IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA,	**Civil Action No. 93-0949 (JGP)**
Plaintiff,	
v.	
AMERICAN NATIONAL RED CROSS, a corporation,	
Defendant.	

MOTION FOR ORDER TO SHOW CAUSE WHY DEFENDANTS SHOULD NOT BE HELD IN CIVIL CONTEMPT OF AND TO MODIFY THE CONSENT DECREE OF PERMANENT INJUNCTION

Plaintiff, the United States of America, on behalf of the United States Food and Drug Administration ("FDA"), moves this Honorable Court to hold American National Red Cross ("ARC"), a corporation, and its President and Chief Executive Officer, Executive Vice President and Chief Executive Officer of Biomedical Services, Chief Operating Officer of Blood Services, Senior Vice President of Quality Assurance and Regulatory Affairs, Biomedical Services, and ARC's other principal officers in civil contempt for failure to comply with the Consent Decree of Permanent Injunction entered by this Court on May 12, 1993 ("the Decree"). The factual and legal support for the motion are set forth more fully in the attached legal memorandum, declarations, and other exhibits.

1. Despite significant, sustained efforts by FDA, including almost 33,000 inspection hours, warning correspondence, threatened and actual license revocations, meetings with senior ARC officials, and a voluntary compliance agreement, as well as the entry by this Court of the 1993 Decree, ARC -- which supplies nearly half of this nation's blood and blood products -- continues to conduct its blood service operations with a cavalier disregard for the critical current good manufacturing practice (“CGMP”) regulations that have been promulgated by FDA, and

explicitly enforced by this Court's 1993 Decree. CGMP are designed to stem the spread of infectious disease by ensuring the safety, purity, and potency of blood and blood products, and compliance with these procedures by blood processing facilities is critical to the public health. See 21 U.S.C. § 351(a)(2)(B); 42 U.S.C. § 262; 21 C.F.R. Parts 210, 211, 606, and 640.

2. While blood transfusions can be lifesaving and are necessary to perform many modern medical procedures, release of unsuitable blood products is a hazard to individual blood recipients and to the public health. Observations made by FDA during inspections of ARC National Headquarters over the last several years and more recently at ARC's Salt Lake City facility make it impossible to be confident that ARC products meet required quality and safety standards.

3. Because of ARC's pervasive and long-standing violations of CGMP and the 1993 Decree, and ARC's demonstrated pattern and practice of promising corrective action after FDA inspections disclose violations, only to have FDA later find virtually identical violations in the same and other ARC facilities, it is necessary for the government to file this motion. As is demonstrated by the legal memorandum, declarations, and other exhibits supporting this motion, six post-Decree inspections by FDA at ARC National Headquarters, which serves as the quality assurance center for ARC's 36, geographically dispersed, regional facilities, show that ARC fails to comply with CGMP. The most recent inspection of ARC National Headquarters, conducted in February-April 2000, documented that ARC's violative conduct includes, but is not limited to:

a. incorrect labeling and release of blood contaminated with cytomegalovirus ("CMV"), a virus that may cause severe illness, blindness, or death when transfused into vulnerable CMV-negative patients, such as premature infants or transplant patients;

b. lack of quarantine and inventory control, resulting in lost products, and in the distribution of unsuitable blood products;

c. careless donor registration controls, which could result in the release of unsuitable blood products and the inability to recall such products;

d. protracted, unexplained delays in correcting duplicate and discrepant donor records, creating the potential for acceptance and processing of unsuitable blood products;

e. erroneous, premature release of computerized "holds" on donated blood, creating the potential for release of unsuitable products;

f. failure to properly update and check the registry of donors who have been found to be unsuitable to donate blood, resulting in the inability to properly screen out unsuitable donors and creating the potential for release of unsuitable products;

g. failure to address errors in the computerized handling of test results for blood products, interfering with the ability to screen out unsuitable donations and to retrieve unsuitable products that have been released;

h. failure to properly defer certain donors with syphilis; and

i. failure to prevent the use of improper test procedures to test donor hematocrit values, placing anemic blood donors at risk and resulting in the release of subpotent blood products.

4. The foregoing violations are of particular concern because they occur at critical and sequential stages of ARC's blood processing operations and therefore undercut CGMP safeguards, which are designed to be partially overlapping and to provide cumulative protection. *For example*, poor inventory control can undo preceding CGMP measures such as donor and blood sample testing; when, as at ARC, the preceding CGMP measures are not performed properly, the failure to control the last step before distribution becomes of even greater concern. Also, proper blood processing depends, in large part, on scrupulous record keeping that links donor identification, medical history, and test results to all products derived from the donor. When, as at ARC, the links in the chain are not continuous, and not readily traceable, the risk of releasing unsuitable products increases.

5. ARC National Headquarters' continuing failure to exercise control over its regional offices was confirmed by FDA's March-May 2001 inspection of ARC's Salt Lake City facility. The inspection of the Salt Lake City facility revealed that ARC National Headquarters, despite

assurances that it would do so, failed to verify that the regions implemented specified corrective actions in response to FDA's February-April 2000 inspection of ARC National Headquarters. Among other things, the Salt Lake City inspection showed that: (1) supervisors were not reviewing quarantine and inventory reconciliations; (2) supervisors were not reviewing returned blood products to assure suitability before re-release; and (3) the facility was not reviewing product disposition reports on a daily and weekly schedule. In addition, FDA discovered that the Salt Lake City facility failed to document the training of employees before allowing them to perform critical, safety-related tasks and the facility made hundreds of errors in failing to defer unqualified donors, including those who answered "yes" to questions designed to identify donors at a high risk of being infected with HIV/AIDS.

6. ARC does not dispute that it has continuing, significant CGMP problems. For example:

a. In an April 27, 2000 letter to then FDA Commissioner, Jane E. Henney, ARC's President and Chief Executive Officer, Dr. Healy[1], characterized FDA's February-April 2000 inspection of ARC's National Headquarters as a thorough, eye-opening evaluation that shows that ARC has a way to go under the Decree.

b. During an August 14, 2000, meeting between Dr. Healy and Dr. Henney, Dr. Healy stated that ARC had no disagreements with the findings made by FDA during the February-April 2000 inspection and that she had uncovered both a wilfulness and lack of urgency on the part of some ARC staff.

c. In a May 15, 2000 letter to FDA, Jacquelyn Fredrick, ARC's then Executive Vice President for Biomedical Services, succinctly and accurately characterized the four themes that underlie FDA's recent inspection findings: deficient timeliness in responding to problems and complaints reported to ARC National Headquarters by the ARC regions, deficient thoroughness in assessing problems and complaints, deficient monitoring of the effectiveness of corrective actions to ensure appropriateness, and deficient decision making and implementation.

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7. Based upon ARC's 16 year pattern and practice of admitting violations, promising corrective action, admitting further, similar violations, and offering further promises, FDA started discussions, in August 2000, in an effort to reach agreement with ARC to seek amendment of the Decree to include *prospective* penalty provisions, in the event ARC remained non-compliant with the law.

8. When negotiations proved unsuccessful, the government agreed to mediation in August 2001. Mediated discussions ultimately ended in early December 2001, when ARC refused to agree to a series of meaningful prospective enforcement provisions in an amended decree.

9. At various times, ARC officials have advised FDA that the situation is not serious because it has not been proven that anyone has been harmed as a result of ARC's inadequate manufacturing practices. Absence of documented injuries, however, is a notoriously unreliable and dangerous index of actual harm, for several reasons, including: when injuries are not acute (*i.e.*, do not happen right after transfusion), they may not be ascribed to the transfusion; even when an injury is temporally related to a transfusion, it may be erroneously attributed to other causes; and, when injuries are properly diagnosed, they may not be reported by physicians to FDA.

10. The government has exhausted its efforts to reach a settlement and its resources and regulatory tools in an effort to make ARC comply with the law, to little avail. In light of ARC's history, the length of time that ARC has remained non-compliant with the law, and the potential harm that may ensue by waiting longer, the government turns to this Court to help it in this critical endeavor.

11. Accordingly, the government asks this Court to issue an Order to Show Cause requiring ARC and its principal officers to demonstrate why they should not be found in contempt of the Decree and to enter the Proposed Order ("Order") to supercede the Decree and impose prospective fines for future violations of the law by ARC. These fines would become

payable following entry of the Order if, and only if, ARC fails to comply with the Order and the laws designed to protect the public health.

WHEREFORE, plaintiff, the United States of America, respectfully requests that this Court:

I. Adjudge the defendants in civil contempt;

II. Enter the Order requiring the defendants to:

(a) bring their systems and operations into compliance with CGMP within the time frames and in the manner specified;

(b) pay fines in the amounts specified for future failures to comply with specified requirements;

III. Pursuant to paragraph VIII of the 1993 Decree, order the defendants to pay plaintiff the attorneys' fees, court costs, and investigational costs incurred in the investigation and prosecution of this motion; and

IV. Grant such other relief as the Court deems just and proper.

Respectfully Submitted,

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v.	)	
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Defendant.	)	

DECLARATION OF ROBERT LEE BOWERS

I. INTRODUCTION

1. I am the Director of the Baltimore District Office, United States Food and Drug Administration (FDA), located at 900 Madison Avenue, Baltimore, Maryland. In this capacity, I direct and supervise enforcement of the Federal Food, Drug, and Cosmetic Act in Virginia, West Virginia, Maryland, and the District of Columbia. Official FDA records, which are located in the Baltimore District Office and over which I have official custody, form the basis of my testimony in this declaration.

2. I am familiar with the history of FDA inspections of American National Red Cross (ARC) Blood Services Biomedical Headquarters, ARC National Testing Laboratories, ARC's National

Confirmatory Testing Laboratory, and ARC Regional Blood Service Centers, which led to a voluntary agreement between FDA and ARC in 1988 and to a Consent Decree of Permanent Injunction in 1993 (the Decree). I am familiar with FDA inspections of ARC that were conducted following entry of the Decree and that resulted in ten letters issued to ARC by FDA pursuant to ¶ VI.A of the Decree. I am also familiar with reports and correspondence submitted to FDA by ARC following entry of the Decree. My knowledge of the foregoing is the basis of the following compliance history of ARC.

II. ARC STRUCTURE

3. In 1948, ARC was issued establishment and product license #190, pursuant to the Public Health Service Act for the purpose of shipping blood and blood components (blood products) in interstate commerce. The ARC National Biomedical Headquarters (ARC National Headquarters), presently located at 1616 Fort Myer Drive, Arlington, Virginia, is responsible for establishing and maintaining management control of blood services and a quality assurance program to ensure that blood products manufactured, processed, packed, held, and distributed by ARC's thirty six (36) blood service regions, eight (8) national testing laboratories, a national confirmatory laboratory, and numerous donor centers have the safety, quality, identity, potency, and purity they are represented to possess.

As the Quality Assurance command post for ARC, National Headquarters is responsible for, among other things, detecting system-wide problems; designing, implementing, and monitoring effective corrective actions for system-wide problems; communicating corrective actions to all ARC facilities; creating, updating, and modifying standard operating procedures; and implementing an effective system-wide training program. No manufacturing processes are performed at the ARC National Headquarters. The blood service regions, which are located throughout the United States, collect, process, pack, hold, and distribute blood products in interstate commerce.

4. Blood products are drugs within the meaning of the Federal Food, Drug, and Cosmetic Act, 21 U.S.C 321(g)(1). Blood products are also biological products within the meaning of the Public Health Service Act, 42 U.S.C. 262. Blood products are subject to the current good manufacturing practice regulations for drugs, 21 CFR Parts 210 and 211, and to the biological products regulations, 21 CFR Parts 600-680, including the current good manufacturing regulations for blood products, 21 CFR Part 606, and additional standards for blood products, 21 CFR Part 640.

III. SUMMARY OF DECLARATION

5. In the succeeding paragraphs of my declaration, I will discuss ARC's long history of failure to comply with the laws and regulations administered by FDA applicable to the manufacturing, processing, and distribution of blood products. These laws and regulations are referred to by FDA and the regulated industry as current good manufacturing practice (CGMP). The purpose of CGMP is to so carefully control the process for making drugs and biologics that the end products will be safe, pure, and potent, and will have the quality characteristics necessary to work effectively.

The discussion, which focuses on FDA inspections of ARC regional and National Headquarters facilities, ARC's numerous broken promises to correct the deviations observed by FDA investigators, the measures FDA has taken to encourage compliance by ARC, and ARC's failure to respond to those measures, is organized as follows:

IV. Compliance History Before 1988 Voluntary Agreement, ¶¶ 6-8,

V. 1988 Voluntary Agreement, ¶ 9,

VI. Compliance History Under The Voluntary Agreement, ¶¶ 10-34,

VII. 1993 Consent Decree, ¶¶ 35-36,

IV. COMPLIANCE HISTORY BEFORE 1988 VOLUNTARY AGREEMENT

6. ARC has a long history of noncompliance with FDA laws and regulations dating back to 1985. In 1985, FDA inspected ARC's Central California Regional Blood Center twice and issued a Notice of Adverse Findings (NAF Letter) to ARC after each of those inspections. The inspection findings cited in the NAF Letters included incomplete donor consent forms and failure to maintain complete donor history records.

7. In November 1986, FDA inspected ARC's St. Louis, Missouri Regional Blood Center and found that ARC had distributed blood products collected and processed by an unlicensed contract manufacturer. On January 21, 1987, FDA issued a Regulatory Letter to ARC, advising it of the violations observed during the November 1986 inspection and requesting prompt corrective action.

8. Inspections conducted by FDA in 1988 at ARC regional blood service centers revealed significant violations of FDA regulations that resulted in the erroneous release of blood products that were not suitable for transfusion (use in patients). The inspection findings showed ARC National Headquarters had *failed to establish management control over regional operations and an adequate quality assurance program capable of identifying, correcting, and preventing deficiencies in its manufacturing and control systems*. (Throughout this declaration, italics indicate that the same deficiency was observed by FDA in its most recent inspection of ARC National Headquarters, discussed below, and is cited as evidence to support the Government's contempt motion.) Those manufacturing and distribution errors observed by FDA were the result of ARC's failure to:

a. *investigate deviations in order to identify system deficiencies, and implement corrective action for known system problems*;

b. *ensure the accuracy and integrity of its donor information databases*;

c. *establish adequate standard operating procedures (SOPs);*

d. *ensure that SOPs were fully implemented and followed by the regions*;

e. validate computer systems and software;

f. *establish and implement an adequate quality control program for equipment used in ARC's blood products manufacturing operation*;

g. *ensure correct labeling of blood products; and*

h. maintain records concurrently with each significant step of the manufacturing process.

V. 1988 VOLUNTARY AGREEMENT

9. In an attempt to foster compliance by ARC, FDA entered into a Voluntary Agreement with ARC on September 14, 1988. ARC agreed, among other things, to standardize, revise, and update SOPs used by all regional blood service centers; to conduct a comprehensive evaluation of computer systems and submit to FDA within thirty (30) days a plan to implement and verify corrections; to establish written SOPs to conduct and document periodic assessments of the accuracy and integrity of the donor deferral registry; to develop and implement within thirty (30) days an effective training program for all employees, and to develop and implement within ninety (90) days an effective training program for employees in computer related jobs; and to establish written SOPs for a revised internal audit program, submit the SOPs to FDA within thirty (30) days, and implement

them within thirty (30) days of FDA approval. (See copy of the Voluntary Agreement, attached hereto as Tab 1.)

VI. COMPLIANCE HISTORY UNDER THE 1988 VOLUNTARY AGREEMENT

10. During December 1988 and January 1989, FDA inspected ARC's Albany Regional Blood Service Center, Albany, New York, and found significant CGMP deficiencies that contributed to the release of unsuitable blood products collected from approximately one hundred eleven (111) donors. FDA found that incorrect test procedures used by ARC employees caused blood samples from those donors to be erroneously identified as non-reactive to hepatitis testing. Other CGMP deficiencies included failure to train employees to operate the automated hepatitis testing equipment, failure to establish an SOP to operate automated hepatitis testing equipment, failure to perform quality assurance reviews of hepatitis test results to ensure that laboratory personnel were performing test procedures correctly, and failure to maintain records concurrently with each significant step of the manufacturing process. As a result of this inspection, on February 14, 1989, FDA issued a Notice of Intent to Revoke ARC's establishment license for the Albany Regional Blood Service Center. (A Notice of Intent to Revoke is an administrative action used by FDA to advise a licensed blood manufacturing establishment that FDA has found continuing

deviations from CGMP that, in FDA's view, are so significant that FDA intends to revoke that establishment's license and withdraw authorization to ship blood products in interstate commerce.) (See copy of February 14, 1989 Notice, attached hereto as Tab 2.)

11. In June 1989, FDA inspected ARC's Pacific Northwest Regional Blood Service Center, Portland, Oregon, and found significant CGMP deficiencies that led to the release of unsuitable blood products collected from donors who had positive infectious disease test results. Those CGMP deficiencies included failure to follow SOPs pertaining to donor deferral data entry, failure to retain records of initial infectious disease test results, *failure to adequately quarantine unsuitable blood products to prevent their release*, and failure to adequately train computer system operators how to correctly assess donor suitability system information to prevent the release of unsuitable blood products.

12. During December 1989 - Feburary 1990, FDA reinspected ARC's Albany Regional Blood Service Center, and again found significant CGMP deficiencies, including *failure to maintain accurate and complete donor deferral records, which led to the release of* sixty three (63) *unsuitable blood products*; incorrect interpretation of viral marker test results, which led to the release of unsuitable blood products; failure to follow

SOPs for performing viral marker tests; and failure to establish adequate quality assurance and training programs. Following this inspection, FDA notified ARC in a May 2, 1990 letter, that the Albany establishment license was revoked. By letter dated May 9, 1990, ARC waived its opportunity for a hearing and voluntarily requested revocation of its license for the Albany region. (See copies of the May 2, 1990 letter and the May 9, 1990 letter, attached hereto as Tabs 3 and 4, respectively.)

13. In January 1990, FDA reinspected ARC's Pacific Northwest Regional Blood Service Center and again found significant CGMP deficiencies, including failure to follow SOPs requiring duplicate re-testing for hepatitis, in that only one re-test or no re-test was being performed, and failure to retain original, unaltered records of human immunodeficiency virus (HIV) and hepatitis test results. FDA sent a letter to ARC on March 13, 1990, advising it of these deficiencies. In a letter dated March 22, 1990, ARC promised corrective action. In May 1990, FDA conducted a third inspection of ARC's Pacific Northwest Regional Blood Service Center and found nine unregistered ARC collection centers. FDA issued a Notice of Adverse Findings to ARC on August 6, 1990. ARC responded by letter dated August 31, 1990 and promised compliance. (See copies of the August 6, 1990 and August 31, 1990 letters, attached hereto as Tabs 5 and 6, respectively.)

14. In February 1990, FDA inspected ARC's Wichita Regional Blood Service Center, Kansas City, Missouri and found significant CGMP deficiencies, such as ARC's *failure to: ensure the accuracy and integrity of donor information records* to prevent release of unsuitable blood products, *identify and resolve duplicate and discrepant donor records in the computer system*, maintain records concurrently with each significant step of the manufacturing process, perform and maintain a record of quality control procedures required for equipment used in the manufacturing process, and monitor shipping temperatures for blood products distributed for transfusion. FDA considered, but did not issue, an NAF Letter because it decided to rely on ARC's promises to implement corrective action.

