Memorandum

Date JUN 4 1997

From for June Gibbs Brown
Inspector General

Subject Review of the Food and Drug Administration's Inspection Process of Plasma Fractionators (CIN: A-03-97-00350)

To Michael A. Friedman, M.D.
Lead Deputy Commissioner
Food and Drug Administration

The attached final report provides the results of our review of the Food and Drug Administration's (FDA) inspection process of plasma fractionators. This review was performed at the request of the Chairman, Subcommittee on Human Resources, House Committee on Government Reform and Oversight.

The Subcommittee specifically asked us to examine concerns regarding FDA's: effectiveness in conducting inspections of plasma fractionators; communication of a plasma product recall; and handling of an industry-wide plasma saline contamination problem.

On June 3, 1997, we received FDA's comments on our findings and recommendations. We have incorporated these comments where appropriate.

Our work was conducted under an unusually tight time frame, and we appreciate FDA's efforts to help us complete our report in a timely manner. We would like to be advised of any further action taken or contemplated on our recommendations within the next 60 days. If you have any questions, please call me or have your staff contact Joseph J. Green, Assistant Inspector General for Public Health Service Audits, at (301) 443-3582.

Attachment

Department of Health and Human Services

OFFICE OF INSPECTOR GENERAL

REVIEW OF THE FOOD AND DRUG ADMINISTRATION'S INSPECTION PROCESS OF PLASMA FRACTIONATORS

JUNE GIBBS BROWN
Inspector General

MAY 1995

EXECUTIVE SUMMARY

BACKGROUND

At the request of the Subcommittee on Human Resources, House Committee on Government Reform and Oversight, the Office of Inspector General (OIG) reviewed selected aspects of the Food and Drug Administration's (FDA) Center for Biologics Evaluation and Research (CBER) and Office of Regulatory Affairs (ORA) regulation of blood plasma fractionator industry. The CBER is responsible for regulating products used for the prevention, treatment or cure of diseases and injuries including blood products, vaccines, serums, and toxins. The ORA directs the agency's field force, which performs inspections of FDA-regulated establishments.

Certain blood products are made from plasma, which is the portion of blood containing nutrients, electrolytes, gasses, albumin, clotting factors, and salts. Blood plasma fractionators, which number 26 worldwide, separate the various active components of plasma.

The FDA is responsible for inspecting licensed plasma fractionators every 2 years. The purpose of the inspection is to ensure that the products are safe, effective, and contain the quality and purity they purport to possess and are properly labeled.

CBER vs. ORA Inspections

Prior to 1996, CBER headquarters staff, located in Rockville, Maryland, performed inspections of plasma fractionators and initiated regulatory enforcement stemming from such inspections. That CBER performed these inspections was unique because FDA's field force, directed by ORA, conducted inspections of all other FDA-regulated products, including drugs, devices and foods. The ORA inspectors are generalists who have expertise in Good Manufacturing Practices (GMP). The CBER inspectors are scientific experts in the fractionation process. Beginning in Fiscal Year 1997, FDA authorized ORA to have "lead" responsibility for inspecting plasma fractionators, except pre-licensing inspections, and to assume the lead role for other biological products over a 3-year period.

Inspection reports are to be completed within 30 work days of completing a violative inspection, and within 45 work days of a non-violative inspection. Inspections with objectionable conditions can result in FDA initiating regulatory action including, for example, issuing warning letters and revoking establishment licenses.

Inspections Reviewed by OIG

We reviewed 63 inspection files for 25 of the 26 plasma fractionator inspections conducted between August 10, 1992 and March 21, 1997. During that period, several changes were made in the fractionator inspection process, leading to more ORA involvement in the process. Of the 63 GMP inspections, 33 were conducted by CBER staff only, while the remaining 30 were joint inspections conducted by CBER and ORA staff.

OBJECTIVE

The objective of our review was to respond to the Subcommittee's concerns in the following three areas:

(1) Plasma fractionator inspection process: The Subcommittee was concerned about CBER's effectiveness in conducting inspections of plasma fractionators when compared to inspections conducted by ORA. It was also concerned whether CBER routinely notified plasma fractionators in advance of upcoming inspections.

(2) FDA's handling of Centeon's albumin recall: The Subcommittee was concerned about the appropriateness of the agency issuing a talk paper rather than a press release to communicate a 1996 recall of plasma products made by Centeon, a plasma fractionator; and how this situation compared with a recall of a juice product.

(3) FDA's handling of an industry-wide plasma saline contamination problem: The Subcommittee was concerned that FDA, instead of taking enforcement action against a plasma fractionator, elected to participate with an industry-sponsored committee established to address the problem.

SUMMARY OF FINDINGS

Overall, we found that FDA was aware of the Subcommittee's concerns and, for this and other reasons, had begun taking steps to ensure that plasma fractionators and other biological manufacturers are properly inspected and held accountable for regulatory violations. The most significant improvement has been for ORA to assume the lead inspection role for plasma fractionators. However, as delineated below, we believe FDA can do more to strengthen its regulatory oversight of the plasma fractionator industry.

Regarding the specific Subcommittee concerns, we found that:

(1) Inspections of plasma fractionators in which ORA was involved resulted in more reported observations of objectionable conditions and more enforcement actions against plasma fractionators than inspections conducted solely by CBER.

- ✓ Inspections involving ORA staff (these inspections also involved CBER staff and are referred to in this report as joint inspections) resulted in four times as many observations being reported, and five times as many enforcement actions as inspections involving CBER staff only.

- ✓ Timeliness and documentation problems previously reported by internal FDA reviews continue. We noted delays in the preparation of Establishment Inspection Reports (EIRs) and warning letters. Most of the delays and missing documentation were associated with CBER inspections.

- ✓ CBER's policy was not and is not to pre-notify plasma fractionators located in the United States of upcoming inspections. To ensure that requests for production schedules are requested on a consistent basis and do not amount to a *de facto* prenotification of an inspection, CBER recently established new guidelines for requesting production schedules. These guidelines, however, were not being complied with, and there is no assurance that the intent of the guidelines are being met.

(2) The FDA's issuance of a talk paper in lieu of a press release was effective in communicating the recall of the plasma product albumin; however, an internal review disclosed serious problems with the recall.

- ✓ Although FDA did not issue a press release on the plasma product albumin, it issued a talk paper, which was distributed outside the agency. In addition, it initiated an interview by the Associated Press (which represents about 6,000 newspapers) with the appropriate CBER official.

- ✓ Significant problems surrounding the albumin recall were reported in an internal review made for the Department of Health and Human Services Blood Safety Committee. The focus of the problems dealt with the FDA's inadequate response to a MedWatch[1] adverse event report, and to previous inspection results.

- ✓ The Commissioner of Food and Drugs responded that corrective action was taken and planned. A task force was established to identify areas where improvement is needed in the handling of adverse event reports.

- ✓ Our review showed there is a need to ensure that adverse event reports are used to target plasma fractionators and/or products for inspection. Albumin

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1. MedWatch is a voluntary reporting system by health professionals of adverse events and problems. MedWatch is operated by a contractor and does not assess the reports. The FDA's Center For Drug Evaluation and Research evaluates and processes the adverse event reports on all drugs and biologics.

was regularly in the top five of all plasma products reported via adverse event reports, but inspections were not focused on the product until the Centeon recall.

(3) ***The CBER's participation with the plasma industry's work group established to study the problem of saline contamination was neither illegal nor unethical, but CBER was not consistent in its handling of devices found to be involved with the contamination.***

- ✓ The CBER chose not to implement the ORA's Chicago District Office recommendation to revoke the license of a plasma fractionator because a CBER Health Hazard Committee determined that a health hazard did not exist.

- ✓ In lieu of an enforcement action CBER chose to participate with an industry work group. According to the HHS Office of General Counsel and the OIG Office of Counsel, CBER's participation with the industry group was neither illegal nor unethical.

- ✓ An ORA recommendation to conduct a follow-up inspection of viral inactivation procedures at a plasma fractionator (Baxter's Hyland facility) was rejected by CBER. A regularly scheduled inspection conducted subsequently gave no indication that the viral inactivation procedures were reviewed.

- ✓ The problem of saline contamination was traced to a plasma collection device, the majority of which are produced by two manufacturers. For one device, FDA issued a safety alert thus requiring FDA follow-up to ensure that the problems were corrected. For the other device, no safety alert was issued, and FDA follow-up was not required, and not made.

- ✓ CBER was unaware of a saline contamination problem for about 5 years because firms are not required to report it if the product is not released. We believe this needs to be changed since saline contamination, according to CBER, has the potential to affect the entire source plasma industry.

RECOMMENDATIONS

We, therefore, recommend that FDA:

1. Review the proposal on the inspection process originally drafted by ORA's Biological Advisory Committee in April 1997 and implement it to the extent feasible.

2. Ensure that CBER has a viable plan, with appropriate milestones, to transfer and expand ORA's lead inspection responsibilities to all biological products currently being inspected by CBER.

3. Adhere to time frames established for the preparation of EIRs and the issuance of warning letters.

4. Instruct employees of the importance of completing the classification of inspections; and require CBER to classify the inspections identified in this report as lacking documentation and take whatever enforcement actions that are appropriate based on the classifications.

5. Require CBER to comply strictly with the policy on requesting production schedules from biological establishments.

6. Require the FDA task force, established in response to the internal report for the Blood Safety Committee, to determine if the intelligence gathered by the adverse event reports could be put to better use in planning inspections, particularly with regard to the targeting of plasma fractionators and/or plasma products.

7. Verify that the inspection of Hyland, ongoing as of May 12, 1997, includes a review of viral inactivation procedures. If the procedures were not included, require such an inspection.

8. Review the changes made to the plasma collection devices to determine whether they meet the criteria for classification as medical device safety alerts.

9. Consider requiring plasma collection and testing facilities to report all incidents involving saline contamination.

10. Finalize and implement the draft changes to the inspection guide for source plasma establishments, and the compliance program for plasma fractionators.

On June 3, 1997, we received FDA's written response to the recommendations contained in a draft of this report. The comments consisted of editorial and factual comments and the status of implementation of our recommendations. We made those editorial and factual changes to this report that were appropriate and supported by documentation. We have summarized FDA's response regarding the implementation of our recommendations along with our comments on page 32. The FDA's written response is included in this report as Appendix F.

The FDA generally agreed with our recommendations and has begun implementing them. Most importantly, FDA has developed a plan for regulating all biologic products. The plan entitled, "Team Biologics--A Plan for Reinventing FDA's Ability to Optimize Compliance of Regulated Biologics Industries," is dated May 28, 1997. It redefines the working relationship between CBER and ORA. It also sets dates to transition lead inspection responsibilities for all biologic products currently being inspected by CBER to ORA. The FDA also noted that the ongoing inspection of Baxter's Hyland facility (OIG recommendation number 7) resulted in a Class III recall. Specifically, Baxter has recalled 9 lots of Antihemophilic Factor (Human). While FDA's response to our report was generally positive, we believe further actions are required for two of our recommendations dealing with the possible need for safety alerts (OIG recommendation number 8) and the mandatory reporting of saline contamination incidents (OIG recommendation number 9).

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INTRODUCTION

BACKGROUND

The Food and Drug Administration (FDA) receives its primary regulatory authority through the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. The FDA is responsible for helping to ensure the safety of blood and biological products, food, cosmetics, human and veterinary drugs, medical devices, and electronic products that emit radiation. The Office of the Commissioner (OC) is responsible for all FDA operations. Oversight responsibilities of FDA are divided among the following five centers.

- Center for Biologics Evaluation and Research (CBER) which regulates blood, blood products and biologics,
- Center for Food Safety and Applied Nutrition (CFSAN) which regulates all foods for human consumption, except meat and poultry products, and cosmetics,
- Center for Drug Evaluation and Research (CDER) which regulates human drugs,
- Center for Veterinary Medicine (CVM) which regulates animal drugs, animal feed, and drugs and chemical residues in foods derived from animals, and
- Center for Devices and Radiological Health (CDRH) which regulates medical devices and controls the unnecessary exposure to radiation from medical, occupational, and consumer products.

Also reporting to the OC is the Office of Regulatory Affairs (ORA). The ORA conducts inspections and investigations for the five FDA centers with oversight responsibilities, although its relationship with CBER is unique among the five centers. Prior to April 1992, CBER inspected some blood and biological establishments, including plasma fractionators and manufacturers of plasma derivatives (hereafter referred to in this report as plasma fractionators). Since then, ORA has been given an ever increasing role in the inspection process. In 1994, ORA was involved in the inspection of all plasma fractionators, with CBER taking the lead role. In 1997, lead responsibility in all biennial inspections of fractionators was transferred to ORA.

Blood and Blood Products

Blood and blood products have been licensed and inspected since 1946 under Section 351 of the Public Health Service Act (42 U.S.C. 262). In 1972, this statute was amended to

transfer regulation of biological products to FDA. The CBER is the Center within FDA that regulates blood, blood products and other biologics.

Blood is the tissue circulating through arteries and veins that contains the components needed to sustain bodily functions. Plasma is the liquid portion of blood containing nutrients, electrolytes (dissolved salts), gasses, albumin, clotting factors, hormones, and wastes. Plasma is a straw-colored, clear liquid that is 90 percent water.

