been distributed. (Emphasis supplied).

The characterization of the FDA's inspection of our Rocky Mount plant as "limited" is inaccurate. The fact is that in January, 1971, FDA concluded at the Rocky Mount facility a series of in-depth inspections

as part of their Intensified Drug Inspection Program (IDIP). This IDIP had been conducted over a period of nearly a year, in a series of inspections. The company's manufacturing and sterility practices were given a thorough scrutiny. The agency concluded that Abbott's practices were admirable and stated so in a letter to the company dated January 20, 1971.

In addition, when reports of septicemias reached FDA through CDC, FDA sent inspectors to Abbott specifically to look for any deficiencies in manufacturing, equipment, or practices that might be a basis for the perceived problem. No cause for the reported septicemias was found in these inspections. It is important to point out that the "deficiencies" noted as a result of the March-April, 1971, inspection, after CDC had identified the presence of bacteria under the cap, were not noted in January-February, 1971.

Finally, no cause or causes for the alleged contaminations were ever identified by FDA in the manufacturing procedures used for our LVPs. There has never been an allegation by the government that Abbott in any way failed to conduct its sterility testing in a proper manner.

THE CRIMINAL CASE

The statements on page 16 of the draft concerning the criminal prosecution of Abbott and five of its employees are inaccurate, incomplete and misleading. The bases for the original dismissal of the 360 count indictment were that personnel of the Department of Justice and the FDA had deliberately disseminated prejudicial pretrial publicity that would deny the defendants a fair trial, and the misconduct of Department of Justice attorneys before the grand jury. This decision was overturned by the Fourth Circuit which, although agreeing that the government had caused prejudicial publicity, said that voir dire could guarantee a fair

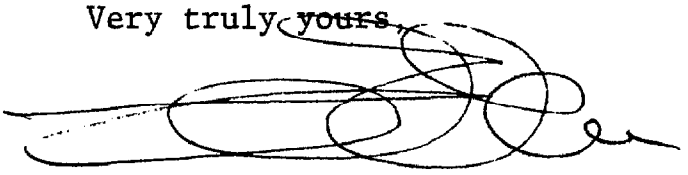
trial and that the prosecutor's misconduct before the grand jury should not vitiate the indictment. The Supreme Court did not grant certiorari and the case went to trial on July 21, 1975. On August 5 and 12, 1975, all counts of the indictments against the individual Abbott employees and the corporation were dismissed on motion of the government. In order to settle and terminate this expensive and time-consuming proceeding, the corporation agreed to enter a plea of nolo contendere to a new one count misdemeanor information, filed that day. This information did not charge or allege any fact that would constitute a violation of the Federal Food, Drug and Cosmetic Act.

1969 RECALL

The draft report also discusses in some detail the recall by Abbott of intravenous solutions in 1969. This occurred many years ago, and Abbott has not been able, in the very short time allotted, to research the numerous statements set forth in the report. However, a quick review of these statements indicates that they contain many factual errors. As with the discussion of the 1971 recall, there is an emphasis here on the findings of the FDA, particularly as to manufacturing practices. The statements as to manufacturing practices are the unilateral and personal conclusions of an FDA inspector or inspectors, and do not necessarily present an objective or expert analysis of our practices. Suffice it to say that when FDA completed its evaluation of the 1969 situation, the agency concluded that no violations of the law had taken place with respect to our manufacturing practices and the government decided to undertake no legal actions against Abbott in any regard. FDA's final conclusion was that there was no evidence supporting the allegation that defective containers were being used by Abbott, and also that there was insufficient evidence to establish that Abbott's manufacturing procedures were not meeting current GMP's.

Perhaps more important than the inaccuracies summarized above are the many omissions of relevant facts which would place the accounts of these recalls in their true perspective. In view of such inaccuracies and omissions, your draft does not, in our opinion, provide even an appropriate starting point for an accurate and objective report of these events. We must, therefore, seriously question the value of this report to the United States Senate, or to anyone else, as a basis for judging the facts involved in these LVP recalls.