15. In May 1990, FDA inspected ARC's Carolina Lowcountry Regional Blood Service Center, Charleston, South Carolina, after ARC had recalled thirty six (36) unsuitable units of blood, collected from donors who had positive Anti-HIV 1 test results, indicating that the donors were infected with HIV. The inspection revealed that the erroneous release of these products was caused by inadequate computer software validation. In July-August 1990, FDA reinspected ARC Carolina Lowcountry Regional Blood Service Center and found that the region *did not perform adequate and complete investigations* of reported cases of transfusion-associated AIDS and that records related to ARC's

investigation of and follow-up actions for transfusion-associated AIDS cases were also incomplete. Following that inspection, FDA issued to ARC a Notice of Adverse Findings dated September 21, 1990. (See copy of NAF Letter, attached hereto as Tab 7.)

16. During April - May 1990, FDA inspected ARC's National Headquarters, then located in Washington, D.C., and found a wide range of significant CGMP deficiencies. These deficiencies (which foreshadow many of the current violations at ARC's National Headquarters) included:

a. *failure of ARC National Headquarters to ensure that corrective actions, promised in response to inspectional findings from various regional blood service centers, had been implemented*;

b. *failure to implement SOPs for handling error and accident reports submitted to ARC National Headquarters by regional blood service centers*;

c. *failure to promptly report errors and accidents to FDA*; d. failure to conduct adequate adverse reaction investigations associated with suspected cases of post-transfusion HIV;

e. failure to establish control over computer systems used in regional blood service centers; and

f. *failure to establish adequate SOPs to ensure prompt and accurate donor deferral registry updates*.

In a July 25, 1990 letter, ARC promised correction of the deficiencies found by FDA. (See copy of July 25, 1990 letter, attached hereto as Tab 8.)

17. During June - August 1990, FDA conducted an inspection of ARC Washington Regional Blood Service Center, Washington, D.C. (This regional facility was different from the ARC National Headquarters facility in Washington, D.C., in that it collected, processed, packed, held, and distributed blood products.) This inspection was not a general inspection, but primarily focused on the findings from the just-completed inspection of National Headquarters showing that National Headquarters had failed to ensure that the Region adequately investigated suspected cases of post-transfusion HIV that had been reported to the Washington Regional Blood Service Center. This inspection revealed that the regional facility failed to adequately investigate over two hundred (200) reported adverse events to determine whether suspected post-transfusion HIV cases were associated with the transfusion of erroneously released unsuitable blood products. The inspection also focused on ARC's donor deferral registry, which is supposed to accurately identify unsuitable donors to prevent inappropriate collection and release of unsuitable blood products. By letter dated November 1, 1990, ARC responded to a

Notice of Adverse findings issued by FDA, following the June-August 1990 inspection. In the letter, ARC informed FDA that it had closed the Washington Regional Blood Service Center in May 1990, and it promised to investigate suspected post-transfusion HIV cases and take appropriate follow-up action. ARC estimated that the corrective action would take two years to complete. (See copy of November 1, 1990 letter, attached hereto as Tab 9.)

In September 1991, ARC informed FDA that ARC's investigation revealed that two hundred eighty one (281) *donors, who had positive test results for anti-HIV 1* in 1985 and 1986, *were not appropriately listed by ARC on its donor deferral registry* as of July 29, 1991, *and that subsequent donations from some of those donors had been distributed*. In October 1991, ARC notified FDA that it had identified additional unsuitable donors and the total had increased to 318.

18. On September 10, 1990, FDA Acting Commissioner James S. Benson issued a letter to George Moody, ARC's Chairman of the Board of Governors, in which he expressed FDA's concerns regarding ARC's failure to honor commitments made in the 1988 Voluntary Agreement. The letter specifically noted ARC's continuing release of unsuitable blood products and reminded ARC of its responsibility to ensure the safety, purity, and potency of blood products. Attached to the letter was a summary of FDA findings and issues that advised ARC National Headquarters of

continuing deficiencies found during recent inspections of its regional and headquarters facilities, for which it was responsible, including:

a. *failure of the Responsible Head of ARC to exercise clear and complete control over all operations* that may affect compliance with the Voluntary Agreement and applicable regulatory standards,

b. *failure to ensure consistent interpretation of SOPs throughout all regions*,

c. failure to implement SOPs to prevent release of unacceptable products by notifying donors found to be unsuitable,

d. failure to ensure that auditors have the training, experience, and authority necessary to identify and correct deficiencies,

e. failure to establish a national training program,

f. *failure to ensure that computer systems will prevent the release of unsuitable blood products*,

g. failure to establish clear guidance and control over implementation and use of utility programs intended to identify duplicate and invalid donor information in the computer system, and

h. *failure to ensure that utility program SOPs are consistently followed throughout all regions*.

ARC promised corrective action in a letter dated December 6, 1990. (See copies of September 10, 1990 letter and summary, and December 6, 1990 letter, attached hereto as Tabs 10 and 11, respectively.)

19. During March - April 1991, FDA reinspected ARC Pacific Northwest Region and found that blood products that were not fully tested for hepatitis and HIV had been released. (See ¶¶ 11 and 13 above.) The inspection also revealed significant CGMP deficiencies, including *failure to maintain complete and accurate donor deferral records*; *failure to report to FDA the release of unsuitable blood products*; failure to maintain SOPs for all steps of blood manufacturing processes, including collection, processing, storage, and distribution; failure to maintain records of quality control procedures performed for equipment used in the blood manufacturing process; and failure to maintain records concurrently with each significant step of the blood manufacturing process. Following the inspection, ARC recalled nine (9) whole blood units and associated components. As a result of these inspection findings, on April 17, 1991, FDA issued a Notice of Intent to Revoke ARC's establishment license for the Pacific Northwest Region. (See copy of April 17, 1991 Notice, attached hereto as Tab 12.)

20. In March 1991, FDA reinspected ARC's Carolina Lowcountry Regional Blood Service Center and found that four (4)

units of blood had been incorrectly tested for blood type and released. (Transfusions of incorrect blood type can result in adverse reactions in recipients, ranging from mild to life-threatening, and death.) The inspection also revealed significant CGMP deficiencies, including failure to establish SOPs for all steps of the blood manufacturing process, such as for viral marker and blood type testing; failure to ensure that SOPs were properly reviewed and approved prior to implementation, and to ensure that obsolete procedures were removed from use; failure to adequately perform quality control procedures for reagents used to test blood; failure to adequately perform quality control procedures for equipment; failure to maintain records concurrently with each significant step of the manufacturing process; failure to ensure that personnel have capabilities commensurate with their assigned functions, a thorough understanding of the manufacturing operations which they perform, and the necessary training and experience relating to specific products involved in their work; and failure to obtain approval from FDA's Center for Biologics Evaluation and Research for changes to blood product manufacturing procedures. On March 28, 1991, FDA issued to ARC a Notice of Intent to Revoke ARC's establishment license for the Carolina Lowcountry Region. By letter dated April 12, 1991, ARC promised corrective action. (See copies of March 28, 1991 Notice

and the April 12, 1991 letter, attached hereto as Tabs 13 and 14, respectively.)

21. During April - May 1991, FDA reinspected ARC's Wichita Regional Blood Service Center and found significant CGMP deficiencies, including failure to follow hepatitis test kit manufacturers' instructions, resulting in the release of unsuitable blood products; failure to ensure that laboratory personnel had the training and the experience necessary to perform infectious disease testing; failure to follow SOPs for anti-HIV testing; *failure to quarantine suspect units of blood product; failure to promptly update the donor deferral register* with positive hepatitis results, leading to the release of unsuitable blood products.

22. By letter dated July 30, 1991, FDA's Kansas City District Director requested a meeting with ARC to discuss the Wichita Region inspection and the agency's concerns regarding ARC's continuing failure to comply with the law and the 1988 Voluntary Agreement. In the letter, FDA told ARC that the agency was concerned about ARC's pattern of correcting problems only when brought to ARC's attention by FDA on an FDA-483 List of Observations. FDA advised ARC that the agency could not continue to function as ARC's consultant by identifying and solving ARC's problems. FDA further stated in the letter that ARC had *failed to establish management control of regional blood*

service center operations, failed to conduct meaningful internal audits, failed to ensure that employees are adequately trained and sufficient in number, and *failed to adequately investigate and identify the causes of errors and accidents*. (See copy of the July 30, 1991 letter, attached hereto as Tab 15.)

During the August 5, 1991 meeting at the Kansas City District Office, ARC promised to establish a national training department in ARC National Headquarters, to revise training SOPs and internal audit procedures, and to transform and consolidate blood service regions. FDA attendees included W. Michael Rogers, Kansas District Director and Cheryl A. Boyce, Acting Director Compliance Branch, Kansas District. ARC attendees included Jeffery McCullough, Responsible Head and Senior Vice President, Biomedical Services, and Kathleen Houlihan, General Manager, Operations. (See copy of August 5, 1991 meeting minutes, attached hereto as Tab 16.)

23. In June - July 1991, FDA reinspected ARC's National Headquarters, Washington, D.C. The inspection revealed ARC's continuing *failure to establish management control over regional blood service center operations* and to exercise control of the regional centers in all matters related to compliance with FDA regulations. Other significant CGMP deficiencies observed during the inspection included *failure to establish an adequate quality assurance program; failure to maintain a complete and*

accurate donor deferral registry; failure to maintain written SOPs for regional computer operations and control; *failure to report errors and accidents to FDA*; *failure to adequately investigate errors and accidents; failure to establish adequate error and accident reporting SOPs;* and failure to provide adequate training for error and accident reviewers. In a letter dated August 27, 1991, ARC promised correction of the deficiencies identified by FDA. (See copy of the August 27, 1991 letter, attached hereto as Tab 17.)

24. In an October 29, 1991 meeting between ARC and FDA, ARC management admitted to FDA that it had failed to fulfill the conditions of the 1988 Voluntary Agreement. ARC further acknowledged its continuing failure to establish operational control over ARC regions. The discussion focused on ARC's National Headquarters' failure to control the computer system and the continuing release of unsuitable products associated with computer system problems. The meeting was attended by Jeffery McCullough, ARC Senior Vice President, Biomedical Services; Kathy Houlihan, ARC General Manager, Blood Services and Regulatory Affairs; Kristine Rapp, ARC General Manager, Compliance; and Joseph O'Malley, Medical Associate, Regulatory Affairs. Attendees for FDA included Thomas L. Hooker, Baltimore District Director, and Gary Pierce, Baltimore Director,

Investigation Branch. (See copy of the meeting minutes, attached hereto as Tab 18.)

25. During July - October 1991, FDA inspected ARC's Rochester Regional Blood Center, Rochester, New York, and found significant CGMP deficiencies, including *failure to establish adequate SOPs to ensure the accuracy and integrity of donor registration databases and the donor deferral registry, resulting in the release of unsuitable blood products; failure to establish adequate SOPs to identify and resolve duplicate and discrepant donor records; release of unsuitable blood products caused by duplicate and discrepant donor records; and failure to follow ARC's own error and accident reporting SOPs.* In a letter dated October 28, 1991, ARC promised to correct the deviations identified by FDA. (See copy of ARC's October 28, 1991 letter, attached hereto as Tab 19.)

26. During December 1991 and January 1992, FDA inspected ARC's Tri-State Regional Blood Center, Huntington, West Virginia. The inspection revealed that ARC had distributed three hundred sixty three (363) unsuitable blood products collected from donors who had positive Anti-HIV 1 test results. Additional significant CGMP deficiencies observed during the inspection included *failure to ensure the accuracy and integrity of the donor deferral registry;* failure to follow SOPs requiring recall of distributed unsuitable blood products at the time of

donor deferral; failure to immediately notify consignees of recalled unsuitable blood products, as required by ARC SOPs*;* failure to report errors and accidents to FDA*; and failure to investigate the disposition of blood products manufactured from whole blood collected from a donor who had positive anti-HIV 1 test results.* In a letter dated January 17, 1992, ARC promised corrective actions and future compliance. (See copy of the January 17, 1992 letter, attached hereto as Tab 20.)

27. On January 15, 1992, FDA and ARC met in the FDA's Baltimore District Office to discuss the Tri-State Region inspection. During this meeting, FDA expressed concern, not only about the Tri-State inspection findings, but about *ARC actions to ensure that deficiencies in the donor deferral registry databases were identified and corrected in each of its regional blood centers*. FDA also expressed concern about *whether ARC headquarters monitors each region's periodic use of utility software programs and retrospective reviews of the donor deferral records to identify and correct duplicate and discrepant donor records*. Again, ARC representatives promised corrective action. FDA attendees included Carl Turner, Baltimore Director Compliance Branch; and Ellen Morrison, Consumer Safety Officer. ARC attendees included Denzil Smith, Assistant Principal Officer, Tri-State; Mary B. Taylor, Principal Officer Tri-State Regional Blood Center; and Sheila Porter, Compliance

Manager, Biomedical Headquarters. (See copy of meeting minutes, attached hereto as Tab 21.)

28. On February 20, 1992, FDA met with ARC again to discuss ARC's progress in correcting deficiencies identified during the June-July 1991 inspection of National Headquarters. FDA again reminded ARC of its obligation to identify and correct CGMP deficiencies prior to FDA inspections. ARC described its plan to implement a single, standardized computer system over a period of three years. FDA asked how ARC intended to ensure that regional centers would periodically run utility software programs to detect and resolve duplicate and discrepant donor records. ARC responded that regional compliance with utility program requirements had been audited and that SOPs required compliance statements from management in each region. During the meeting, ARC also provided a letter to FDA, dated February 19, 1992, *promising to develop a plan to conduct a comprehensive review of donor deferral records in all ARC regions to determine whether unsuitable donors had been properly entered into the donor deferral registry*. FDA attendees included Thomas Hooker, Baltimore District Director, and Gary Pierce, Baltimore Director Investigations Branch. ARC attendees included William Sherwood, Responsible Head of ARC and Chief Operating Officer; Nancy Brenner, Acting Vice President Blood Services; Kathleen Houlihan, General Manager Operations; and Mark Cochran, General

Manager, Blood Computer Systems. (See copy of meeting minutes, attached hereto as Tab 22.)

29. In April 1992, FDA inspected ARC's Buffalo Regional Blood Service Center, Buffalo, New York. The inspection revealed that ARC had improperly *released* sixty four (64) *unsuitable blood products, collected from donors who had positive hepatitis test results*. Other significant CGMP deficiencies observed by FDA included: *failure to ensure the accuracy and integrity of donor registration and donor deferral records; failure to follow ARC's own SOPs for use of utility software programs intended to identify duplicate and discrepant donor records*; failure to validate utility programs, prior to use; implementation of software by the region prior to ARC management approval; failure to maintain records concurrently with each significant step in the manufacturing process; inadequate training of employees to ensure that they have knowledge of SOPs applicable to the performance of their assigned functions; failure to perform quality control procedures for reagents used in blood tests to determine donor suitability; and *failure to ensure donor safety*. This inspection resulted in the recall of unsuitable blood products. In a May 29, 1992 letter, ARC promised corrective actions. (See copy of ARC's May 29, 1992 letter, attached hereto as Tab 23.)

30. On May 22, 1992, FDA met with ARC to discuss ARC's progress in implementing corrective actions following the June-July 1991 inspection of National Headquarters. ARC described systemic changes and its plans to use FDA inspection observations to identify systemic and organizational problems. FDA informed ARC that it was ARC's responsibility to identify the cause of problems found in its facilities, to consider the national implications of local findings, and to implement whatever corrective action was necessary to prevent recurrences of the problems. During the meeting, when FDA inquired about the progress of a retrospective review of the donor deferral registry that ARC had said it was going to do, ARC's Responsible Head advised FDA that *ARC had decided not to conduct a retrospective review of the donor deferral registry.* FDA attendees included Thomas Hooker, Baltimore District Director, and Gary Pierce, Baltimore Director Investigations Branch. ARC attendees included Peter Tomasula, Responsible Head, Biomedical Services; William Kline, National Director, Testing Laboratories; Mark Cochran, General Manager, Blood Computer Systems; Kathleen Houlihan, General Manager, Operations. (See copy of meeting minutes, attached hereto as Tab 24.)

31. In April - June 1992, FDA inspected ARC's Birmingham Regional Blood Services, Birmingham, Alabama, and found that forty nine (49) unsuitable blood products had been released. The

inspection revealed that *ARC's failure to identify and resolve duplicate and discrepant donor records caused the release of the unsuitable products.* ARC responded by letter dated June 19, 1992, and promised corrective action. On June 22, 1992, FDA issued a Warning Letter to ARC, advising it of the deficiencies, requesting prompt corrective action, and warning of possible further regulatory action, such as injunction and license suspension. By letter dated June 30, 1992, ARC responded to the Warning Letter by assuring FDA that it was committed to taking every necessary action to correct the deficiencies and to prevent future release of unsuitable products. ARC further stated that it takes very seriously any deviations from the Code of Federal Regulations and ARC's own SOPs. (See copies of the June 19, 1992, June 22, 1992, and June 30, 1992 letters, attached hereto as Tabs 25, 26, and 27, respectively.)

32. In May - June 1992, FDA inspected ARC's Nashville Regional Blood Services Center, Nashville, Tennessee, and found significant CGMP deficiencies, including failure to maintain records concurrently with each significant step in the manufacturing process; failure to investigate adverse reactions experienced by blood donors; failure to maintain quality control records for manufacturing equipment; failure to follow ARC donor screening SOPs; *inadequate inventory management*; inadequate labeling SOPs; and inadequate training of personnel responsible

for collection, processing, testing, storage, and distribution of blood products. By letter dated July 16, 1992, ARC promised corrective action. (See a copy of the July 16, 1992 letter, attached hereto as Tab 28.)

33. In May - June 1992, FDA inspected ARC's Los Angeles/Orange County Regional Blood Services Center, and found that ARC had released unsuitable blood products. The inspection also found significant CGMP deficiencies, including *failure to identify and resolve duplicate and discrepant donor records, failure to maintain records of the disposition of blood components, failure to identify and correct computer system defects,* failure to adequately validate computer systems, failure to perform prompt investigations and notification in suspected cases of post-transfusion HIV infection, and *failure to follow error and accident reporting SOPs*. On July 8, 1992, FDA's Los Angeles District Office recommended revocation of ARC's license for the Los Angeles/Orange County Regional Blood Service Center.

34. In August 1992, FDA inspected ARC's Carolinas Regional Blood Service Center, Charlotte, North Carolina, and found the following significant CGMP deviations: *failure to identify and correct system problems*; failure to follow SOPs pertaining to prompt investigation and notification in cases of suspected post-transfusion infection; inadequate computer system

validation; inadequate storage facilities for blood, blood components, reagents, and testing supplies; failure to ensure adequate storage conditions for blood products; failure to adequately train employees responsible for labeling and quarantine of blood and blood components; and failure to establish deionized water specifications and quality control procedures to ensure its suitability for use in the manufacturing process. By letter dated September 23, 1992, ARC promised to correct the noted deficiencies. (See a copy of the September 23, 1992 letter, attached hereto as Tab 30.)