Plasma is collected by plasmapheresis, a procedure that removes blood from a donor and separates plasma from the formed elements. Plasma may also be obtained by separation from collected whole blood. The formed elements of the blood include erythrocytes, leukocytes, and platelets. Some formed elements are returned to the donor. Once collected, plasma is shipped to pharmaceutical manufacturing sites. At each site, plasma is pooled into processing lots up to as many as 60,000 units.

The primary fractionation process chemically separates the various active components of plasma. Primary fractionation takes place on both human and animal plasma. Derivative therapeutic products are also manufactured from intermediate material obtained from primary fractionators. One component, albumin, is used to restore plasma volume in treatment of shock, trauma, surgery, and burns. Another component, antihemophilic factor concentrate, treats bleeding episodes in hemophiliacs.

There are 26 sites world-wide licensed by FDA to fractionate plasma and manufacture plasma derivatives. There are 13 primary fractionators of human plasma, 5 primary fractionators of animal plasma, and 8 manufacturers of plasma derivatives from intermediate material obtained from primary fractionators. Nine of the fractionators also manufacture products that are regulated by other FDA centers. These fractionators are termed dual processors. A listing of licensed fractionators can be found in Appendix A.

Biologics are defined under the Public Health Service Act section 351(a). Drugs are defined in section 201 (g)(1) of the Federal Food, Drug, and Cosmetic Act. Biologics, which are also drugs, are used for the prevention, treatment, or cure of diseases or injuries. Biologics include bacterial vaccines and antigens, viral and rickettsial vaccines, toxins and antitoxins, and therapeutic serums.

The Center for Biologics Evaluation and Research

Much of CBER's regulatory authority is found in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. It has focused on disease prevention and eradication through pre-market approvals. The CBER regulates about 150 establishments that produce vaccines, plasma and other biologics.

The CBER's Office of Compliance coordinates inspection activities through its Inspection Task Force (ITF). The ITF schedules and participates in the planning of establishment

inspections. Within CBER, blood and blood product inspections are conducted by the Office of Blood Research and Review (OBRR) and the Office of Establishment Licensing and Product Surveillance (OELPS). Members of OBRR have scientific expertise. Members of OELPS have expertise in current Good Manufacturing Practices (GMP) which cover such areas as organization and personnel; buildings and facilities; equipment; control of components, product containers and closures; production and process controls; packaging and labeling controls; holding and distribution; laboratory controls; records and reports; and licensing. The Office of Compliance is responsible for addressing enforcement action recommendations.

The Office of Regulatory Affairs

Much of ORA's regulatory authority is found in the Federal Food, Drug, and Cosmetic Act and the Public Health Service Act. Its focus has been on product adulteration and mislabeling through post-market controls. In addition, ORA conducts pre-approval inspections for drugs and devices. It is responsible for several thousand establishments which produce food, drugs, cosmetics, medical devices, and veterinary products.

The ORA's inspection activities are performed by a decentralized field organization of five regional offices. There are 3 to 5 district offices within each regional office for a total of 21 districts. Each district office is usually comprised of three to four branches, including a compliance branch or an enforcement branch which is the primary regulatory contact within a district office. Inspections are conducted by field investigators who are generalists, that is, trained to inspect more than one product area, i.e., foods, drugs and devices for GMP compliance. Supporting the field activities in headquarters is the Office of Regional Operations under the direction of an Associate Commissioner for Regulatory Affairs.

Other Agencies with Oversight Authority of Blood, Plasma, and Biologics

Other agencies within the Department of Health and Human Services (HHS) share with FDA the responsibility for safeguarding the nation's blood supply. These agencies include the Centers for Disease Control and Prevention (CDC), the Health Care Financing Administration (HCFA), and the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI).[2] In addition, the Blood Products Advisory Committee, composed of government, industry, and consumer representatives, provides scientific advice and expertise to FDA on blood issues.

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2. The HCFA inspects facilities that perform viral testing procedures and blood transfusion services that are reimbursed through Medicare and Medicaid. The CDC collects data on incidents of infectious disease, including blood borne ailments. The NHLBI sponsors blood-related research such as developing virus screening tests.

To further improve safeguards over the nation's blood supply, the HHS Secretary, in testimony before the Subcommittee on October 12, 1995, announced the appointments of a Blood Safety Director, a Blood Safety Committee, and an Advisory Committee on Blood Safety and Availability. The Assistant Secretary for Health was named Blood Safety Director and coordinates HHS blood safety programs. The Blood Safety Committee advises the Director. It includes the FDA Commissioner and Directors of the CDC and NIH. The Advisory Committee, whose members include representatives of industry, consumers, and scientific experts, provides advice to the Secretary and the Assistant Secretary. None of these functions supersede FDA's regulatory authority.

Prior OIG Reviews Concerning Blood Safety

This is the third review by the OIG concerning blood safety issues. The prior two reviews addressed CBER's processing of error and accident reports by blood establishments. The first review concluded that the reporting process used by blood establishments to notify CBER of errors and accidents is a valuable management tool but needed certain improvements. The second review, which was a follow-up to the previous review, noted that CBER did not properly process 5 of the 17 error and accident reports reviewed that were identified as potential blood recalls.

SCOPE OF REVIEW

Our review, which was conducted in accordance with generally accepted government auditing standards, was in response to a request from the Subcommittee on Human Resources, Committee on Government Reform and Oversight, United States House of Representatives (hereafter referred to as the Subcommittee). The Subcommittee was concerned about CBER's lead role in the inspection of plasma fractionators and requested that we review:

1. The CBER's effectiveness in conducting inspections of plasma fractionators when compared to inspections conducted by ORA; and whether CBER routinely notified plasma fractionators in advance of scheduled inspections.

2. The appropriateness of FDA issuing a talk paper for a recall of a plasma product versus the issuing of a press release in the recall of a juice product.

3. The appropriateness of FDA's role in participating with an industry work group established to study a saline contamination problem rather than taking enforcement action.

To achieve these objectives, we reviewed the provisions in statutes concerning blood and blood products found in the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act. We reviewed FDA regulations, policies and procedures found in Section 21 of the Code of Federal Regulations (CFR), FDA's Regulatory Procedures Manual,

Compliance Policy Guide and Investigations Operations Manual, CBER's Inspection Manual, and ORA's Warning Letter Reference Guide. We also reviewed FDA training manuals, Standard Operating Procedures (SOPs) and internal memorandums concerning the inspection process of plasma fractionators.

We interviewed FDA officials in the Rockville, Maryland headquarters including those from CBER, ORA, and the Office of Public Affairs. We also interviewed ORA staff in the Chicago District Office who had participated in several inspections of plasma fractionators and a plasma testing facility. Some of these individuals were identified by the Subcommittee as being knowledgeable in the issues addressed by our review.

We reviewed 63 inspection files for 25 of the 26 plasma fractionators (the remaining fractionator was not identified by CBER until our review was near complete) representing inspections conducted between August 10, 1992 and March 21, 1997. During that period, several changes were made in the fractionator inspection process, leading to more ORA involvement in the process. Of the 63 GMP inspections, 33 were conducted by CBER staff only, while the remaining 30 were joint inspections conducted by CBER and ORA.

Of the 25 fractionators in our review, 17 underwent at least one inspection by CBER and one inspection by a joint CBER/ORA team. The 17 fractionators accounted for 50 of the 63 inspection files that we reviewed. The remaining eight fractionators were inspected at least once by either CBER or by a CBER/ORA team. The following table shows by fiscal year, the number of inspections of plasma fractionators that were conducted solely by CBER and the number conducted by a joint CBER/ORA team.

OIG REVIEW OF INSPECTIONS OF PLASMA FRACTIONATORS			
Fiscal Year	CBER Inspections	Joint Inspections	Total
1992	4	0	4
1993	11	1	12
1994	7	6	13
1995	8	3	11
1996	3	11	14
1997	0	9	9
Total	33	30	63

In reviewing the use of a talk paper versus a press release, we reviewed the files of the two specific recalls, the internal review that was conducted at the request of the HHS Blood Safety Committee, and FDA's response to the report. Our objective was not to determine the overall effectiveness of either recall, but to ascertain if the use of a talk

paper adversely affected the recall of the plasma product. We also reviewed reports of adverse events reported to FDA.

In reviewing the appropriateness of FDA's role with the industry work group, we consulted both the OIG Office of Counsel, and HHS Office of General Counsel. We also reviewed the inspection report which first alerted CBER to the saline contamination, interviewed the ORA inspector from the Chicago District Office, and reviewed subsequent inspection reports of other source plasma collection facilities. We also interviewed various CBER officials and reviewed the report prepared by these officials which summarized the industry's work group activities.

We conducted our audit field work from December 17, 1996 through May 28, 1997.

FINDINGS AND RECOMMENDATIONS

INSPECTIONS OF PLASMA FRACTIONATORS

Prior to December 1995, inspections of plasma fractionators were conducted primarily by CBER. Since then, ORA has gradually assumed a lead role in the inspection process. Additional changes have been proposed that will further strengthen the inspection and enforcement process not only for plasma fractionators, but for all biological establishments now being inspected by CBER. Also, CBER has issued a policy statement clarifying its policy for requesting production schedules so as to preclude inadvertent notification of scheduled inspections.

The CBER cited several factors that caused them to re-examine their role in GMP inspections. These include concerns of the CBER inspection process previously expressed by the Subcommittee, and FDA's efforts to downsize, streamline, improve consistency and eliminate redundancy. Another factor, in our opinion, is that CBER has been aware of weaknesses in its inspection process since at least 1992.

An internal review conducted by CBER in that year reported delays in the preparation of Establishment Inspection Reports (EIR). The internal reviewers also reported EIRs were not always completed and that Form FDA 483, Inspectional Observations (key to documenting observations of objectionable conditions and practices) were frequently incomplete, and not forwarded to the appropriate authorities. In 1993, the FDA's Office of Special Investigations (OSI) reported similar findings. Inspection files were missing or incomplete, there were significant delays in writing reports, and the average CBER inspection of biologics establishments was only 16 hours.

Our review has shown that the changes made in the inspection and enforcement process have resulted in more effective inspections, but that further actions need to be taken. Specifically, we found that:

- ✓ Past inspections of plasma fractionators conducted solely by CBER were not as effective as joint inspections involving ORA in reporting observations of objectionable conditions and practices, or in generating enforcement action. We were unable to determine the definitive cause for the apparent difference in inspection results since both CBER and ORA inspected the same establishments and used the same regulatory criteria when conducting the inspections. We noted, however, that joint inspections involving ORA generally involved more staff and took longer to conduct. Also, ORA is staffed with personnel whose primary function is conducting inspections while CBER is staffed with scientists whose involvement in inspections is essentially part-time.

- ✓ As previously reported in FDA internal reviews, past inspections have not met specific time frames established by FDA for completing EIRs and for issuing warning letters. Also, classifications were not completed for all inspections as required.

- ✓ Although CBER has recently clarified its policy of requiring production schedules from plasma fractionators, the policy was not being complied with.

- ✓ A plan of action to further improve the inspection and enforcement process proposed by ORA with some CBER input will, if implemented, further improve the overall process.

The gradual expansion of ORA's role in the inspection process has strengthened the overall inspection and enforcement process as it pertains to plasma fractionators. We believe, however, that the process can be further strengthened by timely implementation of an ORA proposed plan of action, and by expanding ORA's inspection role to biologic establishments that are currently being inspected by CBER, and by correcting the deficiencies included in this report.

FDA Inspection Process and Requirements

Federal regulations (21 CFR 600.21) require that, once licensed, a facility should be inspected at least once every 2 years. These are referred to as GMP inspections. Inspections may also be conducted if special circumstances warrant. These are referred to as directed inspections.

The purpose of an inspection is to ensure that biological products are safe, effective, contain the quality and purity they purport to possess, and are properly labeled. Facilities under inspection must conform to:

- o the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 374(a)) and/or the Public Heath Service Act (42 U.S.C. 262-264), and

- o Good Manufacturing Practices as defined under 21 CFR Parts 210-211, 600-680, and, if a device, Part 820.

The official notice of inspection to a facility is made through a Form FDA 482 which must be signed by each inspector. Inspection warrants can be sought if an inspection request has been refused or significantly limited. Facilities and production methods are observed and reviewed. The inspectors report significant observations of objectionable conditions and practices on Form FDA 483, Inspectional Observations. The observations could relate to such areas as faulty manufacturing, processing and packaging; violations of the law or deviations from applicable standards, deviations from commitments included in

the approved license application or from written SOPs; unsanitary conditions or practices which may render the product injurious to health; and undesirable conditions or practices resulting in contamination with filth.

At the completion of the inspection process, the inspectors present their observations to the firm, and subsequently prepare the EIR to formally summarize their activities and findings. The EIR narrative includes the following: the reason for the inspection; a brief history of previous findings; refusals, voluntary corrections, and promises made by the firm's management; and a concise summary and evaluation of current findings. The EIR is required to be completed within 30 work days after completion of a violative inspection, and within 45 work days of a non-violative inspection.[3]

An endorsement of the EIR serves to classify an inspection's reported observations as follows:

- ✓ No Action Indicated. Indicates that no objectionable conditions or practices were found and that no further action is necessary.

- ✓ Voluntary Action Indicated. Indicates that objectionable conditions were found but none serious enough to warrant advisory, administrative, or judicial action. Corrective actions are voluntary.

- ✓ Official Action Indicated. Indicates that objectionable conditions of a serious nature were found and corrective measures must be taken. These include advisory, administrative, or judicial actions.