Very truly yours,



LRL:mrb

APPENDIX VI

CUTTER *Laboratories,* Inc. FOURTH AND PARKER STREETS • BERKELEY, CALIFORNIA 94710 • (415) 841-0123

January 7, 1976

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

Dear Mr. Ahart:

I am writing to reply to your letter of December 23, 1975 concerning your report to Senator Nelson on recalls of Large Volume Parenterals manufactured by Cutter Laboratories, Inc.

It appears that your draft reflects the opinions and conclusions of personnel of the F.D.A. and perhaps the Center for Disease Control concerning the incidents discussed. As you might expect, there are instances where our opinions and conclusions concerning the incidents are different. However, because of your time limitations, it does not appear that your report lends itself to an attempt to present fully both sides of the very complex chain of events which took place in 1972 and 1973. For this reason we prefer to withhold comment on your draft.

Sincerely,

David L. Cutter

David L. Cutter
Chairman of the Board

DLC/mgh

APPENDIX VII

TRAVENOL LABORATORIES, INC.

Law Department
Writer's Phone: (312) 948-4916

Deerfield, Illinois 60015
Telex: 724497
Cable: Travenol
Deerfield

January 6, 1976

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

Re: B-164031(2)

I have been asked to reply to your letter addressed to Mr. John T. Kimbell, dated December 23, 1975. This letter asked for our review and comments on excerpts from a draft report to be sent to Senator Gaylord Nelson regarding recalls of Large Volume Parenterals. Our comments are as follows:

1. The proper entity is Travenol Laboratories, Inc. (or just Travenol) which, as you know, is the manufacturing and marketing corporation.

2. The draft opening paragraph might be construed to imply that all lots of 5% Dextrose Injection packaged in plastic containers manufactured by Travenol were recalled. As is noted later in the draft narrative, in fact only one lot was involved in the recall, and this lot was distributed to only one customer. For these reasons we would suggest that the opening paragraph be modified to read as follows:

> Baxter/Travenol
>
> On June 22 1973, Travenol recalled one lot of 5% Dextrose Injection LVP Solution packaged in plastic containers. This lot was manufactured in May, 1973 at Travenol's Kingstree, South Carolina plant. Only six cases (72 units) of this lot were distributed to one account in South Carolina. The unshipped units (the entire remainder of this lot) were destroyed at the manufacturing facility.

3. The final paragraph of the draft should also be modified to more accurately reflect the facts. First, we have reviewed our files and we were unable to

find any information that would confirm that a Travenol employee attributed the Pyrogen problem to "improper sanitation." The official FDA publication of this recall which appeared in the FDA Press Release dated November 7, 1973 lists as the reason for the recall simply "Pyrogens." A copy is attached. The second sentence to the draft paragraph states that Travenol planned no changes in its control procedure as a result of the recall. This is not accurate. A number of modifications and improvements in the manufacture of 5% Dextrose in plastic containers were implemented at Kingstree following the May, 1973 FDA inspection. Also, a follow up inspection was conducted by the FDA between August 13 and August 15, 1973, and additional modifications and improvements were made. Further improvements and modifications were under consideration. However, Travenol had constructed a new facility for the manufacture of LVPs in North Cove, North Carolina and it was decided to discontinue the manufacture of LVPs at the Kingstree plant. We would suggest that the facts as set forth below be included in the final report and would suggest that the last paragraph of the draft be revised by deleting the draft paragraph beginning "FDA's November 8, 1973, summary ..." and substituting in its place:

> A follow up inspection of the Kingstree facility by the FDA was conducted between August 13 and August 15, 1973. Modifications and improvements in the LVP manufacturing facilities were made as a result of the inspection in May and also the August inspection. Further improvements were being considered for this facility. As a new facility for the manufacture of LVPs had been constructed by Travenol in North Cove, North Carolina, in November, 1973 Travenol decided to discontinue manufacture of LVPs at its Kingstree, South Carolina plant.

We hope the comments that we have made are helpful and constructive. Thank you for affording us the opportunity of commenting on your draft, and if I can be of further assistance or provide additional clarification, please call.

Finally, we would appreciate receiving a copy of the final report language as it relates to Travenol.

Sincerely,

TRAVENOL LABORATORIES, INC.

Maynard L. Youngs

MLY/ka

GAO note: Attachment has been deleted from this report.