VII. 1993 CONSENT DECREE

35. As a result of the above findings, FDA concluded that ARC had repeatedly failed to live up to the 1988 Voluntary Agreement, that progress did not appear likely under the voluntary regime, and that a court-enforceable order was necessary. On May 12, 1993, a Consent Decree of Permanent Injunction was entered, requiring ARC, among other things, to establish management control over all blood service operations and to establish a quality assurance program to ensure that ARC would not manufacture or distribute adulterated or misbranded blood products. The Decree contained provisions specifically focusing on areas that FDA, through its inspections, had found to be in violation of the law, including management controls,

quality assurance/quality control programs, and employee training.

36. Since entry of the Decree, FDA has spent nearly thirty three thousand *inspection* hours at ARC facilities to evaluate ARC's state of compliance with the law, regulations, and the 1993 Consent Decree. These hours do not include the substantial amount of time spent by FDA's Center for Biologics Evaluation and Research and Office of Regulatory Affairs officials reviewing and evaluating inspection findings and ARC reports, or meetings between ARC officials and agency managers, including senior managers. (Since entry of the Decree, FDA spent the following amounts of time inspecting ARC facilities: 374 hours in fiscal year 1993, 5536 hours in fiscal year 1994, 5629 hours in fiscal year 1995, 3675 hours in fiscal year 1996, 3586 hours in fiscal year 1997, 3953 hours in fiscal year 1998, 3712 hours in fiscal year 1999, 3565 hours in fiscal year 2000, and over 2600 hours during the first three quarters of fiscal year 2001 .) As shown below, ARC has failed to comply with the Decree and continues to rely on FDA to find problems at ARC, and, as before entry of the Decree, even when FDA finds problems, ARC does not take appropriate action to correct the problems on a system-wide basis.

VIII. ARC'S FAILURE TO COMPLY WITH THE DECREE

A. VI.A LETTERS

37. Since entry of the Decree, FDA has issued eleven (11) letters pursuant to ¶ VI.A of the Decree, which provides a formal mechanism for FDA to bring significant violations to ARC's attention. In these letters, which are summarized in the succeeding paragraphs, ARC was notified of inspection findings that FDA believes are significant deviations from the law, regulations, and the Decree. Because the purpose of the VI.A letter is to *advise* ARC of FDA's significant inspection findings, FDA did not issue such a letter following each violative inspection. For instance, in October 1999, FDA issued a VI.A letter following an inspection of ARC's Southern Regional Blood Service Center. After the inspection, ARC promised corrective action. (See ¶ 47 in this declaration.) Following an inspection of ARC's Pacific Northwest Regional Blood Service Center, FDA found CGMP deficiencies similar to those found in the Southern Region. However, based on ARC's promise to correct the earlier, similar deficiencies, FDA elected not to issue another VI.A letter. (See ¶ 48 in this declaration.)

38. On February 23, 1994, as a result of an October - November 1993 inspection of ARC's Lewis and Clark Regional Blood Service Center, Boise, Idaho, FDA issued a VI.A letter that included a Notice of Intent to Revoke the establishment license

for that ARC region. The inspection findings included significant CGMP deficiencies, such as failure to maintain and calibrate manufacturing equipment in accordance with ARC SOPs and equipment manufacturers' instructions; *failure to follow ARC SOPs pertaining to the collection, processing, storage, and distribution of blood products*; failure to maintain records of each significant step of the manufacturing process; *and failure to follow ARC quality assurance SOPs*. By letter dated March 7, 1994, ARC promised corrective actions. (See copies of VI.A letter and ARC's March 7, 1994 letter, attached hereto as Tabs 31 and 32, respectively.)

39. On September 21, 1994, as a result of a March - April 1994 inspection of ARC's Penn-Jersey Regional Blood Service Center, Philadelphia, Pennsylvania, FDA issued a VI.A letter to ARC. The inspection findings included significant CGMP deficiencies, such as failure to follow ARC SOPs for performing viral marker tests; failure to maintain records of each significant step in the manufacturing process; inadequate donor screening procedures; failure to adequately train employees responsible for performing regulated processes; *failure to establish an adequate quality assurance program*; failure to validate computer software; use of computer software revisions, prior to their approval; failure to establish computer system functional specifications and test programs; and shipment in

interstate commerce of unlicensed blood products. By letter dated September 30, 1994, ARC promised corrective action. (See copies of VI.A letter and ARC's September 30, 1994 letter, attached hereto as Tabs 33 and 34, respectively.)

40. FDA issued its third VI.A letter on November 2, 1994, following inspections of ARC's National Reference Laboratory for Infectious Diseases, Rockville, Maryland. The inspections, conducted in September - October 1993 and in May - September 1994, revealed significant CGMP deficiencies, including failure to follow test kit manufacturers' directions for performing infectious disease testing; failure to identify donors whose blood samples had been incorrectly tested for infectious diseases; use of testing procedures that had not been approved by FDA; failure of quality assurance personnel to detect test result interpretation errors; failure to maintain complete blood test records; failure to review blood test records for quality assurance; and failure to establish and follow SOPs. In a letter dated November 16, 1994, ARC promised corrective action. (See copies of VI.A letter and ARC's November 16, 1994 letter, attached hereto as Tabs 35 and 36, respectively.)

41. FDA issued a VI.A letter on December 9, 1994, following an inspection of ARC's National Headquarters, Arlington, Virginia. The inspection, conducted in January - March 1994, revealed ARC failed to *establish, implement, and*

maintain an effective quality assurance program; failed to provide a sufficient number of quality assurance personnel to properly audit all regional and headquarters operations on an annual basis, as required by ARC's SOP; *and failed to investigate and promptly correct system problems identified during internal quality assurance audits*. ARC responded to the inspection findings by letter dated April 5, 1994, in which it stated that ARC had undertaken an extensive study to assess its ability to build and sustain long-term compliance with the Decree, its own SOPs, and the law. ARC stated that the results of the study were likely to have a significant impact on the corrective action taken in response to certain of the recent inspection findings. In a letter dated December 23, 1994, ARC denied that it failed to comply with the 1993 Consent Decree and the law, yet promised corrective actions. (See copies of ARC's April 5, 1994 letter, the VI.A letter and ARC's December 23, 1994 letter, attached hereto as Tabs 37, 38, and 39, respectively.)

42. FDA issued a VI.A letter on December 13, 1994, after an inspection of ARC's Pacific Northwest Regional Blood Service Center, Portland, Oregon. (See ¶¶ 11, 13, 19 for a description of earlier inspections of this region.) The inspection, conducted in March - April 1994, revealed significant CGMP deficiencies, including failure to validate the computer system;

failure to promptly correct known computer system problems; failure to resolve duplicate and discrepant donor registration records to prevent release of unsuitable blood products; inadequate donor suitability screening practices; failure to follow the manufacturer's instructions for the deionized water system; *failure to implement ARC SOPs*; failure to maintain records of expiration dates assigned to specific blood components; and distribution of unlicensed blood products. While ARC denied failing to comply with the Decree or violating the law, in a letter dated December 28, 1994, ARC stated that it had completed numerous corrective actions following the FDA inspection. (See VI.A letter and ARC's December 28, 1994 letter, attached hereto as Tabs 40 and 41, respectively.)

43. FDA issued a sixth VI.A letter on December 28, 1994, following an inspection of ARC's Heart of America Regional Blood Service Center, Peoria, Illinois. The inspection, conducted in April - June 1994, revealed significant CGMP deficiencies, including failure to maintain records of distribution or disposition of blood products; *failure to ensure the accuracy and integrity of donor registration records to prevent release of unsuitable blood products;* failure to ensure that personnel had capabilities commensurate with their assigned duties and adequate training and experience to perform those duties; failure to ensure that manufacturing equipment quality control

procedures were performed in accordance with ARC SOPs and manufacturers' instructions; *failure to ensure donor safety*; failure to follow ARC SOPs for error and accident reporting and for product labeling; failure to ensure that products were labeled with expiration dates; *failure to establish an SOP requiring corrective actions for all deficiencies identified during internal quality assurance audits*; and distribution in interstate commerce of unlicensed blood products. By letter dated January 11, 1995, ARC stated that it had substantially completed corrective action. (See VI.A letter and ARC's January 11, 1995 letter, attached hereto as Tabs 42 and 43, respectively.)

44. FDA issued a VI.A letter on August 29, 1995, after a second post-Decree inspection of ARC's Lewis and Clark Regional Blood Service Center. The inspection, conducted in May 1995, revealed continuing significant CGMP deficiencies, including *failure to ensure the accuracy and integrity of donor information records; failure to follow ARC SOPs for resolving duplicate and discrepant donor records*; failure to follow ARC SOPs for error and accident reporting; failure to ensure that personnel have capabilities commensurate with their assigned functions and adequate training to perform those functions; failure of quality assurance personnel to detect errors in equipment quality control records; failure to follow ARC

manufacturing equipment quality control SOPs and to maintain accurate records of quality control procedures; and failure to maintain records concurrently with each significant step of the manufacturing process. By letter dated September 13, 1995, ARC promised to correct the specific deficiencies observed during the FDA inspection and to take steps to improve quality assurance and quality control systems. (See copies of VI.A letter and ARC's September 13, 1995 letter, attached hereto as Tabs 44 and 45, respectively.)

45. FDA issued a VI.A letter on March 6, 1996, following a second, post-Decree inspection of ARC's Pacific Northwest Regional Blood Service Center (and the fifth inspection of this region). The inspection, conducted in September 1995, revealed significant CGMP deficiencies, including *failure to ensure the accuracy and integrity of donor information records*; *failure to follow ARC SOPs for resolving duplicate and discrepant donor records; failure to correct a known computer software defect that had allowed unsuitable donors to donate blood*; *failure to maintain accurate records of blood product distribution*; failure to ensure that personnel have capabilities commensurate with their assigned functions and adequate training to perform those functions; failure to follow SOPs for computer system security; failure to document installation and testing of computer systems; failure to follow ARC manufacturing equipment quality

control SOPs and to maintain accurate records of quality control procedures; and failure of quality assurance personnel to detect errors in equipment quality control records. In a letter dated March 20, 1996, ARC promised to conduct a thorough analysis of the deficiencies noted by FDA and to develop remedies for improving ARC's compliance. (See copies of VI.A letter and ARC's March 20, 1996 letter, attached hereto as Tabs 46 and 47, respectively.)

46. On February 9, 1998, FDA issued a VI.A letter to ARC, advising it that inspections conducted during the preceding year revealed continuing and cumulative deficiencies related to ARC's employee training program, including failure to ensure that training was conducted by qualified personnel and was adequate to ensure that personnel understood and could properly perform their assigned duties; failure to establish and implement a system to document completion of training by employees, prior to assumption of duties; failure to ensure that annual competency reviews were conducted; failure to ensure that personnel who did not satisfactorily perform their duties were not allowed to perform duties independently; and failure to maintain complete employee training records. FDA also advised ARC in that letter that despite assurance in 1996 from ARC that a revised master training plan would address all training deficiencies, FDA inspection findings showed that the revised plan did not resolve

ARC's training problems. By letter dated February 25, 1998, ARC acknowledged the inadequacy of its training program and committed to implementing corrective action. (See copies of VI.A letter and ARC's February 25, 1998 letter, attached hereto as Tabs 48 and 49, respectively.)

47. FDA issued the tenth VI.A letter on October 20, 1999, after an inspection of ARC's Southern Regional Blood Service Center, Atlanta, Georgia. The inspection, conducted in June - July 1999, revealed significant CGMP deficiencies, including *failure of quality assurance personnel to review and approve audit plans and results*; failure to ensure that personnel had capabilities commensurate with their assigned duties; *failure to ensure adequate quarantine*, storage, handling, *and disposition of unsuitable blood products; failure to follow ARC SOPs for relating or tracing each unit of blood through its final disposition; failure to investigate computer data discrepancies to determine the cause of those discrepancies; failure to follow ARC SOPs to resolve deviations in a timely manner*; failure to calibrate and maintain equipment, according to ARC SOPs; and failure to maintain equipment calibration and maintenance records. In a letter dated November 2, 1999, ARC promised corrective action and committed to full compliance in all ARC regional blood centers. (See copies of VI.A letter and ARC's

November 2, 1999 letter, attached hereto as Tabs 50 and 51, respectively.)

48. FDA issued the eleventh VI.A letter on October 19, 2001, after an inspection of the ARC Lewis and Clark Region's Salt Lake City Blood Service Center. The inspection, conducted in March – May 2001, revealed significant CGMP deficiencies, including *failure to establish, implement, and maintain a comprehensive quality assurance program*; failure to maintain management control of quality control procedures, in that there are inadequate numbers of supervisory personnel; *failure to establish a system to ensure and document that each employee has successfully completed an appropriate training program, prior to assuming their assigned duties*; *failure to adequately determine donor suitability,* including collecting blood from donors who self-administered health history records stated that they had AIDS or were at a high risk for having AIDS; *failure to follow ARC SOPs*; and *failure to establish and implement procedures to maintain strict control over labels issued during labeling operations and for reconciliation of quantities of labels issued, used, and returned*. (See copy of VI.A letter attached hereto as Tab 60.)

B. ADDITIONAL POST-DECREE WARNINGS TO ARC

49. FDA inspected ARC's Pacific Northwest Regional Blood Service Center, Portland, Oregon for a sixth time in August and September 1999, and found significant CGMP deficiencies, including *inadequate blood product inventory management,* inadequate SOPs for inventory reconciliation and investigation, and inadequate manufacturing equipment quality control. As discussed in ¶ 37 of this declaration, despite the seriousness of those deficiencies, FDA chose not to issue another VI.A letter to ARC. Instead, in a letter issued on January 28, 2000, FDA advised ARC of its concerns regarding an apparent systemic inventory management problem, in that similar inventory management deficiencies had been observed during FDA's June-July 1999 inspection of ARC's Southern Regional Blood Service Center, which were described in the October 20, 1999 VI.A letter. (See copy of January 28, 2000 letter, attached hereto as Tab 52.)

50. After entry of the Decree, FDA issued five additional letters to ARC, addressing ARC submissions under the Decree and FDA inspection findings. One such letter, issued on July 11, 1994, advised ARC of FDA's concerns about continuing *failure to establish management control over regional operations, failure to establish an adequate quality assurance program, and continuing deficiencies in ARC's computer systems and records management*. Those continuing CGMP deficiencies were observed

during FDA inspections of ARC regional blood service centers and National Headquarters, during the period December 1993 through June 1994. (See copy of July 11, 1994 letter, attached hereto as Tab 52.)

51. By letter dated June 26, 1995, FDA advised ARC that inspections of ARC facilities, conducted during the period July 1994 through July 1995, found continuing *failure to follow ARC SOPs, failure to ensure the accuracy and integrity of donor information records,* and failure to follow manufacturers' directions for infectious disease test kits. FDA also advised ARC that, in its opinion, ARC should direct its attention to managing donor deferral registry audits in all regions, *to correcting computer software defects, and to ensuring regional use of utility software programs intended to identify duplicate and discrepant donor records*. (See copy of June 26, 1995 letter, attached hereto as Tab 52.)

52. By letter dated October 9, 1996, FDA advised ARC that findings from inspections of ARC facilities, conducted during the period April 1995 through August 1996, raised concerns about ARC's continuing failure to adequately train ARC employees and ARC's *lack of progress in assessing the accuracy and integrity of donor information databases used to prevent release of unsuitable blood products*. (See copy of October 9, 1996 letter, attached hereto as Tab 52.)

53. By letter dated April 2, 1997, FDA advised ARC that findings from twenty inspections of ARC facilities, conducted by FDA during the period August 1996 through March 1997, revealed *continuing failure to follow SOPs*, *inadequate record maintenance,* inadequate employee training, deficiencies in laboratory deionized water systems, and an *inadequate quality assurance program*. (See copy of April 2, 1997 letter, attached hereto as Tab 52.)

54. By letter dated April 15, 1998, FDA advised ARC that findings from inspections of ARC facilities, conducted by FDA during the period April 1997 through March 1998, revealed continuing *failure to establish and follow ARC's SOPs*, inadequate employee training, and deficiencies in laboratory deionized water systems. (See copy of April 15, 1998 letter, attached hereto as Tab 52.)

C. POST-DECREE COMPLIANCE HISTORY OF ARC NATIONAL HEADQUARTERS

55. During January - March 1994, FDA inspected ARC National Headquarters, Arlington, Virginia and found significant CGMP deficiencies. FDA issued a letter to ARC under ¶ VI.A of the Decree. The contents of the letter are described in ¶ 41 above.

56. In January 1995, FDA conducted a limited, two day inspection of ARC National Headquarters and found that, although ARC was aware of a syphilis testing problem as early as April 1993, National Headquarters *took no action to notify its regional blood service centers or to resolve the problem* for a year, until April 1994. Specifically, National Headquarters had been notified by a region of a discrepancy between ARC syphilis testing SOPs and a syphilis test kit manufacturer's instructions for use. The discrepancy resulted in ARC's inaccurate interpretation of test results and the recall of 166,072 blood products. The inspection also found significant CGMP deficiencies, including failure to follow infectious disease test kit manufacturer's instructions, *failure to follow SOPs requiring that errors and accidents be reported to FDA promptly, and failure to establish an adequate quality assurance program, in that a known deficiency was not promptly corrected*. ARC promised corrective action in a letter dated February 14, 1995. (See copy of ARC's February 14, 1995 letter, attached hereto as Tab 53.)

57. During October-November 1995, FDA inspected ARC National Headquarters and found *deficiencies in ARC's audit of the national donor deferral registry*; the audit was required by ¶ III.B.11 of the Decree. The purpose of the audit was to assess the integrity of ARC's databases used to establish

suitability of donors. The inspection found that *ARC's quality assurance program failed to ensure that all duplicate and discrepant donor records that had been identified during the audit were resolved and* that computer systems were adequately validated. ARC responded by letter dated December 14, 1995 and promised corrective action. (See copy of ARC's December 14, 1995 letter, attached hereto as Tab 54.)

58. During March - April 1998, FDA inspected ARC National Headquarters and found that the *audit of the regional and national donor deferral registry databases, required by the Decree, was not completed within agreed upon time frames by all regions and that seven (7) regions had not completed recalls of all unsuitable blood products identified during the audit.* (Paragraph III.B.11 required ARC to submit to FDA a plan to assess the integrity of ARC's donor deferral registry. Paragraph III.B.11.c of the Decree required ARC to submit to FDA a specific plan that included procedures and time frames to correct errors found in the donor deferral registry. ARC failed to meet the time frames, established in its March 14, 1994 plan, for completion of the audit.)

The inspection also found significant CGMP deficiencies, including *failure of the quality assurance program to establish written procedures to ensure that the audit of the national and regional donor deferral registry databases was conducted*

effectively and that all detected errors were corrected to prevent subsequent collection of blood from unsuitable donors; failure of the quality assurance program to ensure effectiveness of the donor deferral audit, in that it did not provide prompt responses to regional blood service center questions regarding the audit procedure; failure to ensure that employees performing blood manufacturing functions are trained in those functions; and failure to follow ARC's HIV "lookback" SOP for donor samples with confirmed positive HIV p-24 antigen test results, a result that indicates that the donor is unsuitable. ARC's failure to follow its own HIV lookback SOP resulted in delays of up to eight weeks in notifying consignees of confirmed positive results. ARC responded by letter dated May 15, 1998 and promised corrective action. (See copy of the ARC's May 15, 1998 letter, attached hereto as Tab 55.)