Advisory actions include a warning letter or an untitled letter. A warning letter notifies a firm that a product, process, or other activities violate government regulations but there is no imminent public safety threat. This should be done within 30 work days after completion of the inspection if the recommendation for the warning letter was initiated by ORA and approved by CBER. If the warning letter recommendation is generated by CBER, it must be issued within 15 work days after the inspection. An untitled letter notifies the firm of circumstances that do not violate government regulations. A written response from the firm is required for a warning letter and optional for an untitled letter.

Administrative actions include citations, and license revocation or suspension. A citation notifies the firm that a prosecution recommendation to the United States Attorney is being considered since there is evidence that a law has been violated. A license revocation, resulting from violations of the licensing standards or regulations, withdraws the firm's

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3. A violative inspection is one in which significant objectionable conditions or practices were observed and documented and for which an enforcement action is recommended. A non-violative inspection is one in which any objectionable conditions or practices observed do not warrant a recommendation for an enforcement action.

authority to ship interstate a biological product. A suspension also withdraws the firm's authority to ship interstate a biological product. A suspension is used when a danger to health exists. License revocation or suspension must be approved by CBER.

Judicial actions include seizures, injunctions, or prosecutions. Judicial actions are conducted through the United States Attorney's Office. Seizures remove adulterated or misbranded products from the market. An injunction is a civil process initiated to stop or prevent violation of the law, to prevent the flow of defective products through interstate commerce, or to correct the conditions that caused the violations to occur. Injunctions may be preliminary or permanent or simply a temporary restraining order. Prosecutions are sought for criminal violations. In most instances, referrals for criminal prosecutions proceed only after the firm has had an opportunity to address the charges.

Product recalls may be undertaken at any time on the initiative of manufacturers and distributors. The FDA may also request a firm to initiate a recall when the firm has not already done so and the action is needed to protect the public health and welfare. Section 351(d)(2)(A) of the Public Health Service Act authorizes FDA to order a biologic recall upon a determination that a batch lot or other quantity of product presents an imminent or substantial hazard to the public health.

Prior to April 1992, CBER inspected plasma fractionators. In April 1992, CBER and ORA formalized an agreement to conduct joint inspections of dual processors. A dual processor is a manufacturer of a biological and non-biological drug and/or device at a specific location. There must be shared pieces of manufacturing equipment and/or systems and includes personnel, storage area, and quality control. In August 1994, CBER and ORA conducted a Biologics Conference to update and enhance the joint inspection process agreed to in April 1992. Inspections of fractionators, who were also dual processors, were to be conducted jointly by CBER and ORA, with CBER leading. The CBER retained responsibility for assigning the classification, preparing the endorsement, and initiating regulatory action.

In December 1995, CBER and ORA issued a SOP concerning the joint inspection program. The CBER and ORA shared the lead for inspections of dual processors. The CBER led all other inspections, and continued with classification, endorsement, and regulatory actions. If CBER disagreed with ORA on its recommendations for regulatory action, ORA could appeal through an FDA ad hoc committee chaired by the Director of ORA's Office of Enforcement, and consisting of representatives of ORA, CBER, FDA's Office of Chief Counsel and, when appropriate, ORA's Office of Criminal Investigations.

For Fiscal Year (FY) 1997, FDA approved a change giving ORA the lead in all GMP inspections of plasma fractionators, except for pre-licensing inspections.[4] The ORA

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4. The purpose of a pre-licensing inspection is to ensure that the plasma fractionator can produce its products in a manner that conforms to government laws and regulations.

assumed responsibility for classification and endorsement of the inspectors' observations. The first ORA lead GMP inspection was conducted in November 1996.

Joint Inspections Were More Effective Than CBER Inspections

Joint CBER/ORA inspections of fractionators lasted three times as long, reported four times as many observations of objectionable conditions and practices, and resulted in five times as many enforcement actions as inspections involving CBER only. The following table summarizes the comparison between CBER and joint inspections.

OIG SUMMARY ANALYSIS OF INSPECTIONS REVIEWED			
	CBER	JOINT	TOTAL
Inspections	33	30	63
Observation-Average Form-483 Items Per Inspection	6	26	
Observation-Average Discussion Items Per Inspection	4	4	
Classification-No Action Indicated	6	2	8
Classification-Voluntary Action Indicated	17	15	32
Classification-Official Action Indicated	1	12	13
Enforcement Action-Warning/Untitled Letters	2	9	11
Enforcement Action-Intent-to-Revoke License/ Court Injunction	0	2	2

The 33 inspections conducted by CBER reported 201 observations of objectionable conditions and practices (Form FDA 483 observations), an average of about 6 per inspection. The 30 joint inspections reported 787 observations, an average of about 26 per inspection. The initiation of enforcement actions increased from 2 for CBER inspections to 11 for joint inspections (at the time of our review, CBER was considering taking enforcement action on 1 additional joint inspection).

Causes for the Differences in Observations

We were unable to determine the definitive cause for the increase in the number of reported observations resulting from the joint inspections. For the most part, the same fractionators were inspected by both groups of inspectors. Fifty of the 63 inspections that we reviewed involved fractionators that were inspected first by CBER and then jointly. Furthermore, both groups were required to use the same regulatory criteria in conducting

inspections, and based on our analysis of the types of observations reported, it appears as if the same criteria was used.

We did note, however, that the joint inspections generally resulted in a significantly higher number of observations in two categories--quality control/quality assurance (QC/QA) observations and air/environmental monitoring and water systems (AEMWS). The CBER inspections resulted in 18 QC/QA observations (9 percent) compared to 169 observations (21.5 percent) from joint inspections, and 22 AEMWS observations (10.9 percent) compared to 176 observations (22.4 percent) from joint inspections. Appendix B summarizes the findings of the 63 GMP inspections that we reviewed.

We did identify certain issues which we believe contributed to the differences in the numbers of observations reported. First of all, the number of inspectors increased in the joint inspections. On average, the 33 CBER inspections were conducted by 2 employees, while the joint inspections were conducted by 3 employees. Second, the time spent on-site at the fractionators increased under the joint inspections. The average CBER inspection lasted 3 days while the average joint inspection lasted 9 days on-site.

Perhaps the most significant issue, however, involved the inspectors themselves. The CBER inspectors were first and foremost scientists whose primary duties were not the inspection of plasma fractionators. According to information provided to us by CBER, the scientists who conducted the inspections spent only a very small percentage of their total time on inspections. Further, their limited experience was primarily in the area of pre-licensing inspections which were for the purpose of supporting pre-approval decisions relating to establishment and product licenses and supplements or amendments to these licenses. These inspections were not designed to support post-market obligations--primarily assuring compliance with GMPs. Conversely, ORA inspectors were full time inspectors with more experience in conducting GMP inspections.

Causes for Differences in Enforcement Actions

In our opinion, a primary cause for the increased number of enforcement actions resulting from joint inspections is the corresponding increased number of observations of objectionable conditions and practices being reported by inspectors. The number of observations reported by the joint inspections increased by 333 percent as compared to the number reported by CBER's inspections. Absent these observations, enforcement actions are extremely unlikely.

Since the classifications of the observations determine to a large degree whether enforcement action is appropriate, we reviewed the classifications that were completed on the 63 inspections that we reviewed to determine if CBER's classification threshold for its inspections was higher than the classification threshold for the joint inspections. As shown in the following table, that was not the case.

AVERAGE NUMBER OF REPORTED OBSERVATIONS BY CLASSIFICATION		
Classification	CBER	JOINT
No Action Indicated	0	0
Voluntary Action Indicated	7	15
Official Action Indicated	25	45

The Official Action Indicated classification is the most serious as it indicates that objectionable conditions of a serious nature were found and that corrective action must be taken. In the 1 CBER inspection that resulted in a warning letter, 25 observations were reported. In the 11 joint inspections that resulted in enforcement actions and 1 joint inspection under consideration for an enforcement action, the average number of reported observations was 45. Based on this analysis, it appears as if the number of reported observations is more likely to account for the difference in enforcement actions than a higher CBER threshold of enforcement.

In our review of the 63 inspection files, we noted 5 instances (3 involving CBER inspections and 2 involving joint inspections) where CBER did not agree with the inspectors' recommendation for enforcement action. The disagreements were generally based on lack of documentation or evidence supporting the recommendations. The CBER's nonconcurrence with the recommendations of inspectors does not appear to be inconsistent with the experiences of the other FDA Centers. For instance, in FYs 1995 and 1996, the FDA Centers with oversight responsibility approved, on average, 67 percent of ORA's recommendations for warning letters. During this same period, CBER approved 29 of 43 warning letter recommendations for all biologic products, also a 67 percent approval rate. The following table summarizes the warning letter activity.

FDA WARNING LETTERS -- FYs 1995 and 1996						
Action	CBER	CDER	CDRH	CFSAN	CVM	Total
Recommended	43	165	164	192	41	605
Approved	29	123	103	132	20	407
Disapproved	12	12	61	52	21	158
Open	0	30	0	0	0	30
Abeyance	1	0	0	5	0	6
Unresolved	0	0	0	3	0	3
Withdrawn	1	0	0	0	0	1
Approval Rate	67%	75%	63%	69%	49%	67%

Timeliness and Documentation Problems Continue

Problems with timeliness and completeness of inspection documentation, some of which were previously reported in FDA internal reviews, continue. We noted delays in the preparation of the EIRs and the issuance of warning letters. We also noted that inspection files were missing classifications, and that some inspections were never classified; thus essentially precluding any enforcement action that might be appropriate.

Delays in the Inspection and Enforcement Process

As previously reported in internal reviews conducted by CBER and OSI, EIRs were not prepared timely. The CBER report stated that in the majority of instances the time between the inspection visit and the preparation of the EIR exceeded the recommended time frame for report preparation. According to the report, it is critical that the time frame be met for violative inspections to provide CBER officials the opportunity to critique the adequacy of the inspection, and to make the necessary recommendations regarding licensure, reinspection, or to issue warning letters. The report states further that timely EIR preparation is needed for all other inspections as well to enable CBER officials the opportunity not only to evaluate the inspection but to follow-up in a timely manner any areas that they feel may be problematic.

Our review of 48 non-violative EIRs showed that 25 exceeded the 45 work day time frame. On average, 136 work days were required to prepare these EIRs. The CBER inspections accounted for 18 of the EIRs that were late while the joint inspections accounted for 7 of the late EIRs. Our review of seven violative EIRs showed that four exceeded the 30 work day time frame. Three of the EIRs resulting from joint inspections exceeded the 30 work day time frame by 1 to 4 work days. The one EIR resulting from a CBER inspection required 125 work days to prepare.

Delays in preparing the EIRs contributed to delays in issuing warning letters. The one warning letter resulting from a CBER inspection was issued 180 work days after completion of the inspection. Much of this delay was traced to the fact that the EIR was not prepared until 125 work days after the inspection. Five warning letters issued as a result of joint inspection required an average of 60 work days to issue, an improvement over the CBER inspection but still far exceeding the maximum 30 work day time frame. In our opinion, the effectiveness of a warning letter is diminished if it is not issued timely upon the completion of the inspection.

Missing Documentation on Classifications

Our review of the 63 inspection files disclosed that documentation supporting the classification of 15 inspections (24 percent) was missing. Classification of an inspection occurs when CBER reviews and endorses the EIR. The classification is based on the

seriousness of the observed objectionable conditions and practices, and determines whether some form of corrective action or sanction is appropriate.

Of the 15 classifications missing from the inspection files, 11 were associated with CBER inspections and 4 were associated with joint inspections. While 8 of these inspections had fewer than 4 observations reported, 7 of the inspections had from 8 to 45 observations reported. We requested CBER to provide us with the missing documentation for the 15 classifications. We were informed that:

- 6 of the 15 classifications were never made. Three of the EIRs had 3 or less observations but the other 3 EIRs had 21, 23, and 25 observations, respectively. The CBER indicated that it would have sent out a warning letter to the fractionator with the 21 observations had it received the EIR timely (report was prepared about 64 days after the close of the on-site inspection). It did not comment on any appropriate enforcement actions for the EIRs with 23 and 25 observations.

- 8 classifications were made, according to CBER, but documentation to support the classifications were not present in the case files.

- 1 classification was made after we first brought the matter to CBER's attention. It was classified Voluntary Action Indicated and had eight observations.

CBER's Policy On Requesting Production Schedules Was Not Being Complied With

The Subcommittee requested that we determine if CBER's policy is to give plasma fractionators advance notification of inspections. It is not CBER's policy to provide advance notification to fractionators located in the United States. Advance notification could inadvertently result, however, from requesting production schedules only from those fractionators scheduled for inspections. Realizing this, CBER recently revised its policy regarding production schedules. Our review showed that the policy is not being complied with in that letters were not sent to licensed manufacturers requesting production schedules. As a result there is little documentation to show if and/or when the requests were made.

The CBER policy limits prenotification. A CBER SOP dating back to at least 1988 concerning pre-notifications states:

> "It is not the policy of CBER to announce annual inspections; however, prenotification is permitted under 21 CFR 600.21 and some inspections are routinely announced, e.g., all foreign inspections, all prelicense inspections, and

some scheduled inspections where active processing/manufacturing has not been observed for the last several inspections."

The SOP instructs inspectors to clear any prenotification with CBER's Office of Compliance and the Division that has product line responsibility. The CBER Inspection Manual, issued November 20, 1992, restates this longstanding policy.