59. During November 1998 - February 1999, FDA inspected ARC National Headquarters and found that *ARC was not adequately controlling the donor deferral registry audit,* in that during an assessment of the audit, it failed to recognize that four (4) regional blood service centers had not completed recalls of unsuitable blood products identified during the audit. These unsuitable blood products included thirty nine (39) units collected from donors who were not adequately tested for HIV and hepatitis. Additionally, ARC's training program was found to be

deficient in that new or revised SOPs were implemented, prior to the availability of materials used to train the employees responsible for the functions described in those SOPs. ARC responded by letter dated February 25, 1999, and promised corrective action. (See copy of FDA 483 Inspectional Observations and ARC's February 25, 1999 letter, attached hereto as Tabs 56 and 29, respectively.)

60. Under ¶ III.B.2.B of the Decree, ARC is required to report annually to FDA and state whether ARC is in continuous compliance with the law, ARC SOPs, and the provisions of the Decree. In the annual report submitted to FDA on December 15, 1999, ARC stated that its quality assurance program was successful and that it had provided senior management with the ability to oversee operations and monitor regulatory and procedural compliance. It further reported to FDA that its management control mechanisms contribute to effective oversight by ARC management. (See excerpts of ARC's December 15, 1999 annual quality assurance report, attached hereto as Tab 57.)

61. However, when FDA inspected ARC's National Headquarters in February - April 2000, it was presented with a quite different picture. At the end of the inspection, ARC was given a twenty one page, sixty-three item FDA 483 Inspectional Observations. Among the significant CGMP deficiencies observed during the inspection were *an inadequate inventory management*

and quarantine system that does not prevent release of unsuitable products and resulted in distribution of a unit of plasma that had positive hepatitis C test results and distribution and transfusion of a blood product that ARC had previously recalled, lost, and inadvertently re-distributed*; failure of the quality assurance program to correct high risk deviations found in ARC's inventory system; improper release by ARC of mislabeled cytomegalovirus-positive blood products; donors being associated with incorrect histories; inadequate ARC oversight of system problems*; failure to follow manufacturer test kit instructions (for HIV p24 antigen neutralization), resulting in the failure to perform ”lookback” investigations; *failure to promptly and adequately assess and correct problems; and failure to monitor the effectiveness of corrective actions*. Despite the many troubling observations during this inspection, FDA decided not to issue a VI.A letter. Nevertheless, by letter dated May 15, 2000, ARC stated that it understood the gravity of the issues identified during the inspection and promised corrective action. (See copies of the FDA 483 Inspectional Observations and ARC’s May 15, 2000 letter, attached hereto as Tab 58.)

62. In addition, on June 30, 2000, ARC met with FDA Baltimore District representatives, following the February - April 2000 inspection of ARC National Headquarters. During that

meeting, ARC admitted that it was *aware of the deficiencies* found by FDA, prior to the FDA inspection, *but that it failed to thoroughly investigate the problems, to assess them as systemic problems, to use available data to detect systemic problems, and to promptly correct and prevent problems*. *ARC also admitted that it lacked management commitment to quality and that it had not focused its resources on fixing problems*. ARC further admitted that it has a history of unfulfilled commitments to comply with the law, and that it has lost credibility with FDA. ARC attendees included Jacquelyn Frederick, Interim Vice President, Biomedical Services; Karen Anderson, Interim Chief Operating Officer, Biomedical Services; Stephen J. Stachelski, Jr., Interim Vice President, Quality Systems Support; Glenn Mattei, Interim Vice President, Quality Assurance and Regulatory Affairs; Tom Woteki, Chief Information Officer; and Gail Bredehoeft, Director, Quality Systems Support. FDA attendees included myself; Roberta F. Wagner, Baltimore Investigations Branch Director; Linda S. Mattingly, Baltimore District Investigator; and Mary T. Carden, FDA National Expert/Investigator. (See copy of the meeting minutes, attached hereto as Tab 59.)

IX. HISTORY OF ARC RECALLS

63. A recall is an action taken by a firm to remove from commerce products that FDA considers to be in violation of the law and against which FDA would initiate legal action. FDA classifies recalls according to the relative degree of health hazard presented by the product being recalled. A Class I recall is a situation in which there is a reasonable probability that use of, or exposure to, a violative product will cause serious adverse health consequences or death. A Class II recall is a situation in which use of, or exposure to, a violative product may cause temporary or medically reversible adverse health consequences or where the probability of serious adverse health consequences is remote. A Class III recall is a situation in which use of, or exposure to, a violative product is not likely to cause adverse health consequences. Each recall can involve numerous individual blood components. For example, on October 14, 1999, ARC recalled 50 units of red blood cells, 49 units of platelets, 49 units of platelets collected by pheresis, 10 units of fresh frozen plasma, 2 units of plasma, and additional blood products. (Pheresis is a process for removing one part of a donor’s blood and returning the remaining parts to that donor.) ARC initiated the recall after discovering the units had been incorrectly tested for syphilis,

then distributed. FDA classified ARC's recall of approximately 160 blood products as 4 Class II recalls.

64. A review of ARC's recall history reflects a dramatic increase in the number of unsuitable blood products released by ARC over the years. ARC reported to FDA:

- 36 recalls in fiscal year 1988,
- 83 recalls in fiscal year 1989,
- 61 recalls in fiscal year 1990,
- 207 recalls in fiscal year 1992,
- 186 recalls in fiscal year 1993,
- 161 recalls in fiscal year 1994,
- 290 recalls in fiscal year 1995,
- 310 recalls in fiscal year 1996,
- 655 recalls in fiscal year 1997, and
- 784 recalls in fiscal year 1998.

65. In fiscal year 1999, ARC initiated 522 recalls, involving 3,785 units of blood or blood components. FDA determined that 1,953 of those recalled products presented a Class II health hazard. (Of the 1,953 recalled units that were determined to present Class II health hazards, 1,874 were unsuitable because ARC violated the law.) None of the recalled units were determined to present a Class I health hazard.

66. In fiscal year 2000, ARC initiated 641 recalls, involving 12,701 units of blood products. FDA determined that

11,488 of the recalled units presented a Class II health hazard. (Of the 11,488 recalled units that were determined to present Class II health hazards, 1,958 were unsuitable because ARC violated the law.) None of the recalled units were determined to present a Class I health hazard.

67. The following are examples of Class II recalls that were initiated by ARC after the February-April 2000 inspection of ARC National Headquarters.

a. On October 10, 2000, ARC initiated a recall of 4 units of red blood cells that had not been tested for cytomegalovirus (CMV) in accordance with the test kit manufacturer's instructions and ARC's own SOPs. ARC discovered the error after the units had been tested, labeled as CMV negative, and distributed to consignees for transfusion. Three of the units had already been transfused in patients. FDA classified the action as one Class II recall.

b. On July 13, 2000, ARC initiated a recall of 2 units of platelets collected by pheresis that had not been tested for CMV, but had been labeled as CMV negative. ARC discovered the error after the units had been distributed to consignees for transfusion. Both units had already been transfused in patients. FDA classified the action as one Class II recall.

X. CONCLUSION

68. I believe that the foregoing facts show that FDA has expended an enormous amount of time and resources, and has shown a great deal of forbearance in an effort to encourage ARC to conform its blood processing operations with the law. Despite nearly 33,000 inspection hours, serious CGMP violations too numerous to count, a train of unfulfilled promises by ARC, and an array of moderate enforcement strategies, ARC remains non-compliant with the law. I am therefore asking the Court to do what FDA has been unable to do: order ARC to either comply with the law promptly and continuously, or pay substantial, daily monetary fines, until it does comply with the law.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on:_____2001 _____

Robert Lee Bowers
District Director
Baltimore District
Food and Drug Administration

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA, **Plaintiff,** **v.** **AMERICAN NATIONAL RED CROSS, a** Corporation, Defendant.	Civil Action No.93-0949 (JGP)

DECLARATION OF MARY T. CARDEN

INTRODUCTION

1. I am an investigator for the United States Food and Drug Administration ("FDA"). I have been employed as an investigator with the FDA for approximately 23 years. I have a Bachelor of Arts Degree in Biology, from D'Youville College, Buffalo, New York, and a Master of Science Degree in General Science, from the State University of New York at Buffalo. I have been an FDA National Expert in Biologics since 1988.

2. As a National Expert, my responsibilities include leading complex inspections of blood centers in the United States and in other countries that ship blood products to the United States; training other FDA, state, and foreign

investigators; and developing procedures and policies relating to the inspection of blood banks. I have personally conducted more than a hundred inspections of blood centers. I have also helped draft regulations relating to blood products and "Guidance Documents" to educate the blood banking industry on quality assurance and computer software validation issues.

3. I have testified before congressional committees concerning the blood industry and the FDA's oversight of that industry. In addition, I have testified before federal grand juries and at trial in two FDA cases against blood centers. I have had various responsibilities for oversight of three FDA consent decrees with blood banks, including the May 12, 1993 Consent Decree of Permanent Injunction ("the Decree") against the American National Red Cross ("ARC").

4. I have conducted numerous inspections of ARC, including three inspections of ARC's National Biomedical Headquarters located in Arlington, VA ("ARC National Headquarters") on February 1 to April 26, 2000, June-July 1991, and April-May 1990. Since 1990, I have inspected at least ten other ARC regional blood centers. I have also inspected numerous ARC blood donor centers.

5. The testimony in this declaration is based upon my 23 years as an FDA Investigator, which includes experience in regulating drugs, medical devices, and biologics, including

blood products. It is also based upon my personal observations while conducting the February – April 2000 inspection at ARC National Headquarters with Investigator Linda Mattingly of FDA's Baltimore District Office, and on my review of ARC records during those inspections and of correspondence submitted to FDA pursuant to the Decree.

OUTLINE OF TESTIMONY

6. My testimony in this declaration will discuss the following areas:

III. BLOOD BANKING IN GENERAL

A. Types of Blood Products (¶ 7);
B. Blood Safety (¶ 8);
C. Processing Products in a Blood Center (¶ 11);

IV. THE FEBRUARY-APRIL 2000 INSPECTION AT ARC NATIONAL HEADQUARTERS (¶ 20)

A. Quality Assurance in General (¶ 23);
B. Quality Assurance Under the Decree (¶ 24);
C. Specific Observations at ARC National Headquarters

(1) Distribution of Mislabeled CMV Products (¶ 26),
(2) Inadequate Quarantine and Inventory Control (¶ 39),
(3) Inaccurate Donor Registration (¶ 60),
(4) Failure to Promptly Correct Duplicate or Discrepant Records (¶ 76),
(5) Incorrect Release of Donor Hold (¶ 85),
(6) Failure to Maintain National Donor Deferral Registry (¶ 92),
(7) Failure to Correct Donor Assertion Errors (¶ 103),
(8) Incorrect Release of Deferral Code for Syphilis (¶ 115),
(9) Failure to Use Appropriate Test Procedures (¶ 127);

V. ARC HAS NOT CORRECTED THE NATIONAL HEADQUARTERS OBSERVATIONS: THE RECENT INSPECTION IN SALT LAKE CITY (¶ 145)

VI. CONCLUSION (¶ 162).

BLOOD BANKING IN GENERAL

Types of Blood Products

7. Blood and blood products, like all medical therapies, are not risk-free. The point of having carefully managed blood processing systems with effective quality assurance and quality control is to reduce this risk to the lowest possible level. Each donated unit of blood, referred to as Whole Blood, is usually separated by the manufacturer into multiple components, such as Red Blood Cells, Plasma, and Platelets. To ensure continued safety, purity and potency, components must be stored under specific temperatures and must be used within specific time frames. For example, Platelets are stored at room temperature and may not be used more than five days after collection. In practice, these components are generally transfused to different individuals who need different components, depending on their particular medical condition. For example, Red Blood Cells carry oxygen and are used to treat anemia. Platelets are used to control bleeding in patients with leukemia and other forms of cancer. Fresh Frozen Plasma contains clotting factors and can be used to control bleeding.

Blood Safety

8. The Federal Food, Drug, and Cosmetic Act, the Public Health Service Act, and federal regulations enacted under both those laws require, among other things, that blood and blood products used for medical purposes be manufactured in accordance with current good manufacturing practice ("CGMP") to ensure that blood products are safe, pure, potent and have the appropriate quality that they are supposed to have for medical use. (See 21 U.S.C. § 351(a)(2)(B); 42 U.S.C. § 262; 21 CFR Parts 210-211 and Parts 600-680.) These laws and regulations are also designed to prevent the transmission of infectious diseases such as HIV (Human Immunodeficiency Virus; the virus that causes AIDS), hepatitis B, hepatitis C, HTLV (Human T-Lymphotropic Virus), and malaria. See Declaration of Jay S. Epstein, M.D. (hereafter, "Epstein Dec."), ¶¶ 11-13.

9. CGMP safeguards applicable to the collection, manufacturing, and distribution of blood products include donor screening, donor deferral systems, test systems, quarantine systems, and procedures to detect and investigate manufacturing deviations to learn why they have occurred, to implement corrective action to ensure that they do not recur, and to monitor the corrections to ensure they have been effective. These CGMP safeguards are intended to be complementary so that deviations in one system may potentially be identified through

another system, thus decreasing the likelihood that unsafe blood products will be distributed. It is critical to note, however, that the safeguards are not always congruent and that the degree of assurance of a safe blood supply decreases as the number, relationship, and significance of poor manufacturing practices increase. See Epstein Dec., ¶¶ 8, 15.

10. A brief explanation of CGMP safeguards applicable to the blood industry is as follows:

a. A donor screening system is intended to eliminate unsuitable donors whose behavior is known to increase the risk of infectious diseases, such as HIV, hepatitis B, hepatitis C, HTLV, and malaria. Each person who comes to a blood center to donate blood is asked a series of questions designed to obtain information about his risk for these diseases. For example, donors who indicate they are or have been intravenous ("IV") drug users are known to be at increased risk for HIV and hepatitis infection and would be deferred from donating. If screening is done properly and carefully documented, blood products should not be collected from these individuals because recipients of such products would be put at risk. See Epstein Dec., ¶¶ 11, 16, 18, 19; 21 CFR §§ 640.3(b)(6), (b)(7), (c)(1-3), 610.41, 610.45(c)(1).

b. A donor deferral system is used to identify and keep track of donors who have been indefinitely or temporarily

excluded from donating blood. The system can be a manual or, as at ARC, a computerized database into which various donor names are placed, along with the reason(s) for (e.g., IV drug use) and length of deferral. If a deferred donor fails (whether inadvertently or intentionally) to provide accurate information (e.g., about his IV drug use) on a subsequent donation, a properly designed donor deferral system will identify the individual before unsuitable blood products collected from him have been distributed. Unsuitable blood products should be quarantined and destroyed to prevent their distribution. See Epstein Dec., ¶¶ 13, 16; 21 CFR §§ 606.160(b)(1)(ii), (e), 610.41, 610.45(c).

c. Test systems include testing of the donor's blood for various infectious diseases, such as HIV, hepatitis B, hepatitis C, syphilis, and HTLV. Testing systems are not infallible, however, for several reasons. First, no test system is sensitive enough to identify all infected donors. For example, a donor may be infected with the HIV virus but the donor may not yet have developed substances in his blood that can be detected by the test system. This period of time is referred to as the "window period." Second, the test may be performed improperly. Finally, even if the test does identify an unsuitable donor, the unit collected from that donor may not be removed from processing if the donor's blood sample is not identified

properly. See Epstein Dec., ¶ 15; 21 CFR §§ 606.140 (requiring scientifically sound test procedures to assure safe, potent blood), 610.45 (test for HIV), 610.40 (test for hepatitis B), 211.165 (requiring appropriate testing prior to release for distribution).

d. Quarantine and inventory system. Blood products are required to be placed into designated areas until all testing, processing, and record reviews have been completed. If a donor is identified by the donor deferral system or the testing system as unsuitable, all components originating from that donor must be placed in quarantine. The components are quarantined in two ways. First, the components are identified in the computer as quarantined, i.e. placed in "electronic quarantine." Second, each component must be physically moved from the designated area for in-process blood components to the designated quarantine area for unsuitable components.

When a blood component has passed all necessary tests and has been determined to be suitable, it may be moved from the in-process area, labeled, and released to inventory for distribution. Sometimes, a blood center receives information indicating that components are unsuitable, after the initial, in-house release; these components must be removed from inventory (or, if distributed, retrieved) and placed in quarantine. Because blood components are being frequently

processed, moved, and stored in different locations, blood centers must perform frequent inventories to ensure that they keep track of all blood components (in and out of quarantine), particularly those components that are unsuitable for transfusion. See Epstein Dec., ¶ 15; 21 CFR §§ 606.40(a)(3)-(6), 606.160(b)(1)(viii), 610.46, 610.47; 211.142.

e. The system for detecting, investigating, and correcting problems, more commonly referred to as Quality Assurance/Quality Control, must ensure: that manufacturing deviations will be identified promptly and thoroughly investigated to learn their causes, that corrective action will be implemented, and that corrections will be monitored to ensure that they are effective and will prevent recurrence of the error. See Epstein Dec., ¶ 14; 21 CFR § 211.22; Decree, ¶¶ III.B.1 - 2.B, III.B.14.

Processing Products In a Blood Center

11. The first step in processing blood products is the collection of blood from healthy donors. The results of the medical examination and health history are recorded along with information identifying the specific donor, including his complete name, date of birth, social security number, current address, and telephone number. If the results of the medical examination and health history are unacceptable, the unsuitable donor will not be allowed to donate blood, and will be deferred

either temporarily or indefinitely, depending on the reason for deferral.

12. However, if the results of the medical examination and health history are acceptable, the individual will be allowed to donate a unit of Whole Blood and a Whole Blood number is assigned to the Whole Blood unit that is collected. Pre-printed stickers with the Whole Blood number (and bar code of the Whole Blood number) are used to identify the blood bag(s) and the associated blood samples, which are collected in test tubes; an identification sticker is also placed on the written donor record containing his identification information, medical history, and results of the medical examination.

13. After blood collection, the unit of Whole Blood is sent to a processing area for component manufacture and the test samples are sent to one or more laboratories for testing. At the same time, the donor records are sent to data processing.

14. In the component laboratory, the Whole Blood is further processed into different components, such as Red Blood Cells, Platelets, and Fresh Frozen Plasma. The various components are then stored in quarantine areas for in-process blood, until testing has been completed and the components can be released.

15. While the blood is being processed, the donor's identification information and the Whole Blood number assigned

to the unit donated on that day are entered (registered) into the computer, which compares the information to the identifying information for all donors in the blood center’s system, to determine whether the donor has attempted to or has previously donated. If a donor being registered is listed in the center's donor deferral registry ("DDR") as being in a deferral status, the computer provides the name of the donor in a report, and the blood center reviews all records to determine whether the donor is the same individual as the one identified in the DDR. If the donor is the same individual, all blood components donated by him that day must be removed from storage areas for in-process blood components and placed in quarantine until they have been destroyed.

16. While the blood is being processed and donor registration is occurring, the donor's blood samples are sent to the laboratory for testing. For many of the infectious disease tests, the results are interpreted as initially reactive, repeatedly reactive, or nonreactive (negative). If the test for one of the viral makers, such as hepatitis, is initially reactive, the test must be repeated, in duplicate. If one or both of the duplicate repeat tests are reactive, the final test interpretation must be classified repeatedly reactive. When the test is repeatedly reactive, the components from that donation

are unsuitable and must be quarantined, both physically and electronically, until they are destroyed.