The CBER reported to the Subcommittee that from 1994 through 1996, it had requested production schedules from biologic establishments in advance of 40 of 193 inspections scheduled, or almost 21 percent of the inspections scheduled. The requests varied in relation to the scheduled inspections. For instance, 4 requests were made at least 1 year before the scheduled inspection, 15 requests were made between 3 and 6 months before the scheduled inspection, 6 requests were made less than 3 months before the scheduled inspection, and CBER could not determine when the other 11 requests were made. In fact, all of the data provided to the Subcommittee was based on CBER's institutional memory, since records documenting when the requests for production schedules were made were not available.

On November 21, 1996, CBER issued a SOP, number OD-R-15-96, clarifying its policy on production schedules. The revised SOP states that a letter requesting production information will be mailed from CBER's ITF to each licensed manufacturer of a biological product on a bi-annual basis, or as deemed appropriate.

We requested documentation in the form of these letters to determine if the policy was being complied with. We were informed that CBER had telephoned all of the manufacturers sometime between the date of the SOP--November 21, 1996--and the end of January 1997. Contrary to the requirement of the SOP, letters were not sent. The CBER was able to provide documents showing that 22 manufacturers responded to the telephone contact by submitting production information (CBER provides oversight to approximately 150 biological establishments). The responses generally contained production schedules for the entire 6-month period requested, and were not targeted in on any particular point of time within that 6-month period.

In our opinion, CBER needs to comply with its policy to ensure that all manufacturers are contacted, and, more importantly, that they are contacted at the same time. Contacting only those manufacturers that are scheduled for an upcoming inspection is akin to giving those manufacturers advance warning of the inspections.

ORA's Biologics Advisory Committee Suggests Further Improvements

In April 1997, the ORA's Biologics Advisory Committee with input from CBER's Office of Compliance developed a proposed framework for a comprehensive ORA/CBER partnership for the regulation of the biologics industry. According to the Committee, the

proposal will allow FDA to focus highly skilled resources on violative situations and bring them to an expedited conclusion. The proposal is now being reviewed within FDA. We believe the proposal represents another major improvement in the inspection and enforcement process, not only as it applies to plasma fractionators but to the other biological establishments currently being inspected by CBER.

The proposal was designed to address several critical issues including inconsistencies in the inspection and enforcement process between CBER and ORA and among the ORA district offices, and the process for resolving ORA/CBER differences. Three specific groups, consisting of ORA and CBER representatives, are contemplated:

- An Implementation Group responsible for overall biologics policy as it relates to inspectional activities.

- A Blood Operations Group responsible for planning the direction the inspectional program will take, planning and scheduling work, and providing guidance documents as needed by on-site inspection teams.

- A Core Team of certified ORA investigators and compliance officers responsible for conducting the inspections.

For plasma fractionators, the Core Team would consist of a cadre of specially trained ORA investigators, CBER investigators, and specialized compliance officers from each organization. An ORA team member would serve in the lead role for all biennial or directed inspections. The compliance officers would become involved during the inspection when potential violative situations are identified.

The Committee recommended that the proposal be initially used in the inspection of plasma fractionators, and then expanded to other CBER product areas, such as biotechnology, allergenics and vaccines by October 1, 1999.

The results of our review of 63 inspections of plasma fractionators show that both the number of observations and enforcement actions increased after ORA became involved in the process. We believe that the ORA proposal, specifying the partnership roles of ORA and CBER, lends itself to further strengthening of the inspection and enforcement process.

Conclusions and Recommendations

Based on our review of 63 inspections performed either solely by CBER (33 inspections) or with ORA involvement (30 joint inspections), it is evident that ORA involvement resulted in a greater number of reported observations and enforcement actions.

The CBER proposes to expand ORA's lead inspection role to other biological products over a 3-year period. January 1998 is the anticipated completion date for transfer of biotechnology products; March 1998 for in-vitro diagnostic products; October 1998 for allergenics; and October 1999 for vaccines and remaining products. The ORA, with some CBER input, proposes to refine the entire inspection process. We believe FDA should expedite action on these proposals and ensure that there is a plan to implement them as fast as possible. We also believe that actions need to be taken on the other deficiencies that we have reported on.

We, therefore, recommend that FDA:

1. Review the proposal on the inspection process originally drafted by ORA's Biological Advisory Committee in April 1997 and implement it to the extent feasible.

2. Ensure that CBER has a viable plan, with appropriate milestones, to transfer and expand ORA's lead inspection responsibilities to all biologics currently being inspected by CBER.

3. Adhere to time frames established for the preparation of EIRs and the issuance of warning letters.

4. Instruct employees of the importance of completing the classification of inspections; and require CBER to classify the inspections identified in this report as lacking documentation and take whatever enforcement actions that are appropriate based on the classifications.

5. Require CBER to comply strictly with the policy on requesting production schedules from biological establishments.

USE OF A TALK PAPER IN LIEU OF A PRESS RELEASE IN THE RECALL OF A PLASMA PRODUCT

The FDA issued a press release for the Odwalla juice recall and a talk paper for the Centeon albumin recall. We do not believe that the use of a talk paper in lieu of a press release had a significant impact on the albumin recall, however, deficiencies involving the albumin recall were included in an internal report requested by the HHS Blood Safety Committee.

Among the report's findings were those dealing with the MedWatch adverse event report and the FDA inspection and enforcement process, including FDA's lack of previous inspection coverage of albumin. According to the FDA's response to the report, certain corrective actions have been taken including the increased role of ORA in the inspection and enforcement process. Another cited improvement is the establishment of a FDA task

force to inventory all current procedures for handling reports of adverse events and product problems or defects, and to make changes that will result in a more effective and efficient system.

We believe the actions taken or planned will further strengthen FDA's inspection and enforcement process. While we did not review the effectiveness of the MedWatch system, we did note that albumin was regularly in the top 5 of 22 plasma products which were the subject of adverse event reports. We are recommending that the FDA task force determine if the intelligence gathered by the adverse event reports could be put to better use in the planning of inspections particularly with regard to the targeting of plasma fractionators and/or plasma products.

FDA Requirements For Public Warnings

Public warnings, as one element of a recall strategy, is addressed in 21 CFR Part 7 Section 7.42. The recalling firm, in consultation with FDA, develops a recall strategy. The strategy should consider the need for a public warning. If needed, the recall strategy should determine if the public warning should be through the general news media (national or local) or specialized news media, e.g., professional or trade press, or specific segments of the population (physicians, hospitals, etc.).

The FDA issues publicity when there is a scientific assessment of a likely association of a serious adverse reaction with exposure to the products, and where mass media publicity is felt to be the most effective means of communication, so that people will be aware of the situation and can take necessary precautions. According to FDA officials, publicity frequently needs to be initiated quickly to warn the public in a timely manner. Public warnings are often initiated before all the information, including laboratory tests, has been analyzed by FDA and before a recall has been classified. The FDA's Office of Public Affairs does not have firm criteria specifying which form of publicity to use for recalls. Rather, it has the flexibility to issue a press release, make a public statement, hold a press conference, and/or prepare a talk paper. The Office of Public Affairs determines which communication tool to use on a case-by-case basis, after consideration of such factors as the urgency of the information, the hazard involved, the distribution of the product, market availability, and the number of consumers affected.

A talk paper is prepared by the Office of Public Affairs to guide FDA personnel in responding with consistency and accuracy to questions from the public. The information contained in a talk paper is available to the public upon request. Talk papers are routinely distributed to media and consumers.

Use Of Press Release in Odwalla Recall

Odwalla, Inc. is headquartered in Half Moon Bay, California. Its juice processing plant is located in Dinuba, California. Odwalla products are distributed in California, Colorado, Nevada, New Mexico, Oregon, Texas, Washington, and Canada. Odwalla recalled 16 juice products including 12 apple juice-based juices, apple juice, carrot juice, organic carrot juice, and vegetable cocktail juice between October 31 and November 2, 1996. As of February 21, 1997, Escherichia coli contamination of juice products resulted in the death of a child in Colorado on November 8, 1996 and sickened 66 people.

A chronology of events surrounding the Odwalla recall is included as Appendix C to this report. While we did not evaluate the effectiveness of the recall, it is evident that both Odwalla and FDA reacted swiftly upon being notified of the problem by State and county officials. Odwalla and FDA were notified of the problem on October 30, 1996. Odwalla issued a "news advisory" the same day announcing its product recall. One day later, October 31, 1996, FDA and Odwalla issued a press release announcing the voluntary recall. Odwalla issued subsequent press releases and made the information available on the Internet.

Use of Talk Paper in Centeon Recall

Centeon is headquartered in King of Prussia, Pennsylvania and manufactures albumin in a plant located in Kankakee, Illinois. Between September 23 and October 9, 1996, Centeon conducted four recalls of plasma products, primarily albumin. Between August 23 and September 30, CDC initially identified 33 cases, including 11 deaths, with possible links to the recalled albumin. As of April 21, 1997, CDC was able to classify 2 cases with definite links to albumin, 6 cases with probable links, and 25 cases with no links. According to CDC, none of the deaths could be attributed to albumin.

A chronology of events surrounding the Centeon recall is included as Appendix D to this report. While we did not review the effectiveness of this recall (we were not requested to do so by the Subcommittee and the recall process was not complete at the time of our review), we believe that FDA's decision to issue three talk papers did not have an adverse impact on the recall. In addition to the three talk papers, FDA initiated an interview between the Associated Press[5] and a CBER official. The interview took place on September 27, 1996, 8 days after being informed that the sample tested by its laboratory was contaminated by Enterobacter cloacae, and 4 days after Centeon had upgraded its

5. The Associated Press represents about 6,000 newspapers nationally. We noted that 1 day after the meeting was held between FDA and the Associated Press, an article on the recall appeared in the *Philadelphia Inquirer*.

previous market withdrawal to a recall. The FDA also made the information available on the Internet. Centeon was also active in notifying its accounts, sub-accounts, hospitals and special interest groups of the albumin recall. Among the special interest groups notified were the National Hemophilia Foundation, the World Federation of Hemophilia and the American Blood Resources Association.

The FDA inspection of Centeon which began on September 27, 1996 ended on December 6, 1996. The inspection resulted in 87 observations and subsequently led to a consent decree that was entered on January 28, 1997. The consent decree required Centeon to cease distribution of all but two of its products while it brought its manufacturing standards into compliance with FDA statutes and regulations.

Internal Report on the Centeon Recall

At the request of the HHS Blood Safety Committee, a member of the Office of the Assistant Secretary for Legislation reviewed the circumstances surrounding the Centeon recall of albumin. Among the more serious findings included in the report were those dealing with: (1) FDA's response to the initial MedWatch adverse event report dated on August 24, 1996; and (2) the prior inspections of Centeon.

The report was highly critical of FDA's failure to respond to the adverse event report. Had it not been for the follow-up action taken by the initiating hospital on August 28, the delay in FDA's response would have likely increased. The report recommended that a thorough analysis of the MedWatch system should be considered to ensure that comprehensive medical reviews of adverse event reports are available at all times.

The report also questioned whether the current compliance system at FDA was sufficient to ensure the safety of biologic products. The report pointed out that FDA considered albumin to be a safe product with a long history of low-risk use. According to the report "albumin was not on the compliance radar screen prior to the recent contamination incident." Nevertheless, the report concluded that earlier inspections of Centeon's plant at Kankakee were a sign that environmental controls were insufficient and that there is a need to consider whether more forceful compliance policies are needed.

On January 24, 1997, the Commissioner of Food and Drugs responded to the internal report. He expressed agreement with the general thrust of the report that the Centeon problem could have been handled better. The Commissioner responded that FDA has assessed its performance, identified problems, and has taken steps to prevent future occurrences.

With regard to the MedWatch reports, the Centeon situation brought to light "unique and unjustifiable differences" in the way drugs and biologics adverse event reports were handled. These differences resulted in delays in acting on the Centeon report in a timely way. Improvements were made in policies and practices, and, according to the

Commissioner, since September 27, 1996, all adverse event reports on plasma products have been forwarded to CBER's Division of Biostatistics and Epidemiology within one business day for immediate evaluation which is in accordance with the new policy.

With regard to the inspection process, the Commissioner reported that it was evident in the Centeon situation that a lead FDA office for determining possible enforcement action was not clearly identified. As a result, FDA field offices will now take the lead in determining the necessity of inspection follow-ups. Further, FDA transferred the lead for periodic inspections of plasma fractionators and evaluation of the inspection findings from CBER to the field.

The Commissioner also reported that FDA has formed a task force to inventory all current procedures for handling reports of adverse events and product problems or defects. The task force will examine the ways in which reports are received and how the information is shared within FDA. The goal is to identify areas where improvement is needed and to make changes that will result in a more effective and efficient system.

Conclusions and Recommendations

We do not believe FDA's use of talk papers in lieu of a press release adversely affected the Centeon recall process especially in light of the press interview with the Associated Press and Internet distribution. The deficiencies identified in the report to the Blood Safety Committee are more serious, in our opinion. It appears as if FDA has or plans to make improvements in its inspection and enforcement process. As previously mentioned in this report, we believe ORA's increased role in the process will be extremely helpful. The establishment of a task force to continue monitoring performance is another noteworthy accomplishment.

In our opinion, one of the early focuses of the task force should be on the use of adverse event reports in targeting fractionators and/or products for inspection. The internal report prepared for the Blood Safety Committee stated that albumin was not on FDA's "compliance radar screen" prior to the Centeon incident. Our discussions with CBER personnel confirmed that inspections did not focus on albumin until after that incident because it was considered a safe product. Our review of adverse event reports submitted between January 1991 and April 23, 1997 showed that albumin was regularly in the top 5 of the 22 plasma products on which reports were received (Appendix E). Of the 3,386 adverse event reports received on the 22 plasma products, 209 (6 percent) reports involved albumin. Only four other plasma products were the subjects of more reports during this period. We believe this calls for further review by the task force.

We, therefore, recommend that the FDA:

6. Require the task force established in response to the internal report for the Blood Safety Committee to determine if the intelligence gathered by the

adverse event reports could be put to better use in planning inspections particularly with regard to the targeting of plasma fractionators and/or plasma products.

CBER's PARTICIPATION WITH AN INDUSTRY WORK GROUP TO REVIEW SALINE CONTAMINATION

The CBER chose not to implement the ORA's Chicago District Office recommendation to suspend the license of a plasma fractionator. Instead CBER participated with a work group organized by the plasma industry to address the potentially industry-wide problem of saline contamination. Both the HHS Office of General Counsel and OIG Office of Counsel believe CBER's participation with the industry group was neither illegal or unethical. The CBER prepared a report on saline contamination resulting from the work group activities.

We believe that FDA should consider further actions including: (1) determining if there is still a need to inspect the viral testing/inactivation procedures at the Hyland Division of Baxter Laboratories (Hyland); (2) following up on corrective actions taken by Baxter Healthcare Corporation (Baxter) and Haemonetics which were not previously included in the single safety alert; (3) requiring plasma collection and testing facilities to report all instances of saline contamination regardless of whether the plasma was released; and (4) finalizing the draft guides on the inspections of source plasma establishments and plasma fractionators.

Chicago District Office Inspection Identified Saline Contamination

The issue of saline contamination of samples used for viral testing of source plasma collected by certain plasmapheresis devices involves the backwash of saline into the sample collection tube when saline is reinfused to the source plasma donor at the completion of product collection to aid in volume replacement. Viral marker testing of saline contaminated samples may yield false negative results for hepatitis and HIV, and could result in the inadvertent use of potentially infectious units of source plasma in the manufacture of fractionated products.

Saline contaminated samples were identified during a March 1995 inspection at Baxter Screening Laboratory (BSL) conducted by an ORA inspector from the Chicago District Office. The BSL tests over one million units of plasma a year from 39 plasma centers nationwide. The plasma centers are contracted to supply plasma used in the manufacture of several fractionated products at Hyland. Baxter's Fenwal Division (Fenwal) manufactured the plasmapheresis devices used at the plasma centers. The BSL, Hyland, and Fenwal are related entities of Baxter.

The ORA inspection at BSL documented several samples that the laboratory had determined were saline contaminated, however, the plasma associated with those samples were not used in the manufacture of fractionated products but were discarded. According to a BSL official, saline contaminated samples have been identified by BSL since 1989. The ORA inspection concluded that BSL's investigation into the cause of the saline contamination was inadequate and that procedures may be inadequate to identify other saline contaminated plasma samples. In its March 27, 1995 response to Form FDA 483 findings, Baxter stated that Hyland's plasma pools used for the manufacture of finished products are tested for viruses. The viral load is further reduced by the large plasma pool size and the viral reduction procedures such as heat or solvent detergent treatment used in the manufacturing processes at Hyland. In effect, Baxter's position was that even if saline contaminated plasma was shipped to its Hyland plant, there would be no health hazard due to the testing and manufacturing procedures in place at the plant.

On March 30, 1995, the ORA Chicago District Office recommended that CBER suspend the fractionated product licenses issued to Baxter. The District Office also requested that: (1) other ORA district offices perform follow-up inspections at the plasma centers that had provided BSL with the saline contaminated samples; and (2) the Los Angeles District Office inspect the viral inactivation procedures in place at the Hyland facility where fractionated products are produced.

District Offices Conduct Follow-Up Inspections

Three follow-up inspections of source plasma collection facilities were conducted. The results indicated that BSL was inconsistent in its procedures for notifying collection facilities of saline contaminated samples. The BSL's daily computer test results sent to the facilities listed the contaminated sample as "not tested," rather than identifying the saline contamination problem. Two facilities stated that they had to call BSL to obtain an explanation for the samples not being tested. Only then did they learn of the saline contamination. The other facility reported that BSL notified it by telephone that a sample was saline contaminated. This facility performed an investigation and determined the cause to be operator error.

Two of the three ORA inspections resulted in no enforcement actions. The inspection of the third facility revealed significant deviations from standards and regulations and resulted in a recommendation to CBER for license suspension. Among the findings included an admission by a facility official that other plasma units had been found to be saline contaminated before the samples were sent to BSL for testing, however, no documentation was made of these instances, and no error and accident reports were made

to CBER because the units were not released from the facility.[6] The inspection found significant noncompliance in the areas of training and supervision, donor suitability determinations, record keeping, and standard operating procedures. A CBER Health Hazard Committee agreed that a danger to health existed and CBER suspended the licenses of this facility on April 21, 1995.

CBER's Response to ORA's Inspection

On April 4, 1995, CBER convened a Health Hazard Committee comprised of medical and scientific staff of OBRR to review the ORA recommendation to suspend the product licenses issued to Baxter. The committee concluded that the inspection findings did not provide sufficient information to determine existence of an imminent danger to health that warrants suspension of the licenses. In its April 5 disapproval letter to the Chicago District Office, CBER noted that the investigator's observations concerning sample integrity had identified important issues that warranted further review and follow-up. The CBER stated that it intended to raise these issues during an upcoming meeting with Baxter on April 13, 1995.

On April 6, 2 days after the Health Hazard Committee had met, CBER called the Los Angeles District Office and informed it that it was not necessary to inspect the viral inactivation procedures in place at the Hyland facility as was recommended by the Chicago District Office. The CBER said that the recommendation to suspend Baxter's product license had been disapproved, and that the District Office did not need to go in to verify validation of plasma fractionated products as this was a CBER obligation.

On April 13, representatives of CBER's Office of Compliance and OBRR, the Chicago District Office, and Baxter met to discuss the saline contamination issue. Baxter stated that the saline contamination resulted from failure to adhere to the instructions for use of its Autopheresis C plasmapheresis devices used to collect the source plasma. Baxter provided an action plan including a customer notification letter dated April 13, 1995, stressing adherence to the operator's manual and strongly recommending additional steps to further diminish the possibility of saline contamination. Additional steps included placing a hemostat on the plasma collection tubing at the end of the plasma collection procedure and removing the plasma collection container from the weight scale prior to saline reinfusion. In addition to verifying that all users received the notification, Baxter would modify the operator's manual and training video to reflect the revised procedures, and would audit compliance with the new procedure.

The CBER continued to assess the available information on saline contamination. It determined that two device manufacturers--Baxter's Fenwal Division and Haemonetics--

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6. When an error or accident occurs that may affect the safety, purity or potency of blood, licensed blood establishments are required to self-report the incident to FDA. The FDA has provided guidance to the blood establishments as to what constitutes a reportable error or accident.

produced the majority of the collection devices used in the source plasma industry. The CBER estimated that Haemonetics has about 60 percent market share and Baxter the remaining 40 percent. The CBER also determined that saline contamination had the potential to affect the entire source plasma industry and, therefore, decided to discuss the issue at the July 13, 1995 meeting with the American Blood Resources Association. This association represents firms that collect and produce blood and blood-related products. During the July meeting, CBER presented draft recommendations it developed for source plasma collection and testing facilities. The CBER recommended that these facilities examine and, if necessary, modify their procedures and training programs related to the prevention, detection, and investigation of saline contamination.

Saline Ad-Hoc Work Group Activities

In response to CBER's concerns, the American Blood Resources Association recommended that an ad-hoc work group, made up of plasma collection facilities, testing laboratories, and the two device manufacturers--Baxter and Haemonetics--be formed to discuss the saline contamination issue and to provide recommendations to prevent its occurrence. The group was known as the Ad-hoc Test Sample Dilution Work Group. The CBER was asked to participate in the work group led by the American Blood Resources Association. The CBER participants were from its Office of Compliance and OBRR. The CBER placed its draft recommendations to industry in abeyance until the ad-hoc work group's efforts could be evaluated.

The work group met over the next several months and its activities were documented in an August 19, 1996 summary report prepared by CBER. The CBER's report agreed with proposed ad-hoc work group solutions which included:

- design changes to the collection devices by the two device manufacturers to better detect and prevent saline contamination due to operator error during collection;
- increased training for operators of the collection devices; and
- increased communication between all parties when saline contamination is identified.

In addition to the ad-hoc work group proposed solutions, CBER also issued changes to its guide to inspections of viral testing labs designed to alert inspectors to the possibility of saline contaminated plasma. The CBER made similar revisions to its guide to inspections of source plasma establishments, however, the revisions are in draft form and have not been cleared for final issuance.

CBER's Participation Not Illegal But Further Actions Are Needed

Both the HHS Office of General Counsel and the OIG Office of Counsel believe that CBER's participation with the industry formed ad-hoc work group was neither illegal or unethical. The HHS Office of General Counsel added that the situation was not unusual. The FDA routinely cooperates with industry through such means as conferences and meetings to develop regulatory strategies.

We also solicited the views of a CBER official that participated with the work group. The official did not believe that partnering with industry in this instance represented a conflict of interest. The CBER's participation allowed it to monitor the industry's proposed solutions. Overall, CBER reported that it viewed participation in the ad-hoc work group as a success.

Although the focus of our review was to determine if CBER's participation in the work group was legal and ethical, we did note other issues associated with the saline contamination situation that, in our opinion, need further review by FDA.

Inspection at Hyland

On April 6, 1995, CBER notified the Los Angeles District Office that it was not necessary to inspect the viral inactivation procedures in place at the Hyland facility. We confirmed that the Los Angeles District Office did not make this follow-up inspection. The CBER officials told us that the inspection was not necessary because the members of the Health Hazard Committee which had determined that a health hazard did not exist, were knowledgeable about the effectiveness of the viral inactivation procedures used in the production of Baxter's products and had considered these procedures during their assessment of the health hazard.

We noted that a GMP joint inspection of Hyland was conducted in August 1996. The inspection resulted in 25 observations of objectionable conditions and a warning letter was issued on October 18, 1996. We reviewed the Form FDA 483, the EIR and the warning letter and found no mention made of any review of Hyland's viral/testing inactivation procedures. The ORA inspector who participated in the inspection was not aware that the inactivation procedures were included in the 1996 inspection. He informed us that an inspection of Hyland, including the viral testing/inactivation procedures, is underway as of May 12, 1997. If this is the case, no further action is needed.

Medical Device Safety Alerts

Some of the corrective action proposed by Baxter and all of the corrective action proposed by Haemonetics was not monitored adequately by CBER to ensure that the actions were taken as planned and that they were effective. The reason for this lack of monitoring is

that safety alerts were not issued for these actions. We believe FDA needs to consider if safety alerts are now appropriate.

Based on Baxter's April 13, 1995 action plan, the Chicago District Office recommended to CBER that the firm's actions be classified as a voluntary medical device safety alert.[7] The CBER concurred on November 17, 1995. This was the only safety alert issued relative to the saline contamination situation. No alert was issued for additional actions taken by Baxter that were not included in its initial plan, nor was an alert issued to monitor the corrective action proposed by Haemonetics.

The FDA defines a medical device safety alert as a communication voluntarily issued by a manufacturer, distributor, or other responsible person to inform health professionals and other appropriate persons of a situation that may present an unreasonable risk of substantial harm to the public health by a device in commercial distribution and intended for human use, in order to reduce or eliminate the risk. Safety alerts are handled by ORA district offices in the same manner as recalls. They go through the stages of alert, recommendation, classification, field notification, firm notification letter, effectiveness checks and status reports, FDA audit checks, and termination recommendations.

The Chicago District Office issued audit checks which consist of a personal visit, telephone call, letter or a combination thereof made for the purpose of verifying that all of the firms specified by the recall strategy have received notification and taken appropriate action. Five plasma centers/blood banks were visited and one plasma center was contacted by telephone. All six locations had received the safety alert, and the Chicago District Office concluded that the overall safety alert effort was effective.

In a report to FDA, Baxter estimated that 4,633 Autopheresis C devices were distributed to 95 blood banks and 166 plasmapheresis centers nationwide. Baxter sent notification letters, revised user manuals and training videos to 258 direct accounts and 7 corporate offices of commercial plasmapheresis centers. Baxter confirmed receipt through Federal Express proof of delivery or faxed communications.

Subsequent to the safety alert, Baxter made a software modification that, in Baxter's view, should prevent the potential for saline dilution. At the end of the collection cycle and prior to the saline reinfusion, the operator is prompted to seal the disposable set and remove the product bag and plasma line used for testing. The machine will not allow the operator to continue until the product is removed. This is determined through the product weight scale sensor. Baxter field tested the modification during March 1996 and estimated that implementation would begin in early summer and be completed within 6 months. As of October 1996, Baxter reported that 90 percent of the instrument

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7. An intercenter agreement dated October 31, 1991 between CBER and CDRH specifies that CBER is the lead center for regulating certain medical devices utilized in the collection, processing or administration of biological products.

conversions have been completed. The modification was not subject to a safety alert or to audit checks to determine the effectiveness of the modifications.