In some cases, additional testing, referred to as confirmatory tests, or additional, more specific tests (hereafter "additional tests") may be performed on the sample following a repeatedly reactive test. The results of additional tests are usually expressed as positive, negative, or indeterminate (indicating that a clear determination cannot be made, but that the sample is neither positive or negative).

17. When processing has been completed, results received, and the donation determined to be suitable, blood components may be released for labeling; final record review; and final release to distributable inventory.

18. FDA regulations require that each critical step in the manufacturing process be documented and that blood centers maintain records of the disposition, whether destruction or distribution, of every blood component. These records are indispensable to ensure complete recapture, whether by recall or market withdrawal, of components that have been distributed to hospitals and other consignees (hereafter, consignees) when a deviation that could affect the safety, purity, or potency of the product is identified with a product or with a donor. See also Epstein Dec, ¶¶ 13, 15; 21 CFR §§ 606.160(a)(1), 606.165, 211.150(b), 211.196.

19. Distribution records are also important when a blood center must perform a lookback procedure. Simply stated, lookback refers to the steps taken by the blood center to track potentially unsuitable blood products and, when necessary, to notify recipients of such products when a person who previously donated subsequently tests repeatedly reactive or positive for an infectious disease, such as HIV or hepatitis. The previously donated blood products are potentially unsuitable because the donor may have been in the "window period," that is, the donor was infected with a virus, but had tested negative because the donor had not yet developed substances in the blood that could be detected by the test system. In the case of repeatedly reactive HIV test results, the blood center must complete the notification of consignees of all unexpired components within 72 hours of receiving such test. See Epstein Dec., ¶ 25; 21 CFR § 610.46(a). Upon receipt of this notification, the consignee is required to quarantine any affected blood products. 21 CFR 610.46(a)(2). When the additional, more specific or confirmatory test results are received, all consignees previously notified of the need to quarantine unexpired products must be notified of those results so that the products they are holding in quarantine may be appropriately disposed of. 21 CFR 610.46(b), (d). In addition, if the confirmatory test results are positive, the blood center is required to notify the

consignees of all blood products previously collected from the donor, regardless of whether the products have expired. When the consignee's records document that a patient or patients have been transfused with any of the previously collected products, each patient's physician is asked to inform the patient of the need for HIV testing and counseling. 21 CFR 610.47(a), (b).

THE FEBRUARY-APRIL 2000 INSPECTION AT ARC NATIONAL HEADQUARTERS

20. During the February-April 2000 inspection of ARC National Headquarters (hereafter, "the inspection"), we observed that ARC is not complying with CGMP, ARC's own standard operating procedures ("SOPs"), or the Decree. The 63 observations that we observed and recorded on the FDA Form 483 - List of Observations (See Tab 1) show that ARC's Quality Assurance unit has repeatedly failed to identify critical deviations in the manufacture of blood products and when deviations were identified by Quality Assurance or ARC's regions, Quality Assurance failed to thoroughly investigate the cause(s) of those errors, failed to ensure that adequate corrective action was taken, and failed to monitor the corrective actions it took to ensure the actions were effective.

21. Neither during the inspection, or afterwards, did ARC managers contest the findings made by Investigator Mattingly and myself. For example:

a. In a letter dated April 27, 2000, to then FDA Commissioner Dr. Jane Henney, ARC's President and Chief Executive Officer, Dr. Healy stated that the FDA-483 that Investigator Mattingly and I gave to ARC at the end of the inspection "was a thorough and eye-opening evaluation and shows that we have a way to go under the current consent decree. The Board of Governors and I fully respect the gravity of the findings reported both in this evaluation and in prior ones that have necessitated the consent decree. The American Red Cross will work diligently with the FDA to address and correct the range of issues raised." See Tab 2;

b. On May 4, 2000, Investigator Mattingly and I met with Dr. Bernadine Healy, and ARC's Board of Governors. During that meeting, Dr. Healy said that she was taking the FDA-483 very seriously and promised immediate corrective action. She said she was extremely surprised with the inspectional findings because she was led to believe, by ARC senior management, that ARC National Headquarters was in control. Dr. Healy stated that she believed the FDA-483 could have been much worse because she noted several other issues that could have been further identified, had there been time. Dr. Healy also said that she was concerned about ARC's computer system and whether ARC should even be in the blood business.

c. In a letter dated May 15, 2000, ARC's Interim Vice President of Biomedical Services, Jacquelyn Fredrick, stated, ". . . ARC understands the gravity of the issues identified during this inspection and has taken a series of immediate actions to bring about prompt, comprehensive correction of both the inspection observations and their underlying causes . . . . Both ARC management and governance recognize the significance of the present situation and are committed to timely, definitive resolution of the identified deficiencies and the systemic weaknesses from which they arise." See Tab 3;

d. In the same letter, Ms. Fredrick also described her analysis of our findings, stating:

> "In-depth analysis of the observations reveals four recurring themes:
>
> - deficient timeliness in responding to problems and complaints reported to headquarters by the field,
> - deficient thoroughness in assessing problems and complaints,
> - deficient monitoring of the effectiveness of corrective actions to ensure appropriateness, and
> - deficient decision making and implementation."

Id., p. 1.

22. For purposes of this Declaration, I will discuss just nine examples that illustrate the manner in which ARC violates the Decree. For each example, I will explain the nature of the deviation and how FDA regulations and one or more ARC SOPs were

violated by the occurrence of the deviation and by the failure of ARC's Quality Assurance/Quality Control unit (hereafter, "Quality Assurance unit") to respond appropriately to the deviations. I will also identify the sections of the Decree that most directly apply to our findings. Before discussing the particular findings, however, it is important to understand the concept of Quality Assurance, both as a general matter and under the Decree.

Quality Assurance In General

23. A blood center must establish its own Quality Assurance program to ensure that it remains in continuous compliance with CGMP because FDA investigators cannot identify all of a blood center's deviations (hereafter, "deviation" or "error"), or even all of a blood center's significant errors. Because of limits on their time, limits on familiarity with and access to underlying documents, varying degrees of experience, and other factors, FDA investigators can only provide, on a snapshot basis, assessments of selected procedures and processes to determine whether a facility is in compliance with CGMP. Consequently, when a blood center is not properly self-identifying, investigating, correcting, and monitoring errors with its own Quality Assurance unit, it is a very serious matter. See Epstein Dec., ¶¶ 6, 10; 21 CFR § 211.22 (responsibilities of Quality Assurance/Quality Control Unit).

The existence of a deviation in one system in a regional facility may well indicate that other, similar deviations are occurring that are not being detected. It is the responsibility of the Quality Assurance unit to detect these system wide deviations and ensure that they are effectively corrected. See also Epstein Dec., ¶ 6; 21 CFR §§ 211.22, 211.192, 606.100(c), 606.160(b)(7)(iii).

Quality Assurance Under the Decree

24. The Decree reflects the critical importance of the Quality Assurance function to ensure the purity of ARC blood products. For example, paragraph III.B.1, in part, provides:

> Quality Assurance/Quality Control Programs
>
> Within one hundred fifty (150) days after entry of this Decree, ARC shall establish and implement comprehensive written quality assurance/quality control programs (hereafter, "the program") to ensure that blood products manufactured, processed, packed, held, and distributed by ARC have the safety, quality, identity, potency, and purity (hereafter, collectively, "purity") that they purport or are represented to possess. The program shall address, among other things: computer systems and automated databases; records management systems; procedures for investigating and reporting, both within ARC and to FDA, errors and accidents as defined in paragraph III.B.15; procedures for investigating adverse reactions . . . ; procedures for investigating suspected transfusion transmitted disease . . . ; procedures for investigating "lookback" cases . . . ; and internal audit procedures. (Emphasis added).

25. The Decree also establishes more specific requirements and standards that ARC's Quality Assurance unit must satisfy, again with the ultimate measure being compliance with CGMP. For example:

1. Paragraph III.A.2.c requires ARC's director of Quality Assurance to evaluate information, including "internal ARC audit reports, ARC error and accident reports, recalls by ARC, reports of FDA inspections . . ., and correspondence from FDA," and that "[w]ith respect to information suggesting possible non-compliance, the director of quality assurance shall assess, among other things, the potential public health risks posed by the information, whether the information reflects a deviation from the law, ARC SOPs, or the . . . Decree, and whether the information is similar to information that has come to ARC's attention in the past." (emphasis added);

2. Paragraph III.B.2.B requires that with respect to each new unresolved deviation that FDA brings to ARC's attention after entry of the Decree ARC must, at least annually, review the system, process and control "to ensure: (i) that each of the deviations has been corrected . . . or . . . otherwise been addressed to prevent its recurrence; and (ii) continuous compliance with the law, ARC SOPs, and . . . this Decree";

3. Paragraph III.B.14 of the Decree requires ARC to implement procedures with time frames for "initiating and

completing thorough investigations of errors, accidents, adverse reactions . . . and taking corrective action," when such events occur and to conduct prompt recalls of unsuitable blood products; and

4. Paragraph III.B.16.b and 16.d require ARC National Headquarters to review, within 10 days of receipt, reports from each region involving the release for distribution of any unsuitable blood product caused by a system defect (*i.e.,* an error resulting from a deficiency in an SOP, equipment (such as computer software), or supplies that could affect other ARC regions), and, within 30 days of when such an error is discovered, notify all of its regions of the defect and, when necessary, establish a written plan, with time frames, to correct the defect and prevent recurrence.

Specific Observations at ARC National Headquarters

Distribution of Mislabeled CMV Products

26. CMV (Cytomegalovirus) is a virus that can be transmitted through a blood transfusion and may cause disease in the recipient. In a healthy individual, the disease will cause only minor flu-like symptoms. However, for individuals who have never been exposed to the virus, such as babies born to CMV-negative mothers or individuals who are immunocompromised, the transfusion of CMV-positive blood components presents a significant risk. See Epstein Dec., ¶¶ 22-23. Therefore,

physicians sometimes specifically request CMV-negative blood components for use in low birth weight infants born to CMV-negative mothers and in certain immunocompromised individuals who are CMV-negative. Id., ¶ 23. While blood components that test positive for evidence of CMV or have not been tested for evidence of CMV are suitable for general use (and need not be labeled as CMV-positive or not having been tested for CMV), CMV-positive and untested units may not be safely used in patients at risk. Id. Federal regulations and the Decree require that ARC's component labeling be complete and accurate. See 21 CFR § 211.130 (requiring "written procedures designed to assure that correct labels, labeling, and packaging materials are used for drug products," and mandating that "such written procedures shall be followed"); 21 CFR § 606.122(h) (requiring that component labeling include the names and results of all tests necessary for safe and effective use); Decree, ¶¶ III, III.A.1, B.1, 14, 16.b, 16.d.

27. Blood centers manufacture and store CMV-negative products based on anticipated demand. ARC’s SOP for CMV products states that blood components can be labeled as CMV-negative only if they meet two criteria: First, the donor must test negative for evidence of CMV on the day of donation; second, the donor must have also tested negative for evidence of

CMV on all prior donations at which the test was performed. See Tab 4 (excerpt), p. ii.

28. As discussed more fully below, Investigator Mattingly and I reviewed records showing that product that tested positive for evidence of CMV, product that had not been tested, or product collected from donors who previously tested positive for evidence of CMV had been labeled as CMV-negative and distributed.

29. Because CMV-negative components are specifically ordered by the physician to meet patients' needs, once products mislabeled as CMV-negative have been shipped there is a high likelihood that the component will be transfused to the very individuals who should not receive such components and are particularly at risk. See Epstein Dec., ¶ 23.

30. We reviewed the manner in which Quality Assurance addressed the CMV labeling problem. Although both regions that initially identified and reported the errors to ARC National Headquarters (the Alabama region in February 1998 and the North Central region in November 1998) characterized the deviations as a potential system problem, ARC did not classify them as a system problem until approximately May 1999. See Tab 5 (Exh.#19B, p.2). ARC defines a system problem as a deviation that results from a deficiency in an ARC policy, procedure, type of equipment or supplies requiring corrective action that could

change an ARC-wide policy, procedure, or specification or that could modify or change the operations of ARC-wide equipment. See Tab 5 (Exh.#11B, p.3). ARC records indicate that a change request for the computer system to improve the CMV labeling process had already been identified but we were informed during the inspection that the change request was on hold. Moreover, ARC's files showed that Quality Assurance had closed the file on this system error on an unknown date and with no investigation, change to the computer system, or other corrective action having been documented. Id. (Exh.#19B, p.1).

31. Our review of ARC records showed that on May 18, 1999, the Penn-Jersey Region sent a Clarify® case to ARC National Headquarters stating that the region had physically labeled components CMV-negative when in fact the components were CMV-positive or had not been tested. (The Clarify System is one of ARC's reporting systems used by ARC regions to report deviations and ask questions pertaining to ARC SOPs and ARC's computer system.) The report also stated that four of the ten mislabeled products had been shipped and that the remaining six had been made available for distribution. On July 22, 1999, ARC National Headquarters closed the case stating that it "*is not a potential hazard*" and that the cause of the error was that employees were scanning too fast. See Tab 6 (emphasis added).

32. On May 20, 1999, the Greater Chesapeake and Potomac Region reported another error with products being mislabeled as CMV-negative. The error report indicates that five products were labeled as CMV-negative when they either had not been tested or tested positive for evidence of CMV; the error report also states that a recall was initiated. Additionally, the regional Quality Assurance officer asked that the case be characterized as a "potential hazard" in a Clarify case sent to ARC National Headquarters on May 20, 1999. See Tab 7 (Exh.#19F, p.7). Again, ARC National Headquarters told the regions the problem was caused by scanning too fast or operators not paying attention to screen prompts and messages; once again, ARC National Headquarters determined that the issue was "*not a hazard.*" See Tab 7 (Exh.#19F, p.8). On June 15, 1999, to address these errors, ARC National Headquarters sent a directive (BSL 99-130) to all regions instructing them to slow down when scanning. (Blood Service Letters are another ARC SOP; see Decree, ¶ III.A.1) See Tab 8, p. 7, note 10.

33. During the inspection, we requested that a query be run for all Clarify cases and error reports related to CMV. We were provided with 109 Clarify cases and approximately 50 error reports received by ARC National Headquarters between January 1998 and March 2000. Our review of the error reports revealed that in at least 21 cases the region reported release of one or

more products labeled as CMV-negative, when the component tested positive for evidence of CMV, was not tested, or was collected from a donor who previously tested positive for evidence of CMV. We learned that these reports had not been evaluated by ARC National Headquarters during its handling of this system wide error.

* * *

34. I have reviewed ARC's written responses to the CMV errors reflected on the FDA 483 List Of Observations left with ARC at the conclusion of the inspection. In the first response (May 15, 2000), ARC stated that it would establish "a manual review of the CMV labeling process to prevent mislabeling issues" and that, on a high priority basis, a computer enhancement "will be developed linking CMV test results to CMV labeling." ARC also stated that its analysis of the Clarify cases showed that the majority were associated with the early deployment of a new computer system and that there were a total of twenty-eight CMV labeling error reports in 1998, thirty-seven in 1999, and three in the year 2000, through May 15. See Tab 9 (excerpt), p.18. The second and fourth responses (June 21 and August 24, 2000) provided no new information. The third (July 21, 2000) response stated that ARC had completed an SOP for manual review of CMV labeling. In the fifth response (November 8, 2000), ARC stated that following implementation of several

BSDs the number of errors was declining. See Tab 10 (excerpt), p.6.

35. On December 15, 2000, ARC submitted an Annual Report to FDA, as required under paragraph III.B.2.B of the Decree (hereinafter "Annual Report"). In the Annual Report, ARC states that a BSL (00-131) was released to all facilities on June 30, 2000, which "requires that a second staff person verify that the component has been labeled correctly." See Tab 11 (excerpt of Annual Report), p. 024620. The Annual Report also states that the BSL (00-131) was implemented on August 1, 2000, and that another BSL (00-203) was implemented on October 12, 2000, both of which include additional checks on CMV labeling. Id., p. 024519. The report also states that a software fix has been issued to all regions and was to be implemented by January 31, 2001. Id. The report admits that, as of the date of the report, the data were still being monitored to determine the effectiveness of the corrective action, including the effectiveness of the manual workarounds mandated by the BSLs. Id. (A workaround is a manual or computer procedure developed to prevent specific software related errors.) Even though the effectiveness of the corrective action had not been confirmed, the report states: "Because a manual workaround was issued, this system problem is now closed." Id. at 024620.

36. These responses are not adequate. For example, they do not address why Quality Assurance failed to recognize CMV errors either as potentially very hazardous or as being system wide, why Quality Assurance failed to conduct a thorough investigation of the errors and to implement effective corrective action, how Quality Assurance intends to monitor the situation to prevent recurrence of these errors, and what Quality Assurance intends to do to address the fact that these errors are continuing.

37. Some examples of continuing errors made by ARC even after implementation of corrective action concerning mislabeling of blood products for CMV include:

a. On July 12, 2000, the Pacific Northwest Region allowed two units of Platelets collected by pheresis to be labeled as CMV-negative, when in fact, the units had not been tested for evidence of CMV. The units were both distributed and transfused. See Tab 12;

b. On September 26, 2000, the Northern California Region labeled a unit of Platelets as CMV-negative. The unit was actually CMV-positive. See Tab 13; and

c. On October 23, 2000, the Carolinas Region labeled a unit of Red Blood Cells as CMV-negative without verifying that the unit had been tested for evidence of CMV or verifying the test results. Subsequent testing for the unit was positive. The unit of Red Blood

Cells had been distributed to a consignee for transfusion. See Tab 14.

38. ARC also failed to initiate and complete a thorough and documented investigation of CMV-labeling errors and to take action to correct such errors involving the release for distribution of unsuitable blood product; ARC also failed to establish a written plan, with time frames, to revise procedures to correct the defect and prevent its recurrence.

Inadequate Quarantine and Inventory Control

39. Blood centers collect, test, label, and distribute blood components, simultaneously. Also, blood components are continually being moved from one location to another, based on processing and testing information being received. As a result, adequate quarantine and inventory procedures must be in place and followed at all times to ensure that blood components are in the appropriate inventory location, both physically and electronically, and can be promptly located and tracked. Inventory control is essential to prevent the release of unsuitable blood components. See 21 CFR §§ 211.82(b) (requiring quarantine of components pending release); 211.204 (requiring identification and holding of returned goods); 606.40(a)(3)-(6) (requiring adequate space for storage and quarantine of products); 606.160(b)(1)(viii) (requiring records of quarantined products that test repeatedly reactive for HIV); 606.165

(requiring a system of distribution and receipt records to facilitate ability to locate components and recall, when necessary); see also Epstein Dec., ¶¶ 10, 13.a, 15, 16; Decree ¶¶ III.B.1, 13.a, 13.e, 14, 16.b, 16.d.

40. Routine inventory checks also must be conducted because the large number of components being transported increases opportunities for misplacing components, and the health risks associated with misplacing even a single component of blood must be kept to the absolute minimum. See Epstein Dec., ¶ 7. When components appear to be lost during an inventory check, the missing components must be promptly found, and moved to the proper location, and the records must be corrected promptly and appropriately.