The Haemonetics PCS plasma collection device was also never subject to a safety alert, and thus audit checks were not issued although the Haemonetics reportedly made changes to its device to prevent the potential for saline contamination. These changes included a modification to the collection bottle set tubing by Alpha Therapeutic Corporation, the manufacturer of the bottle and to the PCS pinch valve assembly; and revision of the PCS software that would report a plasma bag weight change greater than 4 grams since the last collection cycle (indicating a possible saline clamp failure). The firm estimated that conversion of all machines would begin in May 1996 and take about 6 months.

Communications

An important recommendation resulting from the ad-hoc work group was to increase communication, documentation and investigation among testing laboratories, collection centers, and device manufacturers when saline contamination is encountered and to document and investigate reports of possible saline contamination. The Chicago District Office's inspection of BSL and subsequent inspections of the collection facilities that had submitted saline contaminated samples revealed that those firms had not adequately reported or investigated the known instances of saline contamination even though most were aware of the problem.

We asked CBER if any of the firms involved in those inspections had submitted reports to CBER, either error and accident reports (EARs) or medical device reports (MDRs), that contained references to saline contamination. The CBER stated that they had not since neither were required under FDA regulations. The CBER stated that under current regulations for EARs, testing laboratories and collection facilities are not required to report identified instances of saline contamination. Units of collected plasma are under quarantine until screening tests are performed. If a unit is found to be saline contaminated or tests positive for HIV or hepatitis the unit is removed from quarantine and destroyed. An EAR would be required only if the contaminated unit was mistakenly released for further processing. An MDR is required for any event associated with a death or a serious injury. Malfunctions of devices that are likely to cause or contribute to a death or serious injury would also be reported under the MDR.

Although communications may have improved among testing laboratories, collection centers, and device manufacturers, there is no assurance that CBER will be connected to the improved communication lines. The BSL knew about the saline contamination problem since 1989 but it apparently did not inform CBER. Other information indicates that Haemonetics was aware of this problem since 1992, but again CBER was not notified. It was not until March 1995 that CBER was made aware of this problem as a result of an inspection conducted by the Chicago District Office.

Since saline contamination is a unique problem--CBER determined it had the potential to affect the entire source plasma industry, and the industry responded with a task force--we believe a unique solution is required. According to CBER, current regulations did not require reporting of the saline contamination through either the EAR or MDR reporting systems. As a result, a problem known to the plasma industry was not reported to FDA. We believe that plasma collection and testing facilities should be required to notify CBER of instances of all known saline contamination regardless of whether the contaminated products were released, until CBER is convinced that the saline contamination problem is corrected.

CBER Guides for Source Plasma Establishments and Fractionators

The CBER is in the process of revising its inspection guide for source plasma establishments and drafting a compliance program guide for plasma fractionators. The revisions to the source plasma guide contain a section dealing with saline contamination. The CBER informed us of the industry's initiatives and alerted the ORA district offices to the saline contamination problem in a September 20, 1995 teleconference. –

One of the purposes of the draft compliance program is to provide information and guidance to inspectors and to prepare them to conduct biennial inspections of plasma fractionators. The draft program mentions the importance of viral inactivation/removal and the need for validation. We believe FDA should accelerate the approval process for the guide and the compliance program.

Conclusions and Recommendations

According to the OIG Office of Counsel and the HHS Office of General Counsel, CBER's participation with the industry work group was neither illegal or unethical. Overall, CBER reported that it views its participation in the ad-hoc work group as a success. Our review, however, identified issues that were not fully addressed during CBER's examination of the saline contamination problem or during its involvement with the American Blood Resources Association's ad-hoc work group. We, therefore, recommend that FDA:

7. Verify that the inspection of Hyland, ongoing as of May 12, 1997, includes a review of viral inactivation procedures. If the procedures were not included, require such an inspection.

8. Review the changes made to the plasma collection devices to determine whether they meet the criteria for classification as medical device safety alerts.

9. Consider requiring plasma collection and testing facilities to report all incidents involving saline contamination.

10. Finalize and implement the draft changes to the inspection guide for source plasma establishments and the compliance program for plasma fractionators.

FDA'S RESPONSE AND OIG COMMENTS

On June 3, 1997, we received FDA's written response to the recommendations contained in a draft of this report. The comments consisted of editorial and factual comments and the status of implementation of our recommendations. We made those editorial and factual changes to this report that were appropriate and supported by documentation. The FDA's written response is included in this report as Appendix F.

The FDA generally agreed with our recommendations and has begun implementing them. Most importantly, FDA has developed a plan for regulating all biologic products. The plan entitled, "Team Biologics--A Plan for Reinventing FDA's Ability to Optimize Compliance of Regulated Biologics Industries," is dated May 28, 1997. It redefines the working relationship between CBER and ORA. It also sets dates to transition lead inspection responsibilities for all biologic products currently being inspected by CBER to ORA. The FDA also noted that the ongoing inspection of Baxter's Hyland facility (OIG recommendation number 7) resulted in a Class III recall. Specifically, Baxter has recalled 9 lots of Antihemophilic Factor (Human).

Although FDA's response to our report was generally positive, we believe two of our recommendations were not fully addressed by FDA. In responding to our recommendation dealing with the possibility of safety alerts for the changes made to the plasma collection devices (OIG recommendation number 8), FDA stated that a safety alert has been issued for the Baxter device, and that CBER was consulting with ORA to determine if any regulatory action is justified for the Haemonetics device. We were aware of the safety alert referred to by FDA in its response. However, as noted in this report, subsequent to this safety alert, Baxter made a software change that, in its opinion, should prevent the potential of saline contamination. We believe that FDA should determine whether this Baxter software modification meets the criteria for classification as a medical device safety alert.

In responding to our recommendation dealing with mandatory reporting of saline contamination incidents (OIG recommendation number 9), FDA stated that it was considering issuing a memorandum to industry clarifying when saline contamination constitutes a reportable event. We believe that the memorandum should be issued and that all incidents of saline contamination should be reported to FDA, regardless of the disposition of the plasma. Without this intelligence, CBER will not have the information needed to assess whether proposed industry solutions have been fully effective in correcting the saline contamination problem.

APPENDICES

PLASMA FRACTIONATORS

Fractionator	Manufacturing Location
Abbott Laboratories	North Chicago, Illinois
Alpha Therapeutic	Los Angeles, California
Baxter Healthcare Corporation	Brussels, Belgium
Baxter Healthcare Corporation	Los Angeles, California
Bayer Corporation	Berkeley, California
Bayer Corporation	Clayton, North Carolina
Cangene Corporation	Winnipeg, Canada
Central Laboratory Blood Transfusion Service Swiss Red Cross	Berne, Switzerland
Central Laboratories of the Netherlands Red Cross Blood Transfusion Service	Amsterdam, Netherlands
Centeon, L.L.C.	Kankakee, Illinois
Centeon Pharma GMBH	Marburg, Germany
Gentrac, Inc.	Middleton, Wisconsin
Immuno-US	Rochester, Michigan
Instituto Grifols, S.A.	Barcelona, Spain
Kabi Pharmacia	Stockholm, Sweden
Massachusetts Public Health Biologic Laboratories	Boston, Massachusetts
Michigan Biologic Products Institute	Lansing, Michigan
Oesterreichisches Institut fur Haemoderivate	Vienna, Austria
Ortho Diagnostic Systems, Inc.	Raritan, New Jersey
Parke-Davis	Dublin, Ireland
Parke-Davis	Rochester, Michigan
Pasteur Merieux Serums et Vaccins	Lyon, France
Speywood Biopharm, Limited	Wrexham, United Kingdom
The Upjohn Company	Kalamazoo, Michigan
V.I. Technologies	Melville, New York
Wellcome Foundation, Limited	Dartford, United Kingdom

FORM FDA 483 OBSERVATIONS

Type of Observation	CBER FDA 483 Observations		Joint FDA 483 Observations	
	Inspections Cited		Inspections Cited	
Air/Water	22	10.9%	176	22.4%
	10	30.3%	24	80.0%
Building/Facilities	10	5.0%	15	1.9%
	7	21.2%	8	26.7%
Equipment	20	10.0%	41	5.2%
	12	36.4%	16	53.3%
Labeling	19	9.5%	19	2.4%
	10	30.3%	13	43.3%
Laboratory	4	2.0%	28	3.6%
	4	12.1%	10	33.3%
Production	26	12.9%	94	11.9%
	11	33.3%	19	63.3%
Quality Control/ Quality Assurance	18	9.0%	169	21.5%
	11	33.3%	23	76.7%
Raw Materials	5	2.5%	23	2.9%
	5	15.2%	7	23.3%
Records	17	8.5%	40	5.1%
	12	36.4%	17	56.7%
Software	0	0.0%	23	2.9%
	0	0.0%	2	6.7%
Standard Operating Procedures	39	19.4%	108	13.7%
	18	54.5%	22	73.3%
Storage	15	7.5%	36	4.6%
	11	33.3%	13	43.3%
Training	0	0.0%	7	0.9%
	0	0.0%	4	13.3%
Unreported Changes	6	3.0%	8	1.0%
	5	15.2%	6	20.0%
Total Observations	201	100%	787	100%
Total Inspections Cited	27	81.8%	28	93.3%

CHRONOLOGY OF EVENTS SURROUNDING THE ODWALLA RECALL

October 21, 1996 Reports of Escherichia coli contamination first surfaced. Initial reports of food contamination were investigated by State and county officials from the Washington State Department of Public Health and the Seattle-King County Department of Public Health.

October 30 State and county officials held a joint news conference regarding the possible contamination of Odwalla apple juice product. The Seattle-King County Department of Public Health asked Odwalla to pull all its products containing apple juice from the retail market until further notice.

Odwalla agreed and issued a "news advisory" announcing its product recall of fresh apple juice, 12 other apple based juice products, carrot juice, organic carrot juice, and vegetable cocktail juice due to several confirmed cases of Escherichia coli bacteria in the State of Washington. In most cases, Odwalla's fresh apple juice was linked to those diagnosed with the bacteria.

The FDA Commissioner was notified of the Odwalla apple juice recall at about 6:00PM EST. A teleconference was set up with CFSAN representatives, the Associate Commissioner for Regulatory Affairs, officials from FDA district offices in Seattle, San Francisco, and Denver, the Seattle-King County Department of Public Health, State Health Departments for Washington, Oregon, Colorado, and California, the Center for Disease Control, and Odwalla. All parties agreed that the epidemiological data from the studies performed by the Seattle-King County Department of Public Health and the Washington State Department of Public Health, very strongly implicated Odwalla apple juice. The FDA initiated an investigation of the Odwalla production plant in California.

October 31 The FDA issued Press Release P-96-17 announcing the voluntary recall of all Odwalla brand apple juice products. The press release noted 13 confirmed cases of Escherichia coli illnesses between October 15 and October 24. Ten of the 13 cases were linked to Odwalla apple juice. Odwalla issued another press release in conjunction with a press conference it conducted regarding its recall. Odwalla also dispatched 175 trucks to remove apple juice products from store shelves throughout the West and parts of Canada.

The FDA and CDC met with various industry groups, including the U.S. Apple Association, to discuss the Escherichia coli outbreak associated with Odwalla apple juice products.

November 1 Odwalla began providing the apple juice recall information on the Internet.

November 2 Odwalla announced that its recall has been completed (product has been removed from shelves in 4,600 retail outlets).

November 4 Odwalla issued a press release confirming FDA's finding of Escherichia coli bacteria.

November 15 Odwalla issued a press release stating that FDA officials have not found any Escherichia coli bacteria in its Dinuba, California plant.

December 16-17 The FDA held a public meeting to discuss the Escherichia coli outbreak.

CHRONOLOGY OF EVENTS SURROUNDING THE CENTEON RECALLS

August 23, 1996 A 50 year old male patient in a hospital in Wichita, Kansas experienced an adverse event after being treated with albumin, a plasma product. One vial of albumin, which was later determined to be contaminated with Enterobacter cloacae bacteria.

August 24 The hospital in Wichita, Kansas reported the adverse event to Centeon and the MedWatch System. According to the MedWatch report filed by the hospital, the patient complained of "shakes and chills" after receiving the first dose of albumin, and again after a second dose. Both the patient's blood and the patient's bottle of albumin were cultured "gram negative rods" which means there is bacteria present.

August 28 An employee of the same hospital contacted ORA's Wichita Resident Post to follow-up on the hospital's report. The employee informed the Resident Post investigator that the patient had suffered from uncontrollable shivering, increase in temperature to 104.9F, and fluctuation of his blood pressure within 5-10 minutes after receiving albumin. The investigator was also informed that both the patient's blood and the patient's bottle of albumin cultured Enterobacter cloacae bacteria. The Resident Post contacted ORA's Kansas City District Office (KAN-DO) who then contacted ORA's Division of Emergency and Investigational Operations (DEIO) for directions on how to proceed.

August 29 The DEIO contacted CBER's OBRR Division of Hematology for guidance. The Division advised DEIO on the sampling and testing procedures and notified CBER's Office of Establishment Licensing and Product Surveillance (OELPS) Division of Product Quality Control (DPQC). The KAN-DO initiated an investigation of the Wichita hospital's pharmacy.

September 3 Centeon mailed a letter describing the incident to CBER's OELPS Division of Biostatistics and Epidemiology (DBE) as a 15-day Adverse Event Report. According to the report filed by Centeon, the albumin bottle used by the patient and the patient's blood both came back with the same isolate, Enterobacter cloacae.

September 4 The Wichita Resident Post collected 10 samples at the hospital.

September 10 The Wichita Resident Post sent samples obtained from the hospital to DPQC for testing.

September 11 The CBER-DBE received Centeon's 15-day Adverse Event Report, which was mailed on September 3rd.

September 13 The FDA test results confirmed the existence of bacterial growth. The DPQC scientists decided additional tests were required to confirm the positive results and asked for more samples of the product. The DPQC also sent isolates from the original sample to one of its contractors to identify the bacteria.

September 16 The DPQC notified the Wichita Resident Post that the first sample was positive for Enterobacter cloacae and additional samples were needed for testing.

September 18 The DPQC reported that the second sample tested negative and requested that the Wichita Resident Post obtain a third sample.

September 19 The laboratory contractor identified the bacterial growth in the original sample as Enterobacter cloacae. The DPQC notified CBER's Office of Compliance of the results and the Office of Compliance called Centeon to determine their intent in light of the results.

September 20 Centeon telephoned 28 direct accounts and 232 sub-accounts that received the defective lot (17,000 vials) and initiated a voluntary market withdrawal. Centeon instructed its accounts to cease use of the lot and return the product to its distribution center in Illinois.

September 23 After Centeon discovered the presence of cracks in the returned vials, it upgraded the market withdrawal to a recall, and re-contacted by telephone the 260 direct and subaccounts. The telephone contacts were confirmed in writing by an "Urgent Biological Recall" notice sent via Federal Express.

September 24 Centeon sent a "Statement on Voluntary Biologic Recall" (dated September 23) via First Class Mail to 7,143 hospitals advising them of the recall. Centeon also sent this document to special interest groups, including the National Hemophilia Foundation, the World Federation of Hemophilia and the American Blood Resources Association. The document was made available to the press upon request.

The CBER-DPQC received the third albumin sample from the Wichita hospital.

September 27 Centeon reported an adverse event in Green Bay Wisconsin to DBE. Between September 6 and September 16 the patient had received 37 vials of the same lot of albumin associated with the Wichita case. On September 16, the patient had a positive blood culture for Enterobacter cloacae.

The CBER completed its health hazard evaluation and within one hour conducted an interview with the Associated Press (AP) detailing the albumin recall. The AP services approximately 6,000 newspapers and news services. The following day, an article addressing the recall appeared in the *Philadelphia Inquirer*. The Centeon corporate headquarters is located in the Philadelphia, Pennsylvania area.

The CBER-DBE reviewed the 15-day alert report mailed by Centeon on September 3rd.

The FDA Chicago District Office initiated, with CBER's permission, an inspection of the Centeon facility in Kankakee, Illinois. The inspection and confirmed that dropped pallets containing vials of albumin and other products caused the problem.

October 2 Centeon expanded the recall of albumin to nine additional lots bringing the total number of vials recalled to over 100,000. During this period the National Notification Center (NNC), contracted by Centeon, telephoned and faxed 7,812 hospitals, clinics, and intravenous infusions centers to the attention of the Director of the Pharmacy and the Director of the Blood Bank, informing them of the recall. The NNC followed up with a first class mailing to the hospitals. These notifications were also made to 2,156 dialysis centers, 167 endocrine/obstetrics specialists, 1,964 fertility clinics and many special interest groups. Recall letters were sent to the estimated 600 direct accounts.

October 3 The FDA issued Talk Paper T-96-65 on the expanded recall, and the AP released an article on the recall.

October 4 Centeon initiated a third recall, for one lot (1,600 vials) of another plasma product, Monoclate P antihemophilic factor (human). Centeon faxed an "Urgent Biologic Recall Notice" to the 24 direct accounts who received the recalled lot. Hard copies were mailed to these accounts on October 7. The FDA issued Talk Paper T-96-67 and the AP released an article on the Monoclate P recall.

October 9--October 11 As a precautionary measure, Centeon expanded the albumin recall to all in-date lots of albumin and Plasma Plex PPF, another albumin product. The expanded recall included an additional 975 lots of albuminar and 290 lots of Plasma Plex PPF. Centeon began telephoning 5,194 sub-accounts informing them of the expanded recall. Between October 9 and 10, NNC telephoned and faxed 7,812 hospitals, clinics, and intravenous infusion centers informing them of the recall. On October 11, the NNC followed up with a first class mailing to 7,812 hospitals, 2,156 dialysis centers, 1,964 fertility clinics, 167 endocrine/obstetrics specialists, and 1,964 fertility clinics.

The FDA issued Talk Paper T-96-69 on the expanded recall. The recall was also covered by the AP.

ADVERSE EVENTS FOR PLASMA PRODUCTS: 1991 - 1997

Plasma Product	91	92	93	94	95	96	97*	TOTAL
Immune Globulin Intravenous (Human)	118	143	87	401	334	255	57	1395
Antihemophilic Factor (Human)	9	20	33	30	68	399	4	563
Alpha-1 Proteinase Inhibitor (Human)	57	34	91	80	160	22	1	445
Immune Globulin (Human)	12	18	28	54	45	87	4	248
Albumin (Human)	23	26	26	25	24	72	13	209
Factor IX Complex	1	4	0	1	2	87	0	95
Rho(D) Immune Globulin (Human)	1	1	1	3	35	47	0	88
Coagulation Factor IX (Human)	2	2	14	11	11	17	0	57
Respiratory Syncytial Virus Immune Globulin Intravenous (Human)	0	0	0	0	0	3	46	49
Thrombin	7	10	3	8	3	10	8	49
Plasma Protein Fraction (Human)	0	3	5	4	9	15	1	37
Rho(D) Immune Globulin Intravenous (Human)	0	0	0	0	4	24	1	29
Cytomegalovirus Immune Globulin Intravenous (Human)	0	0	7	0	8	6	4	25
Digoxin Immune Fab (Ovine)	6	8	3	4	2	0	0	23
Antihemophilic Factor (Porcine)	0	8	5	1	2	2	0	18
Antithrombin III (Human)	0	0	0	1	3	13	0	17
Hepatitis B Immune Globulin (Human)	1	0	3	4	7	1	0	16
Rabies Immune Globulin (Human)	0	2	0	2	4	1	1	10
Anti-Inhibitor Coagulant Complex	1	1	0	0	1	3	0	6
Varicella-Zoster Immune Globulin (Human)	0	0	1	0	3	1	0	5
Tetanus Immune Globulin (Human)	0	0	0	0	1	0	0	1
Hemin for Injection	0	0	0	0	1	0	0	1
TOTAL	238	280	307	629	727	1065	140	3386

* Through April 23, 1997

DEPARTMENT OF HEALTH & HUMAN SERVICES

Memorandum

FDA'S RESPONSE

Date: JUN - 3 1997

From: Lead Deputy Commissioner, FDA

Subject: Review of the Discussion Draft of the Food and Drug Administration's Inspection Process for Plasma Fractionators (CIN: A-03-97-00350)

To: Joseph J. Green
Assistant Inspector General
For Public Health Service Audits

I appreciate the opportunity to review and comment on the Office of Inspector General Discussion Draft of the Review of Food and Drug Administration's Inspection Process of Plasma Fractionators.

I am providing the Food and Drug Administration's (FDA) comments to the report and its recommendations. FDA's comments fall within three major categories, editorial, factual and the status of implementation.

Michael A. Friedman, M.D.

Attachment

AGENCY COMMENTS ON OFFICE OF INSPECTOR GENERAL DISCUSSION DRAFT REPORT ENTITLED, "FOOD AND DRUG ADMINISTRATION'S INSPECTION PROCESS FOR PLASMA FRACTIONATORS" (CIN: A-03-97-00350)

I. Editorial

Executive Summary, page I, second paragraph, third line - insert after the word " responsibility": "This situation stems from the fact that biologic inspections were not conducted by FDA before the responsibility for conducting biologic inspections was transferred to the FDA during the 1972 reorganization ."

Executive Summary, Page ii - Sixth bullet, first, line, change the word "Drugs" to "Drug".

Background, Page 1, first paragraph, first line - Change to read: "The Food and Drug Administration (FDA) receives its **primary** regulatory authority through the Federal Food, Drug and Cosmetic Act. The FDA is responsible for helping to ensure the safety..."

Page 1, first bullet - Rewrite to read: "CBER is the Center within FDA that regulates biological and related products including blood, vaccines, and biological therapeutics manufactured for interstate commerce or sale."

Page 1, third bullet- Rewrite to read: "CDER regulates human drugs manufactured for interstate commerce or sale".

Page 2, first paragraph, third line - Change to read "CBER is the Center within FDA that regulates blood, blood products and other biologics."

Page 2, paragraph 3 at the end of the first sentence - Add "Plasma may also be obtained by separation from collected whole blood".

Page 2 at the end of paragraph 6 - The definition of a biological product is found in the PHS Act section 351(a). Like biologics, drugs are defined in section 201(g)(1) of the FD&C Act. Therefore, biologics are also drugs.

Page 2, last paragraph, line 3 - The number 200 appears to include plasma fractionators but it excludes blood and plasma collection facilities. CBER/OBRR regulates approximately 300 licensed blood establishments and approximately 2300 registered intrastate blood establishments.

Page 2, first paragraph, replace first line with - "CBER's regulatory authority is found in the Federal Food, Drug, and Cosmetic Act, and the Public Health Service Act."

Page 3, first paragraph, replace the second and third sentences with - "The Inspection Task Force (ITF) schedules and participates in the planning of establishment inspections. Within CBER, blood and blood product inspections are conducted by OBRR."

Page 3, first paragraph - Change the first sentence to read "ORA's regulatory authority is found in the Federal Food, Drug and Cosmetic Act and the Public Health Service Act.

Page 3, first paragraph, following the sentence ending in "post-market controls" - Add a new sentence: "In addition, ORA conducts pre-approval inspections for drugs and devices."

Page 3, second paragraph, fifth line - Delete the number "6" and change to "5" regional offices.

In the sentence beginning with,"Inspections are conducted..." following the "trained to inspect", add: "more than one product area, i.e., Foods, Drugs, and Devices. "A specialist is trained to inspect/investigate certain entities and becomes highly skilled in that area. A generalist is trained in multiple areas and disciplines. GMP compliance may be among them."

Page 6 (footnote) -Although the footnote contains three accurate statements about MedWatch, it does not reflect its role in outreach efforts to educate health professionals about reporting and to inform them quickly of important new safety information.

Page 8, first bullet - Change to read "The Federal Food, Drug, and Cosmetic Act 21 U.S.C. 301 et. seq. and /or the Public Health Service Act (42 U.S.C. 262-264), "

Page 8, second bullet - Change to read "Good Manufacturing Practices as defined under 21 CFR Parts 210-211, 600-680, and if a device, Part 820, and"

Page 9, third paragraph, first line - beginning with "An endorsement of an EIR is required to....",Change to read: "An endorsement of an EIR serves to..."

Page 10, second paragraph, Administrative actions, third line - Change to read " A license revocation resulting from violations of the licensing standards or regulations withdraws the firm's authority to ship a biological product in interstate commerce. A suspension also withdraws the firm's..."

Page 10, third paragraph- Judicial actions, seventh line - Change last sentence beginning with Referrals to read: "In most instances, referrals for criminal prosecution proceed only after the firm has had an opportunity to address the charges."

Page 10, fourth paragraph, Product recalls - After the last sentence add, "Section 351(d)(2)(A) of the Public Health Service Act authorizes the FDA to order a biologic recall upon a determination that a batch lot or other quantity of a product presents an imminent or substantial hazard to the public health."

Page 10, fifth paragraph - Sentence beginning with: "Inspections of fractionators":..insert after the word "fractionators" "who were also dual processors, were to be".

Following the last sentence ending in the word action, add a new sentence to read: The 1992 agreement placed a greater emphasis on domestic drug manufacturers. The field staff participation in the inspections of fractionators was enhanced in 1994. The participation of the field staff in the inspections of foreign manufacturers is dependent on available resources, including travel funds and investigators available to travel. (Twelve of the 26 fractionators are foreign manufacturers).

Page 11 - Correct the last sentence by deleting "FDA's Office of General Counsel" and replacing with "FDA's Office of the Chief Counsel and,....".

III. Insert into shaded box on page 11 - **"Joint inspections of Plasma Fractionators involving ORA resulted in more reported observations of objectional conditions and more enforcement actions than inspections conducted solely be CBER."**

Insert in lieu of third paragraph on page 11 - *"Inspections involving ORA staff (these inspections also involved CBER staff and are referred to in this report as joint inspections) resulted in four times as many observations and three times as many enforcement actions as inspections involving only CBER staff."*

Page 18, paragraph 1, last line - Change the word,
"bi-annual" to " semiannual."

II. Factual

Pages I and ii - The report refers to "internal talk papers." Talk papers are public documents routinely distributed to media and consumers, as well as being published on the FDA's Home Page on the world-wide web. To characterize them as "internal is incorrect.