41. During the inspection, Investigator Mattingly and I reviewed ARC quarantine and inventory procedures as a follow up to errors found during an FDA inspection of ARC's Southern Region, in June-July 1999. Because Quality Assurance at ARC National Headquarters did not conduct an investigation to assess the scope and seriousness of the errors, we asked to see all error and accident reports and a list of ARC Clarify cases related to quarantine and inventory, for the period January 1, 1999 through February 2000.

42. Our request uncovered approximately 86 reports and approximately 160 Clarify cases submitted by the regions to ARC

National Headquarters that related to deficiencies in ARC's quarantine and inventory system during the thirteen month period covered by our request. As discussed below, many of the deviations resulted in the release of unsuitable products, violated federal regulations, and showed that the regions had failed to follow ARC SOPs. Nevertheless, despite the high number of inventory and quarantine-related error reports and Clarify cases reported by the regions, ARC failed to identify these errors as a system wide problem; in some cases, these unsuitable components were transfused into patients.

43. The following examples, in which ARC recalled or market withdrew unsuitable components, and later reshipped the same components, illustrate ARC's inadequate inventory and quarantine system and the failure of ARC's Quality Assurance unit to investigate, correct, and monitor ARC's defective quarantine/inventory system.

1. On November 9, 1998, the Southern Region, Atlanta, GA, released three components that had been recalled because the components had been stored at the incorrect temperature. When the components were returned to the region, they were not electronically quarantined and, according to the region's error report, were not placed in a "secure quarantine location." Consequently, the recalled components were later released in error and distributed. The region also reported

it had not followed its BSD. (A BSD is a Blood Service Directive; under ¶ III.A.1. of the Decree, a BSD is an SOP). See Tab 15;

b. On April 28, 1999, ARC's South Carolina Region released an unsuitable blood component that had been recalled; the component was reshipped, in error, and transfused into a patient. The region reported that the error was due to the failure to follow its BSD. See Tab 16; and

c. On February 4, 2000, ARC's Southern California Region reshipped a NAT (nucleic acid testing) pool reactive component (NAT testing is used to identify the HIV and HCV (hepatitis C) viruses) that had previously been withdrawn from the market by ARC. The region's error report indicates that the consignee reported the component had been transfused on an unknown date. The Southern California Region's report cited the ARC BSD that the deviation violated. See Tab 17.

44. Each of these failures to follow ARC SOPs for handling returned products violates 21 CFR § 211.204, which requires that written procedures for holding and reprocessing returned drug products "shall be followed."

45. Another error in ARC's quarantine and inventory system involves the final computer check on components that are designated for shipment. ARC's computer system is set, in some cases, to accept only 20 components per shipping container.

When the operator can *physically* fit additional components into the shipping container, the computer does not *electronically* accept those additional Whole Blood numbers into the database. As a result, no final check can be performed by ARC's computer system to determine whether such components are suitable for shipment and use by patients. This deviation in ARC's inventory management system violates 21 CFR § 606.165(a), which requires that "[d]istribution and receipt procedures shall include a system by which the distribution or receipt of each unit can be readily determined to facilitate its recall, if necessary." See also, 21 CFR § 211.150(b).

46. During our inspection, we reviewed an ARC error report showing that ARC's Gulf Coast Region had been contacted by the Swiss Red Cross ("SRC") on September 7, 1999. The SRC reported that it had received a component from ARC; however, because the ARC Whole Blood number for the component was not on the packing list received by the SRC, SRC destroyed the component. ARC's investigation revealed that the extra component shipped to the SRC had tested repeatedly reactive for hepatitis C. During the inspection, we were told the 20-unit electronic limit may have been part of the reason the error occurred. In addition, ARC's error report submitted to FDA on September 28, 1999, indicates that ARC BSDs in place at the time (BSD 66.101M Quarantine and

Release and BSD 73.200M Shipping) had not been followed. See Tab 18. See also 21 CFR §§ 606.165(a), 211.150(b).

47. An ARC error report dated October 14, 1999 shows that there were two components that could not be located by ARC's Southern Region. One was positive for hepatitis B surface antigen test and was *electronically* located in a quarantine location; the other was reported as positive for hepatitis B core antibody and was *electronically* located in an in-process component location. However, neither of these products could be found by ARC in the *physical* location referenced electronically, or in any other inventory location. See Tab 19. Our review of this report showed that the component that was positive for hepatitis B surface antigen test had been identified as "lost" during an earlier FDA inspection of the Southern Region, in June 1999. During the June 1999 FDA inspection, the component was located behind a platelet agitator; however, following the inspection, it was "lost" again, and to this day has not been located by ARC. Id. See 21 CFR §§ 606.165(a); 211.150(b).

48. On May 11, 1999, the Southwest Region submitted an error report stating that the region had lost track of two components, one suitable, and the other unsuitable because it was repeatedly reactive for HIV. During the region's investigation of this report, the suitable component was eventually located. The suitable component had never been

shipped, even though the Whole Blood number for this component appeared on a packing slip, which indicates shipment to a customer. However, the unsuitable, repeatedly reactive HIV component, could not be located. The consignee who had been identified on the packing slip for the suitable component was contacted by the region to determine whether it had received the missing, unsuitable component. The consignee reported that it had used all the components received in the shipment, and therefore, was not able to verify the Whole Blood numbers of the components it had received. See Tab 20. To date, ARC has not been able to determine the final disposition of this unsuitable component, in violation of 21 CFR §§ 606.160(b)(3)(i), 606.165(a); 21 CFR § 211.150(b).

49. During the inspection, we attempted to verify information provided by ARC to FDA in a March 15, 2000 report required by paragraph VI.B of the Decree. (ARC's report followed an October 20, 1999 VI.A letter that FDA sent to ARC National Headquarters notifying ARC of significant CGMP violations observed by FDA at ARC's Southern Region. Included among FDA observations were deviations in the region's inventory and quarantine procedures. See Bowers Dec., ¶ 47, Tabs 50 and 51. Further correspondence was exchanged that resulted in FDA seeking, and ARC providing, a report assessing the inventory and quarantine systems for all ARC regions.) The March 15, 2000

report stated that ARC's assessment of the inventory and quarantine concerns raised by FDA had revealed that "no findings designated as high risk were reported by any region." See Tab 21 (excerpt), p. 023614. The report defined "high risk" as "risk for erroneous product release." Id., p. 023613.

50. To verify ARC's assessment, during the inspection we requested the underlying reports from each region on which ARC's report was based. Our review of this information, which included an ARC National Headquarters document entitled "Evaluation of Atlanta 483" that reviewed reports and assessments from Quality Assurance officers from all ARC regions, revealed that ARC's March 15, 2000 report to FDA excluded many significant events. For example, ARC's Ft. Wayne Region had reported that two Plasma products that were repeat reactive for HIV had been released for distribution, but not actually distributed. Regional Quality Assurance staff indicated that the error was due to the failure to follow a BSD. See Evaluation of Atlanta 483 and Regional Assessments, attached hereto as Tab 22 (excerpt, Exh.#6G, pp. 2 and 52).

51. During the inspection, we found that ARC National Headquarters had failed to advise FDA, in the March 15, 2000 report, of eleven other significant problems that were discussed in the "Evaluation" and regional assessments. For example, other regions had reported to ARC National Headquarters Quality

Assurance that they had not completed all or some of the inventory reconciliations required by ARC SOPs:

2. The Missouri-Illinois Region reported four of its sixteen inventory locations were either being checked at the wrong time intervals or were not being checked at all. See Tab 22 (excerpt, Exh.#6G, p. 62);

3. The Western Lake Erie Region reported that its employees had stated that, due to staffing levels, they do not routinely visit the quarantine areas to verify whether product is in fact where it is supposed to be. The region also reported that when monthly inventory reconciliation is done “the numbers may be off by one or two units,” but that it does not investigate these discrepancies. Id. (Exh.#6G, pp. 49-51); and

4. The New York Penn Region had reported that its retrospective quarantine report was being reviewed, but as of the date of the report, had identified no issues that were not resolvable or explainable. Id. (Exh.#6G, p. 32).

52. To verify the information in the "Evaluation," we requested regional assessments and any associated deviation or error reports from the New York Penn Region, that were mentioned in the "Evaluation." Our review of these reports showed that in one case the region could not locate one or more components from 64 Whole Blood numbers (See Tab 23); a second report showed that the region "lost" three reactive components (See Tab 24); a

third report showed that 29 components were missing from one inventory location. See Tab 25.

53. ARC's failure to appropriately respond to significant quarantine deviations of which it becomes aware is also illustrated by an unresolved report it received from its Mid Atlantic Region. In a Clarify case from the Mid Atlantic Region, dated September 8, 1999, the region reported that a Whole Blood number for an unsuitable blood unit was not listed on the region’s quarantine report. We noted that this case had not been closed, and was not even in the process of being investigated. When we brought the unresolved report to the attention of Quality Assurance, it was reviewed and the case was closed on March 2, 2000, based on the *region's* decision to close the case with no further investigation. After reviewing the March 2 report, we brought this matter to Quality Assurance’s attention, a second time; we informed ARC that an inaccurate quarantine report was a critical matter and that no investigation had been conducted, either by the region or ARC National Headquarters. ARC returned the case to the Headquarters reviewer for a full assessment; later, during our inspection, we were informed that the deviation was caused by a software bug and that ARC National Headquarters would undertake a full evaluation.

54. ARC has an SOP that requires its regions to report the number of "lost products" and, of the number "lost," the number that are unsuitable. See BSL 97-104, Tab 26. An ARC National Headquarters LOP (Local Operating Procedure, which is another type of ARC SOP; see Decree, ¶ III.A.1) requires that the regional reports be consolidated into quarterly reports at ARC National Headquarters for review by, among others, ARC's Director of Quality Assurance. See LOP 10.518, Tab 27.

55. During the inspection, we requested the quarterly reports for the calendar year 1999, and were told by Glenn Mattei, Senior Director, Quality Assurance/Regulatory Affairs, that they had not been prepared yet, even though ARC's Quality Assurance unit had noted in September 1999 that these reports had not been completed for four quarters (December 1998-September 1999). The reports were later completed and provided to us during the inspection.

* * *

56. I have reviewed ARC's written responses to the quarantine and inventory deviations reflected on the FDA-483 List of Observations issued at the conclusion of the inspection. In the first response (May 15, 2000), ARC indicates two task forces, the Inventory Management Work Group and the Plasma Quality Team would be combined to form a single project team devoted to examining the entire inventory process. The second

response (June 21, 2000) indicates that a number of new procedures would be issued, there would be management review of lost product reports and software enhancements would be evaluated. The third (July 21, 2000), fourth (August 24, 2000), and fifth (November 8, 2000) responses did not provide any additional information.

57. None of ARC's responses address the issue of why the regions were not following ARC SOPs, how changing the SOPs would correct the deviations, why ARC's National Headquarters Quality Assurance unit failed to notice that regional quarterly reports on lost products were still not being submitted, even after the deficiency was pointed out during an internal audit, and why Quality Assurance failed to treat the widespread and serious quarantine and inventory deviations as a system wide problem that needed a prompt and thorough investigation and system wide corrective action.

58. In the Annual Report, ARC represented to FDA that of the 63 observations on the FDA 483 List of Observations left with ARC at the conclusion of our inspection of ARC National Headquarters, only "[t]hree (3) observations are still open." See Tab 28 (excerpt of Annual Report), p. 024473. The three identified, still-open observations do not include ARC's continuing quarantine and inventory deviations, even though elsewhere in the Annual Report ARC states that shipping

discrepancies continued in October 2000, and actually were on the rise in November 2000, despite the two SOPs it had issued on March 20, 2000 to correct inventory and shipping errors (BSLs 00-031 and 00-032). Id., p. 024480. Error reports ARC submitted recently to FDA confirm that the very same types of inventory and shipping errors observed during our inspection are continuing. For example:

5. In October 2000, ARC was notified that the Swiss Red Cross had received two Plasma components that were not listed on the packing slip for the shipment. The deviation occurred because personnel in the Pacific Northwest Region had failed to follow an SOP requiring that units in a shipment be physically counted and compared to the number of units listed on the packing slip. See Tab 29;

6. Two similar errors occurred in the New England Region on November 27, 2000. One unit of Plasma was listed on a packing slip, but had not been shipped to the consignee. Additional investigation by ARC showed that another unit of Plasma in the same shipment had been incorrectly labeled and shipped to the consignee. See Tab 30.

59. Although ARC classified errors of this type as a system problem (#474), see Tab 28 (excerpt of Annual Report), p. 024536, ARC did not include this system problem among the list of 27 still-active system problems, id., p. 024616-627,

even though ARC plans to issue additional corrective BSLs, for which target implementation dates and effectiveness checks have not yet been established. See id., p. 024536.

Inaccurate Donor Registration

60. As discussed in paragraph 12 above, when an individual is accepted as a donor, a Whole Blood number is assigned to his donation on that day. This number must correspond to all testing performed on that Whole Blood unit and be reflected on all distribution records associated with the components derived from the unit. See Epstein Dec., ¶ 13; 21 CFR § 606.160(c) (requiring the donor number to be assigned and to relate to all components derived from the donation, medical records, and all records describing the history and disposition of the components). Blood centers must also maintain records that accurately relate the donor to every Whole Blood number ever associated with the donor, 21 CFR § 606.160(b)(1)(vii). An important purpose of these requirements is to facilitate recall (21 CFR § 606.165(a)) and HIV “lookback.” See Epstein Dec., ¶¶ 13, 15, 16; 21 CFR § 610.46; Decree, ¶¶ III.B.1, 12, 13.a, 14.

61. During ARC's donor registration process, when the operator enters a donor’s name, the computer screen may present several donors' names that are similar to the donor being registered. For example, if the operator entered the name "John

Smith," ten names may appear on the screen with the same date of birth, different dates of birth but the same social security number, or even two different social security numbers for the same individual. Also, one or more of the ten names may not be exactly "Smith" because the system will also identify names that sound like "Smith." Consequently, the operator must carefully look for an exact match on all identification criteria to select the correct donor. A donor will not appear on the list if he is a new donor. Even when a person represents himself as a new donor, the operator must review the list to make sure that the donor is in fact not on the list, because donors occasionally forget about previous donations or deliberately misrepresent their donation history.

62. In ARC's computerized donor registration system, the first name that appears on the list is highlighted on the computer screen, regardless of whether this donor is the same person, or even the best match. Hitting the computer's "enter" key will select the highlighted name. Accordingly, if the operator incorrectly hits the "enter" key without verifying all information, the wrong donor name may be selected and the Whole Blood number will be associated with the wrong donor.

63. For example, donor A is assigned Whole Blood number 12345. During registration, the operator fails to verify all information, and incorrectly selects donor B. The computer will

not assign any of the information for Whole Blood number 12345 to donor A's permanent record. Rather, the computer will place all information for Whole Blood number 12345, including medical history actually obtained from donor A and results of laboratory tests actually performed on a blood sample obtained from donor A, into donor B's permanent record. The error may or may not be identified after additional processing. In this hypothetical example, any positive laboratory test result for donor A will incorrectly be associated with donor B. Donor A's permanent record would contain no documentation of the positive test result or appropriate deferral code. If donor A returns to donate again, his record would show no deferral code, he would be allowed to donate, and components from donor A may be distributed. Although the Whole Blood from donor A's return visit will be tested, if any of the potential test system errors mentioned above in paragraph 10.c occur (see also Epstein Dec. ¶ 15), the unsuitable blood products from donor A may be released and cause recipients to become infected.

64. Another reason that the Whole Blood number must be continuously associated with the correct donor is to enable blood centers to perform the lookback procedure and to conduct effective market withdrawals. As previously discussed, a donor may be in a "window period" and, although testing was properly performed, the results are negative. In these cases, blood

centers will not be able to determine, based on test results, that a blood product is unsuitable and prevent its release and use for transfusion. (See ¶ 10.c above; Epstein Dec., ¶ 25.) Therefore, in another hypothetical example, donor A tests positive for HIV on his twelfth donation. Donor A's Whole Blood number and all associated records for donor A's ninth donation were mistakenly assigned to donor B. The error was not detected. Patients who were transfused with products made from donor A's ninth donation can not be identified when the blood center does a "lookback" through records of past donations for donor A. These patients will not be notified of the risk; nor can in-date products derived from donor A's ninth donation be market withdrawn. Moreover, if a patient received a component from donor A's ninth donation, *was infected* with HIV, and is not notified of the risk, he will not know to seek medical care, to abstain from donating, or to take other measures to prevent the secondary spread of the disease. See also, Epstein Dec., id.

65. During the inspection, we reviewed the manner in which ARC's Quality Assurance unit responded to donor registration errors, and found it to be inadequate and untimely. ARC National Headquarters first became aware of the errors in April 1998 when the South Carolina Region reported an error in a Clarify case and asked for a computer search (query) to assist it in finding other, similar errors. ARC referred the region to

“requirements” (a National Headquarters group that evaluates the capability of ARC's computer system to meet established requirements) for assistance to learn whether a query was possible. The region was told that all records should be reviewed, and the case was closed. See Tab 31.

66. On August 20, 1998 and March 11, 1999, the New England Region asked ARC National Headquarters for a query to help it identify the same type of donor registration errors. ARC’s Clarify case report, dated March 11, 1999, states that the region thought the issue was “very important to the safety of the blood supply.” Nevertheless, ARC closed the case on January 10, 2000, and the region was told that its request would be sent to “enhancement" (a National Headquarters group that evaluates suggestions for changes to the computer system). See Tab 32.

67. On March 22, 1999, two regions (New England and Penn-Jersey) submitted the very same type of error to ARC National Headquarters, characterizing the errors as a potential system problem. See Tabs 33. However, ARC did not assign a system problem number to the errors, until July 7, 1999, three and one-half months later.

68. We requested information on any corrective action that had been taken to address these errors. Despite the obvious significance of incorrect assignment of Whole Blood numbers by multiple regions, we learned that no investigations had been

undertaken and no adequate corrective action had been implemented. ARC's system problem file, which we reviewed, showed that ARC discussed the idea of developing a query to investigate the scope and causes(s) of the deviations; however, we were told that this step had not been taken.

69. We also learned that on January 7, 2000, ARC National Headquarters told all regions that a computer enhancement was *scheduled* and that the regions should remind staff that selecting the correct donor is critical. We were given a note, dated November 30, 1999, indicating that several additional steps had been added to a BSD (43.201M) to address the errors, but that the added steps had not fixed the problem. See Tab 34. We were also told that two BSLs (#99-202 and #99-226) had been released to minimize duplicate donor information; however, we reviewed these BSLs and could not determine that any of the procedures described in them would prevent the types of donor registration errors that we reviewed.

70. In short, the inaccurate donor registration deviations had not been, and insofar as we could tell during the inspection, were not being addressed by ARC's Quality Assurance unit.

71. During the inspection, we tried to learn the *extent* of the donor registration errors by requesting pertinent reports from all ARC regions for the period September 1, 1999 through

March 1, 2000. Approximately 140 such reports were provided to us. Our review of these reports showed that the inaccurate donor registrations continued to occur after ARC's January 7, 2000 notification to its regions. Although ARC had told us that it regarded the January 7, 2000 notification as corrective action, our review of ARC error reports showed that between January 7, 2000 and March 1, 2000, the regions reported 15 additional incidents in which a Whole Blood number had been associated with the wrong donor.

* * *

72. I have reviewed ARC's written responses to the incorrect donor registration issues reflected on the FDA 483 List of Observations left with ARC at the conclusion of the inspection. In the first response (May 15, 2000), ARC indicates it planned to release a BSL in June 2000 to address the donor registration problem, and effectiveness checks would be included in the process. The second response (June 21, 2000) indicates that a BSL (#00-130) was issued instructing the regions to monitor the number of times the wrong donor is selected and report such information to ARC National Headquarters. ARC stated that the BSL would be implemented by August 31, 2000, and that the first data would be reported to ARC National Headquarters by October 10, 2000. The third (July 21, 2000) and fourth (August 24, 2000) responses provided no additional

information; the fifth response (November 8, 2000) indicates that ARC regarded the corrective action for these donor registration errors as completed and verified.

73. These responses are inadequate, for several reasons. First, none of the responses addresses the need to develop computer searches to identify the donor registration errors that may still be in the database(s) and to correct these errors. Second, ARC has provided no information to show that it intends to change the donor registration procedure to ensure errors are identified when they occur so that they may be corrected before unsuitable units are distributed.

74. ARC's Annual Report confirms ARC's decision to take no further action; donor registration errors were not among the three observations listed on the FDA 483 List of Observations that ARC considers still "open." See Tab 35 (excerpt of Annual Report), p. 024473.

75. When ARC National Headquarters learned of the donor registration errors, the Quality Assurance unit failed either to initiate and complete a thorough, documented investigation or to take effective corrective action to prevent recurrence of the errors. The investigation and corrective action should have been implemented immediately because the donor registration procedure is critical to ensure that: (1) ARC can readily track and locate unsuitable components; (2) records can be readily

located; (3) unsuitable components can be properly recalled, when necessary; and that (4) the lookback procedure can be performed properly, when required. In addition, once ARC National Headquarters was made aware of the donor registration deficiency in its computer system, it should have performed a retrospective review of records to identify and correct all inaccurate and incomplete data, so that recalls and lookback could have been performed, as necessary, on products that were previously distributed.

Failure to Promptly Correct Duplicate or Discrepant Records

76. As noted, when individuals register, they may provide incorrect information and, even when the donor provides accurate information, errors occur when the information is misread or entered into the computer incorrectly by the operator.

77. Data entry errors occurring at donor registration can result in a failure to identify a donor as a previous donor. Specifically, when a current donor's information does not precisely match the information he provided in the past, the operator may erroneously classify him as a new donor and create a new record for him in the computer. This results in a duplicate or discrepant record for the same donor. These erroneous records create the opportunity for the release of unsuitable products because, for example, if the donor was previously deferred, his deferred status may not be recognized.

See Decree, ¶ III.B.7 (defining duplicate or discrepant donor). It is therefore very important to correct duplicate or discrepant records as soon as possible because each day the incorrect information remains in the system increases the likelihood that an unsuitable blood component will be released. See Epstein Dec., ¶¶ 7,13,15; 21 CFR §§ 606.160(b)(1)(vii) (requiring records to be maintained that "relate the donor with the unit number of each previous donation from that donor"); 606.160(e) (requiring that "[a] record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed"); Decree, ¶¶ III.B.1, 8, 9, 12, 13.e, and 14.

78. ARC has an SOP (BSD 43.109M, Identification and Resolution of Invalid and Duplicate Records) that requires each region to research, classify, and correct any potential duplicate or discrepant record within 90 days of its first appearance on a duplicate and discrepant record utility report and to report this information to ARC National Headquarters on a monthly basis. See Tab 36, p. ii. Upon receipt of these monthly reports from the region, ARC National Headquarters processes the reports according to LOP 10.504, Management of Donor Deferral Register (DDR) – Related Products. See Tab 37.

79. During the inspection, we reviewed the manner in which ARC National Headquarters responded to the monthly information

received from its regions showing that the region had not resolved the records within 90 days. We found several regions that had taken excessive amounts of time, in one case as long as sixteen months, to correct duplicate or discrepant records, yet ARC National Headquarters failed either to ensure that the records were reviewed and corrected and that all applicable SOPs had been complied with, or to explain why more time was necessary and to implement a plan to investigate and correct the duplicate and discrepant records. In addition, the procedure used by ARC National Headquarters does not address the reporting requirements to FDA. For example:

80. The South Carolina Region identified 14,407 duplicate or discrepant records in October 1999. In December 1999, the region informed ARC National Headquarters that it had been unable to resolve all the records and requested permission to have a full year (October 2000) to complete the project, because the remaining records needed researching through hard copy records. ARC's Vice President of Quality Assurance approved this request on January 21, 2000, without justifying why a longer time period was necessary to correct the records and without implementing a plan to complete correction of the records. See Tab 38. Nor did ARC notify FDA in writing of the region's failure to correct its records, or the remedial actions

that ARC had taken or planned to take to investigate and correct these records.

Because we were not previously aware of the failure to resolve these duplicate or discrepant records, we requested information to learn why ARC National Headquarters had allowed a full year to resolve the records; in response to our request during our inspection, we were provided with a note written by the region stating that it would submit a plan to ARC National Headquarters for approval, by February 7, 2000. The note further explains that between February 8 and February 18, 2000, the region would recruit and train additional staff to review records and that all such records would be resolved by June 2000.

81. In another instance, the Missouri Illinois Region had identified 15,947 potential duplicate or discrepant records, following its conversion to a new computer system in June 1998. In October 1998, the region informed ARC National Headquarters that it had duplicate and discrepant records unresolved after 90 days. These records were not resolved until approximately sixteen months later, in October 1999. ARC National Headquarters did not explain why more than 60 days was necessary to make the corrections or implement a plan to make the corrections. Nor did ARC report to FDA in writing the fact of the region's failure to correct the duplicate or discrepant records, the results of the review and of all remedial action

that had been or would be taken regarding inadequate investigations or corrections. We discovered the region's report during our inspection.

* * *

82. I have reviewed ARC’s written responses to the duplicate or discrepant donor records issue reflected on the FDA 483 List of Observations left with ARC at the conclusion of the February-April 2000 inspection. In the first response (May 15, 2000), ARC states that the Vice President of Quality Assurance instructed the regions to report all failures to correct the records in 60 days to Quality Assurance, and that Quality Assurance would report these incidents to FDA. The second response (June 21, 2000) states that this action was completed, and the third response (July 21, 2000), states that corrective action was verified. The fourth and fifth responses (August 24, 2000; November 8, 2000) provided no additional information.

83. In contrast to ARC's June and July 2000 assurances that it had implemented and verified corrective action resolving duplicate or discrepant records in all regions, ARC's December 15, 2000 Annual Report reveals that additional regions have not resolved duplicate or discrepant records within the time frames required by ARC's BSD. For example, the Annual Report states that the Southern Region has 22,441 potential duplicate or discrepant records that the region discovered on June 16, 2000.

See Tab 39 (excerpt of Annual Report), p. 024582. Nonetheless, ARC has not explained why more than 60 days is necessary to correct the records, even though those duplicates apparently remain unresolved at least as of ARC's December 15, 2000 Annual Report. Nor has ARC notified FDA of the results of ARC's review of the reasons for the region's failure and of all remedial action that ARC proposes to correct the records with time frames.

84. When ARC regions did not resolve duplicate and discrepant records within the time frames required by ARC's BSD and the Decree, the Quality Assurance unit failed either to ensure the records were resolved in an additional 60 days, or to explain why the records could not be resolved within that time frame and implement a plan, with time frames, to complete the review and correction of the duplicate and discrepant records. In addition, ARC National Headquarters failed to notify FDA in writing of these failures within 70 days after it learned of the regions' failures and of the remedial action that had been or would be taken to address the record errors.

Incorrect Release of Donor Hold

85. During the registration process, the computer operator who enters the donor identifying information often may not be able to read the information on the donor card or may be unsure whether the donor being registered exactly matches a donor

already in the system. In these instances, the operator is supposed to place the donation on hold in the computer system until all of the information can be carefully reviewed and, when necessary to resolve the issue, the donor contacted. Only after correct information has been obtained and entered into the database should the hold be released. And, only after the hold has been released, should the corrected information be checked against the donor deferral registry to determine whether the donor is in a deferred status.

86. On July 21, 1999, ARC National Headquarters learned through a Clarify Case (#126528) from the Gulf Coast Region that operators were releasing the hold before correcting the donor information. When holds are prematurely released, new information relating to the donor cannot be screened against the donor deferral registry and unsuitable components may be distributed. See Epstein Dec., ¶ 13; 21 CFR § 606.160(e) (requiring availability of records to identify unsuitable donors to prevent the distribution of products from such donors); Decree, ¶¶ III.B.1, 13.e, 14.

87. ARC apparently recognized the potential serious consequences of this deviation because the notes in the Clarify case file reflect that the case should be upgraded to a "potential hazard." See Tab 40. In its initial attempt to address these errors, ARC National Headquarters sent a BSL (#99-

165) dated July 22, 1999, reminding the regions that donor records should be corrected before releasing the hold. See Tab 41. On September 22, 1999, all regions were also provided with the results of a computer query (BSL-99-208) that ARC had performed to identify each occasion when the hold had been prematurely released by the operator; in the same BSL, ARC National Headquarters asked each region to review its records against donors identified by the query to determine whether unsuitable products had been released.

88. During our inspection, ARC told us that the donor hold error had been corrected with the BSL instructions. However, our review of ARC documents showed otherwise. At our request, ARC performed another query of the regions' database for the period July 22, 1999 (when BSL 99-165 was released) to March 2000. The results of this second query showed that the BSL instruction was not being followed and, as a result, that donor holds were still being released before the donor identification information was changed. For example, the query showed that donor holds were being released before records had been corrected on approximately 480 occasions in the New York-Penn Region, 636 times in the Penn-Jersey Region, and 289 times in the Greater Chesapeake and Potomac Region. When ARC learned, from the query, that the BSL was not being followed, its solution was to again ask the regions to correct their records

based on the second query. This action was not completed before our inspection ended.

* * *

89. I have reviewed ARC's written responses to the donor hold issue reflected on the FDA 483 List of Observations left with ARC at the conclusion of the inspection. In the first response (May 15, 2000), ARC stated that the results of the query that we requested during the inspection were released to the regions with instructions for record review. ARC also stated it would run a query on a monthly basis and that it would "evaluate" a change to the computer system, for future release. The second (June 21, 2000), third (July 21, 2000), and fourth (August 24, 2000) responses did not provide any additional information. The fifth response (November 8, 2000) stated that the corrective action was completed and verified. ARC's responses did not provide any information regarding the number of times that the regions failed to use the correct donor hold sequence, which was the underlying error to be investigated and corrected, or whether any unsuitable products were distributed as a consequence of the donor hold deviations.

90. ARC's Annual Report does not include the inspectional observations relating to the donor hold issue as an "open" matter. See Tab 42 (excerpt of Annual Report), p. 024473.

91. ARC's responses are inadequate. First, the underlying error has not been corrected and, in my opinion, will not be effectively corrected until new computer software is implemented to prevent this type of operator error. Second, ARC's interim solution of running monthly queries is not sufficient. Monthly queries are too infrequent; queries should be run by National Headquarters for each region on a daily basis and reviewed prior to the release of any blood components to prevent their distribution. Monthly queries will only allow ARC to learn about the release of unsuitable components after distribution, in most cases, and a large number of unsuitable components will already have been transfused. Third, ARC has not stated whether it has taken any measures to ensure that unsuitable products were not released as a result of these deviations. Fourth, and most importantly, ARC has not investigated why its own Quality Assurance unit failed to recognize that ARC either did not have procedures in place, or, if it did, failed to follow the procedures, to ensure that each region was complying with the ARC BSL.

Failure to Maintain National Donor Deferral Registry

ARC’s donor deferral registry (“DDR”) is both a regional ("RDDR") and national listing of unsuitable donors; ARC National Headquarters maintains the national registry ("NDDR"). Each month, as required by BSD 43.101M, every

region is supposed to submit the names and identifying information of the donors in its own region who are in specific deferral categories, such as donors confirmed positive for HIV, hepatitis B or C, or IV drug users. ARC National Headquarters adds all of the names received from the regions to the NDDR, which is accessible by all regions. On each donation, each donor is supposed to be checked against both the RDDR and NDDR to determine whether he is deferred. See Tab 43 (43.101M) (excerpt), p. 2-3 (requiring the regions to check donations against the NDDR).

92. If an individual donates at ARC's Los Angeles Region and is deferred because he tests positive for hepatitis, his name should be added to the NDDR. Thus, if the same donor attempts to donate at another ARC region and if his name and identifying information have been processed properly, he will be identified and the blood products from him will not be distributed. This should occur even if the donor tests negative for hepatitis in the other region because, for example, there was an error in testing or sample identification. See Epstein Dec., ¶¶ 13-14; 21 CFR § 606.160(e) (requiring that a "record shall be available from which unsuitable donors may be identified so that products from such individuals will not be distributed"); Decree, ¶¶ III.B.1, B.12, B.13.e, B.14.

93. When a region fails to defer a donor properly or does not process the information within the time frames described in ARC procedures, the effectiveness of the deferral registries is diminished; the donor may subsequently donate at the same region, or any other region in ARC's system, without being identified as a deferred donor and unsuitable blood products from that individual may be released.

94. Errors in processing donor deferral information are identified in various ways, including internal ARC audits, FDA inspections, and Quality Assurance reviews. When a region identifies an error in its RDDR that requires an update to the NDDR, ARC procedures require that the region not only add the donor’s name, identifying information, and reason for deferral to the RDDR immediately (the computer then automatically updates the NDDR), but also require the region to notify ARC National Headquarters of the error and to send Headquarters the donor’s name, identifying information, and reason for deferral. See Tab 43 (43.101M) (excerpt), p. 5-1. ARC's local operating procedure (LOP) 10.515 (Donor File Check Procedures) requires ARC National Headquarters to compile a comprehensive list of deferred donors incorrectly omitted from the NDDR, due to errors by the region. The compiled list is required to be sent to each region with instructions to perform a manual check of its database to determine whether the newly identified individuals have donated

any blood products while they should have been deferred. When this has occurred, ARC's procedures further require the regions to perform a retrospective review and to recall all blood products collected from deferred donors. See Tab 44, p. 3.

95. During our inspection, we reviewed the manner in which ARC National Headquarters implemented its donor file check process. We noted extensive delays between the time the regions submitted the updated deferral information to ARC National Headquarters and the time the information was compiled on the separate list and conveyed back to the regions by ARC National Headquarters. For example, in October 1997, 1,107 names of donors who were repeatedly reactive for hepatitis C were identified by the Southern Region and submitted to ARC National Headquarters. However, ARC National Headquarters did not report this information to other regions until December *1998*, approximately 14 months after the donors had been identified. Every day that a delay occurs in providing critical deferral information to the regions increases the likelihood that unsuitable blood products will be distributed and transfused.

96. Another instance in which ARC casually handled DDR information involved 79 deferred donors that had been submitted to ARC National Headquarters by six regions between April 1998 and January 2000. We were told by Pauline Hartnett, Director of Manufacturing Operations, that these reports were being held at

ARC National Headquarters and were not being distributed to the regions for follow up because of a lack of resources.

97. When we later asked Glenn Mattei, Senior Director, Quality Assurance/Regulatory Affairs, why these prolonged delays occurred, he told us that Quality Assurance was not even aware that ARC had a donor file check process, and had not reviewed any of the donor file check records.

* * *

98. I have reviewed ARC's written responses to the donor file check observations reflected on the FDA 483 List of Observations left with ARC at the conclusion of the inspection. In the first response (May 15, 2000), ARC stated that "ARC understands the criticality of such retrospective reviews, and the importance of completing the review in a timely manner so that component retrievals are identified at the earliest possible time." The response also stated that ARC procedures had not established time frames, promised that the procedures would be amended to require that ARC National Headquarters donor file checks be distributed to the regions each month, and further promised that Quality Assurance would perform a quarterly review of the donor file check program. See Tab 45. ARC's second response (June 21, 2000) stated that the procedures had been updated. The third (July 21, 2000), fourth (August 24,

2000), and fifth responses (November 8, 2000) provided no new information.

99. Although ARC's December 15, 2000 Annual Report does not list FDA's donor file check observation as one that is still open (see Tab 46 (excerpt of Annual Report), p. 024473) or one that constitutes an active or re-opened system problem (id., p. 024616-627), the Annual Report does not explain how the deviation was resolved.

100. None of ARC’s responses explains how such a critical procedure could have been approved without times frames; why ARC's Senior Director, Quality Assurance/Regulatory Affairs, was not aware of such an important procedure; what corrective action would be taken, other than revising procedures, to ensure that Quality Assurance personnel understand and can properly perform their duties; and why adequate resources were not made available to properly perform the donor file check procedure.

101. ARC failed to maintain all necessary records relating to the processing of blood products by not following the SOP that requires National Headquarters to provide ARC regions with a list of donors who should be, but were not, added to the National Donor Deferral Registry. ARC also did not promptly initiate and complete a thorough documented investigation of the failures of its Quality Assurance unit to (a) establish a critical SOP with time frames, (b) give the regions a list of

donors who were incorrectly omitted from the national donor deferral registry (so that the regions could check for unsuitable donors), and (c) take effective corrective action to ensure that the Quality Assurance unit would not repeat such errors.

Failure to Correct Donor Assertion Errors

102. When a donor is either temporarily or indefinitely deferred, a code is used in the computer system to assert (designate) the reason for and length of the deferral. It is essential that blood centers accurately track the specific reasons for deferral so that currently processed blood products may be handled appropriately. See Epstein Dec., ¶¶ 15, 16, 24; 21 CFR § 606.160(e); Decree, ¶¶ III.B.1, B.2.B(i), B.13.e, B.14.

103. ARC's donor deferral code includes a category and subcategory. (For example, X/A1 indicates that the donor's blood sample tested positive on a confirmatory test for HBsAg (hepatitis); X indicates that the donor is indefinitely deferred and that the donor's name and identifying information should be placed in the NDDR; A1 is an ARC code for hepatitis.)

104. In ARC's system, when a donor sample initially tests repeatedly reactive for HBsAg, the donor is placed in a hold category and coded in the computer as 7H. When the *confirmatory* test results for hepatitis are received and entered, ARC's computer system automatically changes the deferral code based on

the latest test result. If the confirmatory test is positive, the donor is placed in category X/A1; if the confirmatory test is negative, the donor is placed in a temporary deferral category, 77.

105. ARC's computer system automatically correlates a donor's test results with a code listed in the assertion tables in the computer. When the tables are not correct, ARC's computer system automatically assigns an incorrect deferral code. One of the defects with ARC's assertion tables, which ARC identified in March 1998, involves donors in category JJ, a surveillance category for a donor who tests repeatedly reactive for anti-HBc (another test for hepatitis B virus). (A surveillance category indicates that a donor had a test result that may, on a subsequent donation, result in the donor's deferral.) If a JJ donor tests repeatedly reactive for HBsAg on a subsequent donation, ARC's assertion table is supposed to change his code to 7H, the code that ARC uses to identify blood components that must, pursuant to ARC's BSD 48.201M (Component Retrieval) (see Tab 47 (excerpt), pp. 1-A-1 and 1-C-1), be retrieved from the market while awaiting receipt of confirmatory results. (As noted, the lookback procedure is done to prevent the transfusion of any potentially contaminated blood product previously collected.) However, because ARC's assertion table was set incorrectly, JJ donors were automatically, and

incorrectly, changed to category X/AA before confirmatory test results were received.