Page ii - The report states: "Although FDA did not issue a press release on the plasma product albumin, it did initiate a meeting with the Associated Press which represents about 6,000 newspapers." A more accurate statement would be: "Although FDA did not issue a press release on the plasma product albumin, it did call the Associated Press and arranged an interview with the appropriate FDA personnel. The AP did publish a story about the albumin recall on its wire which services more than 6,000 newspapers and hundreds of

broadcast outlets (television and radio) across the country."

Page ii, third bullet - concerning CBER's policy to not pre-notify and the SOP on obtaining production schedules. Fourth line down beginning with CBER recently established ....Change to" "CBER recently established a written Standard Operating Procedure (SOP) for obtaining production schedules, dated November 20, 1996. CBER did not comply with the SOP because letters to all licensed manufacturers were not mailed per the SOP. We were informed that the Office of Compliance made a decision to contact the manufacturers by telephone to expedite obtaining production schedules while a draft letter was pending.

Executive Summary, page iii, third bullet - Change to: "CBER concurred with the Los Angeles District's recommendation to defer an inspection of a plasma fractionator that had been recommended by the Chicago District." Continue with, "A regularly scheduled..." following the last sentence of this bullet ending with the word "procedures".

Page 2 - Substitute for Paragraph 5 - There are 26 US licensed plasma fractionators who manufacture plasma derivatives. These 26 manufacturers are located world wide. In fact, 12 of the 26 are located in foreign countries. Twenty of the 26 manufacturers process human blood. The remaining six, process animal blood. Nine of the 26 manufacturers also manufacture products regulated by other FDA Centers. These fractionators are called dual processors. A listing of licensed fractionators can be found in Appendix A. The majority of the 26 manufacturers may be characterized as "primary" fractionators, and may also operate as an "intermediate" in that they may also further manufacture a bulk paste or powder received from another fractionator into a finished product. While some manufacturers may be licensed to manufacture one or more plasma derivatives, they may not have done so for a number of years.

Page 3, first paragraph - Describes the inspection program at CBER prior to implementation of the ORA lead for plasma fractionation inspections. As written, the report suggests that CBER's Office of Establishment Licensing and Product Surveillance (OELPS) has been involved in routine, inspections of plasma fractionators. It should be noted that this has not been the case. From 1992-1995, a total of 40 inspections of plasma fractionators were performed (CBER alone and joint). OELPS' Division of Establishment Licensing (DEL) was involved in only nine of these inspections; four of which were prelicense, and one (Michigan) which resulted in a warning letter. DEL's involvement really began in Fiscal Year 1996, which is the same time that the field's participation grew. It should be noted that there had not been an emphasis on GMPs focus during most of the inspections performed pre-1996.

The increase noted for observations related to GMPs may be due, in part, to DEL's involvement in inspections of plasma fractionators.

Page 3, first paragraph, second sentence - beginning with "The ITF schedules...." following the word "inspections", begin a new sentence to state: "The ITF team members prepare Establishment Profiles which consists of the manufacturer's compliance history, previous EIRs and 483s, a list of pending supplements, errors & accident reports, adverse event reports, and additional information that is necessary to perform an inspection. Profiles are provided to all team members. The team member responsible for the specific product line holds a pre-inspection meeting with both CBER staff and Field ORA staff and during these meetings specific guidance is provided to the inspection team. In addition, during the inspection, the team is encouraged to call the ITF for guidance and direction when it is necessary. The ITF coordinates with ORA's biologics team to resolve problems. In addition, the ITF reviews, endorses, and classifies CBER inspection reports. The team is also involved in developing inspection policy and assists in training FDA inspectors. The Office of Compliance believes that the ITF serves an important function."

Page 9, first bullet - Delete this bullet.

Page 9, Section on "Inspections of Plasma Fractionators" - second paragraph beginning, "At the conclusion ..." ,change the last sentence in the paragraph beginning with: "The EIR ..." to read: "FDA policy states that non-violative EIRs should be completed within 30 days of the inspection. Violative EIRs which are classified OAI and prompt a regulatory action recommendation, i.e., a Warning Letter, which must have Center concurrence, should be completed by the District within 15 days so that the Center has 15 days to review the report and the evidence, that support the issuance of the letter."

Page 16, first paragraph - This should include a statement that the 45 day time frame for non-violative reports was established prior to 1992. In efforts to harmonize with written agency policy, CBER changed the 45 day policy in 1995.

Page 17, following bullets on inspection report classifications - Add a statement: "We have been advised on May 27, by the current team leader of the ITF that those EIRS lacking an endorsement/classification are being classified and evaluated to determine appropriate follow-up action. "

Page 22, paragraph 3 - The quotation from FDA's Office of Public Affairs should be revised to conform with a statement that was provided to Susan Strinkowski as follows:

"FDA issues publicity when there is a scientific assessment of a likely association of a serious adverse reaction with exposure to the products and where mass media publicity is felt to be the most effective means of communication, so that persons will be aware of the situation and can take necessary precautions."

Page 22 - Modify the first sentence of the third paragraph: "According to officials of the FDA's OPA, sometimes public health warnings must be issued before the recall strategy is

formulated and before a direct link has been established between the recalled product and the adverse events."

Page 23, first paragraph, fifth line - The report states: "One day later, October 31, 1996, FDA and Odwalla jointly issued a press release announcing the voluntary recall: A more accurate statement would be: "One day later, October 31, 1996, FDA and Odwalla issued press releases announcing the voluntary recall."

Page 23, third paragraph, fifth line - The report states: "In addition to three talk papers, FDA initiated a communicator to discuss the recall with the Associated Press on September 27, 1996, eight days after being informed that the sample tested by its laboratory was contaminated by Eneterobacter cloacae, and four days after Centeon had upgraded its previous market withdrawal to a recall." With regard to the timing, OPA arranged the interview within an hour of being notified by CBER that it had completed its health hazard evaluation and that it believed general press notification was appropriate even though albumin is administered solely by health professionals and would not likely be in the hands of consumers.

Page 23, third paragraph - Change the last sentence to read "Among the Special Interest groups notified were the National Hemophilia Association, the World Hemophilia Foundation, The American Blood Resources Association, and the Committee of Ten Thousand."

Pages 23,

fourth paragraph, second line and 24 - Change the sentence to read "The inspection resulted in 87 observations and subsequently led to a consent decree that was entered on January 18, 1997. The consent decree required Centeon to cease distribution of all but two of its products while it brought its manufacturing standards into compliance with FDA's statutes and regulations."

and Appendix D - Seem to imply that the September 27, 1996, AP meeting was the only outreach conducted by the Agency. MedWatch played a significant role in disseminating information about the Centeon recall. On October 1, 1996, October 3, 1996, and October 15, 1996, copies of the September 23, 1996 Urgent Recall Notice, the October 3, 1996 Talk Paper, and the October 9, 1996 Recall Announcement were faxed to over 120 health professional organizations who have joined as MedWatch partners. Additionally the October 9, 1996 Centeon Recall announcement was posted on the MedWatch Internet page and was also summarized in the MedWatch column in the March 1997 Medical Bulletin.

Page 24, last paragraph - Change to read "...Centeon situation that a lead FDA office for determining whether an enforcement action was necessary was not clearly identified. As a

result, FDA field offices will now take the lead in determining the necessity of inspection follow-up...."

Page 25 - The draft report refers to a "press conference." To clarify, OPA arranged an interview, not a press conference.

In the Appendix Chronology, the draft report incorrectly states"The FDA (P-96-17) and Odwalla jointly..." the press release was not a joint press release.

Page 25 - Consider "It is important to note that the number of adverse event reports associated with a given product is largely influenced by the frequency with which the product is used in clinical practice as well as the patient population in which it is used."

Page 28, paragraph 3 - Following the Los Angeles District Office, " insert: "to discuss an inspection of Hyland's viral inactivation procedures" following the word "disapproved", please insert a period. New sentence: "The LA-DO recommended that the inspection be deferred due to the disapproval of the suspension. CBER concurred with the District because CBER could verify the validation of the viral inactivation process during the next inspection. The verification of the viral inactivation process was a CBER obligation and responsibility."

Page 30, fourth paragraph, following the opening phrase - "On April 6, 1995, CBER...", change the statement"CBER concurred with the Los Angeles District."

Appendix D - gives the chronology of events for the Centeon recalls. It includes the date of receipt by Division of Biostatistics and Epidemiology (DBE) of the 15-day report from Centeon, but does not include anything about MedWatch's receipt of the report. It may be useful to include the MedWatch information since that may indicate the earliest signal of the problem.

Appendix D, page 2 of 3 under "September 25" - The report cited was not sent to MedWatch but to DBE from Centeon by fax on September 27.

Appendix D, page 3, first line - It is stated that CBER asked the field to limit its investigation to the known defective lot. In fact, CBER asked the field to focus its major attention on the known defective lot, but did seek investigation of other potentially involved lots or products.

Appendix D - The method of computing this table could result in an over count in some cells. It was compiled by adding up numbers (that were provided by DBE) subsetted according to suspect product, manufacturer, and year of report. However, reports with multiple suspect products (e.g. 2 or 3 different brands of Antihemophilic Factor) would be counted multiple times. It is beyond our scope to re-compute the entire table, but to give

one example: FDA received 267 "unique" AHF (Human) AERs in 1996 (not 399 as indicated in the table).

III. Status of Implementation

The OIG recommended that FDA:

1. Review the proposal originally drafted by the Office of Regulatory Affair's ("ORA") Biological Advisory Committee in April 1997 and implement it to the extent feasible.

Status

Relevant FDA staff have reviewed and modified the proposal. FDA conceptually accepts the proposal and is actively implementing the proposal.

2. Ensure that the Center for Biologics Evaluation and Research ("CBER") has a viable plan, with appropriate milestones, to transfer and expand ORA's lead inspection responsibilities to all biological products currently being inspected by CBER.

Status

CBER has already begun implementing a plan, with appropriate milestones, to transfer and expand ORA's lead inspection responsibilities to all biological products currently being inspected by CBER.

3. Adhere to time frames established for the preparation of Establishment Inspection Reports ("EIRs") and the issuance of warning letters.

Status

ORA has taken steps to ensure that its managers will remind their employees of their obligation to adhere to the time frames established for the preparation of EIRs and the issuance warning letters. Specifically, element #2 or ORA's Consumer Safety Officer performance standard and ORA's Field Management Directive manual provide guidance to ORA managers and employees regarding FDA's "reporting writing" requirements (including letters) and the preparation of EIRs.

4. Instruct employees of the importance of completing the classification of inspections; and require CBER to classify the inspections identified in this report as lacking documentation and take whatever enforcement actions that are appropriate based on the classifications.

Status

This task is underway and CBER will complete its classification of the eleven relevant inspections before the June 5, 1997 hearing. Future classifications will be made in the appropriate time frames.

5. Require CBER to comply strictly with the policy on requesting production schedules from biological establishments.

Status

CBER has already taken steps to ensure that requests for production schedules are made on a consistent basis and do not amount to a de facto prenotification of an inspection. As the new inspection plan described above is implemented, CBER and ORA will determine if there continues to be a need for obtaining production schedules.

6. Require the FDA task force, established in response to the internal report for the Blood Safety Committee, to determine if the intelligence gathered by the adverse event reports could be put to better use in planning inspections, particularly with regard to the targeting of plasma fractionators and/or plasma products.

Status

A team of FDA employees has been selected and charged with determining if intelligence gathered by the adverse event reports could be put to better use in planning inspections, particularly with regard to the targeting of plasma products. This team consists of employees from CBER, ORA, and FDA's MedWatch Program. The team will be chaired by the Acting Deputy Director for CBER, Mark Ellengold.

The team members include: CBER employees Dr. John Finlayson, Dr. Norman Baylor, Dr. Gene Murano, Dr. Marcel Salive, and Ms. Peg Tart; MedWatch employee Dr. Steven Goldman; and ORA employee Hector ZuaZua.

7. Verify that the inspection of Hyland, ongoing as of May 12, 1997, includes a review of viral inactivation procedures. If the procedures were not included, require such an inspection.

Status

The inspection of Hyland is ongoing and does include a review of Hyland's viral inactivation procedures. As a direct of this inspection, Hyland has initiated a class III recall of several lots of Factor VIII. Specifically, Hyland has recalled 8 lots of its Hemofil-M and one lot of American Red Cross' AHF-M.

8. Review the changes made to the plasma collection devices to determine whether they meet the criteria for classification as medical device safety alerts.

Status

A safety alert has been issued for the Baxter/Fenwall plasma collection system. CBER is consulting with ORA headquarters and FDA district offices to determine if any regulatory action is justified for the Haemonetics plasma collection system.

9. Consider requiring plasma collection and testing facilities to report all incidents involving saline contamination.

Status

FDA regulations already require the reporting of errors and accidents by licensed firms. Saline contamination of the tubing segment used to test for infectious diseases for Source Plasma (a licensed product) or other plasma products must be reported as an error or accident, if the products are released for distribution. This requirement does not presently exist for registered firms. In accordance with prior OIG recommendations, however, a revised rule has been drafted to extend the above mentioned reporting requirement to all registered firms. CBER is also considering whether to issue a memorandum to the industry clarifying when saline contamination of the tubing segment constitutes a reportable event, and revising the Compliance Program to include a review of the appropriate files to ensure compliance.

10. Finalize and implement the draft changes to the inspection guide for source plasma establishments, and the compliance program for plasma fractionators.

Status

CBER is in the process of finalizing and implementing the draft changes to the inspection guide for source plasma establishments, and the compliance program for plasma fractionators.