106. The danger of this error occurs at the end of each day when processing is complete and the blood center must identify all 7H donors for lookback, and when necessary, perform a market withdrawal of unexpired components. ARC SOPs require that withdrawal be carried out immediately, even though the confirmatory testing has not been received. See BSD 48.201M, "Component Retrieval," Tab 47 (excerpt), p. 1-C-1. As noted, no lookback or market withdrawal could be performed for donors assigned to category X/AA because ARC's computer system was programmed to search for 7H donors to locate products that should be withdrawn.

107. During our inspection, we reviewed the manner in which Quality Assurance handled the assertion table errors. On March 6, 1998, after it became aware of errors in the assertion table in the computer system, ARC National Headquarters issued an urgent directive (BSL #98-036) advising all regions of the JJ errors and how to manually work around the problem. However, ARC waited another month, until April 3, 1998, before issuing a second urgent directive (BSL #98-065) instructing all regions to retrospectively review records and perform the market withdrawals, which under ARC's SOP (BSD 48.201M), should have been conducted when the error was first detected. ARC did not,

at this time, investigate whether other codes were being improperly asserted (or deasserted) by its computer system; did not conduct an investigation to learn the reason(s) why the codes were incorrect in the first place; nor did ARC implement corrective action to prevent these errors from recurring.

108. On February 23, 1999, approximately 11 months after the 7H error was first identified, ARC National Headquarters distributed a third urgent message (BSL #99-030) to all regions; this BSL identified an error with the J8 code, and advised the regions to look for other components that may need to be withdrawn from the market. (J8 is a surveillance category for donors who have previously tested repeat reactive for HIV-antigen.) When, at a later donation, a J8 tests repeatedly reactive for HIV antigen and/or for anti-HIV-1/HIV-2, he *should* be automatically asserted to 8G or 8H, codes that trigger market withdrawals, as required by BSD 48.201M. See Tab 47 (excerpt), p. 1-A-1 (same). However, ARC's computer incorrectly assigned these donors to code X/P3. An error report (#99-090-000029) states that ARC identified one X/P3 donor for which a market withdrawal should have happened but did not, due to the J8 error in the assertion table. See Tab 48.

109. The same February 23, 1999 error report indicated that ARC had reviewed all remaining donor deferral codes to ensure each had a corresponding hold category. Nevertheless, on

July 16, 1999, the Northern Ohio Region reported to ARC National Headquarters (Clarify case #125529) that it identified an error with the X/P3 code, when test results were entered manually. Despite the recent code assertion errors that had been previously reported to ARC National Headquarters, the region was told the case would be followed up when the next software update was released and that a change would be made to the BSDs at that time; ARC National Headquarters took no further corrective action in response to this report. See Tab 49.

110. On December 2, 1999, the Alabama Region reported to ARC National Headquarters (Clarify case #160087) that an error was occurring with automatic assertions of the X/P2 code. ARC National Headquarters referred the region to a BSL (#99-030), which instructed regions to manually apply the X/P2 assertion. This case, too, was closed by ARC National Headquarters without any investigation to learn why the region was not aware of and following the BSL instructing regions how to use manual assertions when the computer failed. Nor did ARC investigate to learn whether this problem was occurring in other regions.

* * *

111. I have reviewed ARC's written responses to the assertion errors reflected on the FDA 483 List of Observations left with ARC at the conclusion of the inspection. In the first response (May 15, 2000), ARC stated that it is confident that

all assertion errors have been identified and corrected. ARC's response did not provide any information showing it had actually investigated why the codes were being incorrectly asserted in the first place, and merely noted that the problem occurred around the time of the system wide conversion to ARC's new computer system. See Tab 50 (excerpt), p. 35. ARC's remaining responses did not provide any additional information.

112. ARC's December 15, 2000 Annual Report similarly provides no additional support for ARC's May 15, 2000 assurance that all assertion errors have been identified and corrected. Without explanation, the Report fails to list FDA's donor assertion observations as still open (see Tab 46 (excerpt of Annual Report), p. 024473) and omits it from the list of active or re-opened system problems. Id., p. 024616-024627.

113. ARC failed to ensure that data entry error identification and follow-up procedures are in place and being implemented; failed to have an effective error correction and prevention system that includes procedures, with time frames, for initiating and completing thorough investigation of errors and accidents; and failed to take corrective action with respect to such errors and accidents. Finally, ARC's Quality Assurance unit failed to review systems in which deviations that may affect the purity of blood products have occurred, to ensure that each of the deviations has been corrected and/or, as

appropriate, has otherwise been addressed to prevent its recurrence.

Incorrect Release of Deferral Code for Syphilis

114. Syphilis is a disease caused by the bacteria Treponema pallidum. 21 CFR § 640.5(a) requires that testing of blood for transfusion include a "Serological test for syphilis" and that "Whole Blood shall be negative to a serological test for syphilis." In addition, federal regulations require that equipment used in the collection and processing of blood must be checked and adjusted regularly and "shall perform in the manner for which it was designed so as to assure compliance" with the biologics regulations. 21 CFR § 606.60(a). See also, Epstein Dec., ¶¶ 7, 15; 21 CFR § 606.160(e); Decree, ¶¶ III.B.1, 14.

115. ARC performs a serological test for syphilis, as an initial screening test, on all Whole Blood donations. If this test is reactive, a confirmatory test may be performed. If a confirmatory test is not performed, or is performed but the result is equivocal, ARC SOPs require that the donor be deferred for 12 months from the date of the initial reactive screening test. See ARC SOP # 43.104M, Donor Deferral Management, Tab 51.

116. When an initial, reactive screening result is obtained, ARC places the donor in deferral category 2H, to indicate that the donor's initial test result for syphilis was reactive and that confirmatory results are pending. If the

confirmatory result is negative, equivocal, or a test was not performed (typically because of an insufficient sample), ARC's computer system should automatically change the deferral category to 2T so that the deferral period will be maintained for 12 months from the date of the initial reactive screening test result. Different, more stringent, deferral criteria apply if the donor tests positive on the confirmatory test.

117. When the confirmatory results are received, the operator is supposed to enter those results into the computer database; the computer is then supposed to automatically assert the correct deferral code and the date on which the deferral expires. At the end of the deferral period, the deferral code is supposed to be automatically deleted ("deasserted"). If an individual is allowed to donate during the deferral period, the blood products should be identified as having been collected from a deferred donor and should be destroyed.

118. During our inspection, we noted that errors have occurred in which the 2T code and the twelve month deferral period were "deasserted" from the system before the deferral period ended, thereby removing a safeguard designed to prevent the release of unsuitable products.

119. Initially, ARC attributed the incorrect deassertion to Y2K and, on January 6, 1999, ARC National Headquarters issued a procedure to all ARC regions describing a workaround that

requires operators to manually apply the 2T codes, when appropriate.

120. Subsequently, on August 23, 1999, ARC National Headquarters released a software change (BSL 99-007) to correct the 2T error. However, it appears that ARC failed to perform adequate validation and testing after installation, but before use, to ensure that the software change would perform accurately and consistently when put in use by the regions. Within three months of the ARC software fix, premature deassertions of syphilis deferral codes occurred again. On November 16, 1999, ARC attributed the errors to faulty installation of the software and concluded that the error only affected four regions. See Tab 52.

121. However, in December 1999, the identical error occurred a third time, and this time, ARC attributed the error to a difference in memory size of one server, which had not been accounted for during installation. See Tab 53.

122. During its investigation of the third incident, Quality Assurance requested each region to review its database to determine whether the error was continuing. That review, which was initiated on December 21, 1999, revealed that six additional regions had incorrect syphilis deferral records in their databases. When ARC looked into these incidents, it determined that the cause was not computer related. Rather, ARC

discovered that these six regions had not routinely followed the workaround BSL that ARC had issued to all regions in January 1999. Despite this finding and the variety of causes ARC had ascribed to the deviations, ARC did not conduct an investigation or formulate corrective action concerning the regions' failure to follow the BSL.

* * *

123. I have reviewed ARC's written responses to the 2T deassertion errors reported on the FDA 483 List of Observations left with ARC at the conclusion of the inspection. In its first response (May 15, 2000), ARC stated that by May 30, 2000, its Information Systems group would (a) update ARC's procedure for "Managing Potential Hazards" (SOP Q017), and (b) address how to monitor workarounds to ensure their effectiveness. The second (June 21, 2000) response states that SOP Q017 had been updated. The third (July 21, 2000), fourth (August 24, 2000), and fifth responses (November 8, 2000) provided no additional information.

124. In its Annual Report, ARC classified the syphilis deferral automatic assertion error as a potential "major" risk (see Tab 54 (excerpt of Annual Report), p. 024478), yet gave no explanation of what steps ARC took to correct the observation (id. at 024473), or of what steps ARC took to avoid similar software validation problems or failures to follow manual

workarounds, which were identified as among the root causes of these assertion errors.

125. These responses are not adequate. Instead of conducting a thorough investigation to determine the real cause(s) of the 2T errors and correcting the cause(s), ARC simply applied a series of interim measures, hoping that the errors would be corrected; nor did ARC monitor the measures it implemented to ensure that they would effectively prevent recurrence of the deviations. As a result, ARC did not learn until December 1999 that six of its regions were not following an SOP that ARC had issued in January 1999, to address the 2T deviations. Also, as a result of ARC's apparent failure to properly validate the 2T software change, the computer system did not perform as intended, as required by the regulations.

(9) Failure To Use Appropriate Test Procedures

126. Before an individual is allowed to donate, a donor history and medical examination are performed to determine whether the donor is in good health, to ensure that the donor will suffer no ill effects from the donation, and to ensure the safety, purity and potency of the blood products derived from the donation. See also Epstein Dec., ¶¶ 28-29. One of the tests performed on donors is a determination of hematocrit or hemoglobin levels. *Hematocrit* is the proportion of Red Blood Cells to Plasma in Whole Blood, expressed as a percentage. The

hemoglobin level is a measure of the concentration of hemoglobin in blood. Id. *Hemoglobin* is the component of Red Blood Cells that transports oxygen and carbon dioxide.

127. Allogeneic donors (those who permit their blood to be given to anyone) must either have a blood hemoglobin level no lower than 12.5 grams (g) of hemoglobin per 100 milliliters (mL) of blood, or a hematocrit value of at least 38%. See Epstein Dec., ¶ 28; 21 CFR §§ 640.3(b)(3), 640.12, 640.21, 640.31 (requiring that allogeneic donors, including those donating Red Blood Cells, Plasma, and Platelets, have a hematocrit value of no less than 38%, or a hemoglobin level of no less than 12.5 grams per 100 milliliters of blood, to be suitable); 606.122(d) (requiring that products available for transfusion bear labeling to include a description of the product, its source, and preparation, including the name and proportion of the anticoagulant used in collecting the Whole Blood from each product prepared); 606.122(h) (requiring that products available for transfusion bear labeling to reflect the names and results of all tests necessary for safe and effective use); 606.122(i) (requiring that product available for transfusion bear labeling to include the use of the product, indications, contraindications, side effects and hazards, dosage and administration recommendations); Decree, ¶ III.A.1, B.1, 14, and 16.

128. During our inspection, we learned that ARC was determining the donor's hematocrit value by collecting a sample of the donor’s blood from a puncture of the ear lobe. After the blood sample is collected, ARC determines the hemoglobin level by using the copper sulfate method, and, when test results fail, by using the microhematocrit test method. If the microhematocrit test results are below 38%, the donor is unsuitable and may not donate.

129. Obtaining an accurate hematocrit/hemoglogin test result is very important because when individuals with low hematocrit values donate blood, they may become anemic and experience symptoms ranging from mild (fatigue, light headedness) to significant (fainting, heart attack, stroke). See Epstein Dec., ¶ 29; 21 CFR § 606.140(a) (requiring blood centers to establish "scientifically sound and appropriate specifications, standards and test procedures to assure that . . . blood components are safe . . . potent and effective"). Obtaining blood with a proper hematocrit value is also important to ensure that the blood recipient receives a potent product. See Epstein Dec., ¶ 29.

130. As early as March 1997, ARC began to receive reports from its regions stating that donors were becoming ill, injured, or had to be hospitalized following donation. For example:

a. in March 1997, the New York-Penn Region reported that a donor had fainted while driving, was involved in an automobile accident, and was admitted to the hospital intensive care unit with liver lacerations, soft tissue injuries, and a lower lip laceration (see Tab 55, Exh.#274, p.1);

b. in August 1998, the Greater Chesapeake and Potomac Region reported that a donor was hospitalized and required transfusion with two units of blood (see Tab 55, Exh.#275, pp. 2 - 3);

7. an undated document in ARC's files shows that the North Central Region reported that from March 1997 and May 1998, eighteen donors had advised the region that they had to seek medical care; anemia was implicated as part or all of the problem in each of the events. See Tab 55 (Exh.#274, p.29).

131. On October 15, 1997, the North Central Region submitted the ear stick sample collection method as a potential system problem to ARC National Headquarters (see Tab 56), and on December 9, 1997, ARC National Headquarters classified the ear stick sample collection issue for determining hematocrit as a system problem. See Tab 56. However, ARC did not even begin to focus on correcting the problem until Investigator Mattingly and I raised the issue during the inspection.

132. During our inspection, Dr. Rebecca Haley, Senior Medical Officer, ARC National Headquarters, provided several e-mails to us reflecting another ARC physician's concern for donor

safety. In an April 8, 1998 e-mail, Dr. Debora Kim, Associate Medical Director, North Central Region, stated:

> **"I personally feel it is unethical to continue to use the earstick and that we need to be especially vigilant about protecting our donors from harm. Additionally, I think that we are incurring a significant regulatory risk by continuing to use this inaccurate, unvalidated method. The FDA is aware that we did the hematocrit study as we promised it as a part of corrective action resulting from a reportable accident. Also, I feel we are at risk from a medico-legal liability standpoint for a practice for which we have little defense."**

See Tab 57 (emphasis added).

133. In a May 7, 1998 e-mail, Dr. Kim stated:

> **"I would like to reiterate my opinion that the continued use of the earstick in light of what we know about this problem is unethical, a medico-legal liability, and constitutes a significant regulatory risk. I also think it is a violation of the Hippocratic Oath in that as physicians, we are first to do no harm. I would hope that the American Red Cross as a humanitarian organization would share this sentiment."**

See Tab 58 (emphasis added).

134. In a third e-mail, dated August 3, 1998, Dr. Kim repeated her concerns in stronger language:

> **"I am well aware of the financial concerns of going back to using the fingerstick. However, based on the results of our two studies and John Miller's study, the earstick is not protecting our donors from developing clinically significant iron deficiency anemia and thus in my opinion it is unacceptable to continue to use it. It is my strong belief that continued use of the earstick constitutes unethical treatment of volunteer blood donors, is a huge regulatory liability (particularly while we are still under a consent decree), and represents a significant medico-legal liability for the organization. This problem needs a systemwide solution ASAP. The Red Cross is a humanitarian organization and we need to protect our donors from harm at any cost."**

See Tab 59 (emphasis added).

135. In an August 18, 1998 report, given to us by Dr. Haley, Dr. Haley described the Greater Cheasapeake and Potomac Region incident as “an example of the kind of medical disaster that can be triggered when hematocrit qualification sample source or methods are inadequate.” Dr. Haley's report went on to state, “We are awaiting the outcome of this anemic donor's diagnostic evaluation for possible stroke following blood donation while she was anemic.” Dr. Haley further stated, “The American Red Cross need[s] to implement conversion to fingersticks or some similar proposal to allow only qualified donors to donate." See Tab 60.

136. Our review of records also showed that ARC had undertaken several studies following the ear stick adverse events, including one parallel study conducted between January and June 1998, comparing the hemoglobin level using samples taken prior to donation from the ear lobe versus samples taken from a vein. This study indicated that 246, or 25.8%, of the 953 *donor* ear stick samples had a hemoglobin level below the acceptable 12.5 gm/ml at the time of phlebotomy.

137. ARC regions and physicians also raised concerns about the safety of the patients who were transfused with blood collected from "ear stick" donors and the accuracy of the labeling of such products:

a. In an e-mail dated April 8, 1998, Dr. Kim stated that the practice in her region was to not ship such units due to potency concerns since ARC's product label requires a minimum of 38% hematocrit per Whole Blood unit of the component. See Tab 57;

b. An undated, unsigned report on the ear stick system problem provided to us during the inspection stated:

> "There is a risk to recipients in that red cell products from donors with a low Hb/Hct may be less potent (the effective dose delivered may be less) than would be the case with products prepared from donors who have higher Hb/Hct levels. Thus recipients of these products may benefit less or require additional transfusion, and be exposed to increased risk of infectious disease."

See Tab 61, p.5 (emphasis added);

c. In her August 3, 1998 e-mail, Dr. Kim stated that the North Central Region needed guidance from National Quality Assurance as to whether the units shipped with a hematocrit below 38% are subject to recall or market withdrawal. See Tab 59. We were unable to find any records to indicate how ARC National Headquarters answered this question.

138. During our inspection we were given a chronology of events prepared by Dr. Rebecca Haley, which reflects that in September 1998, at a Medical Directors' Council meeting, ARC medical directors agreed there was a need to change ARC's hematocrit testing practices. See Tab 62.

139. During our inspection of ARC National Headquarters, we reviewed Quality Assurance's response to these adverse event reports, concerns expressed by ARC doctors, and studies showing the problematic use of the ear stick method. Our review showed that as early as December 1997, Quality Assurance agreed that the ear stick matter was a system problem (see Tab 56), yet failed to either investigate the matter or undertake any corrective action to address the concerns voiced by its own physicians or reflected in the studies that ARC conducted.

* * *

140. I have reviewed ARC's written responses to the ear stick sampling issue reflected on the FDA 483 List of Observations left with ARC at the conclusion of the inspection. In the first response (May 15, 2000), ARC indicates it had decided to discontinue the use of the ear stick for sample collection but that the impact of the change was still under review; no implementation date was indicated. The second response (June 21, 2000) states that the Senior Medical Officer convened a meeting to formalize the decision to discontinue the ear stick method for sample collection and to form a team to handle the issue by the end of June. The third response (July 21, 2000) states that ARC had established an implementation date of August 14, to discontinue the use of the ear stick for sample collection. The fourth response (August 24, 2000) indicates the

change was implemented on August 12, 2000. The fifth response indicates the status of the corrective action was "completed," even though verification by Quality Assurance was pending.

141. ARC's Annual Report parallels ARC's letter responses, stating that all regions switched to the finger stick method by August 14, 2000 (see Tab 63 (excerpt of Annual Report), p. 024569), indicating that the issue has been resolved on a system wide basis (id., p. 024478-79), and omitting the issue from the list of active system problems. Id., p. 024616-625.

142. Although ARC appears to have written an SOP to halt the ear stick method, ARC has not initiated and completed a thorough investigation to learn why the ear stick method was allowed to remain in use more than two years after ARC had received adverse event reports from its regions; after two of its own physicians had expressed serious medical, legal, and ethical concerns about its use; and after ARC became aware of at least one study demonstrating that the ear stick method was not "scientifically sound" to establish an accurate hematocrit level or "appropriate" to assure the protection of its donors. ARC's responses do not show that it has taken action, either to ensure that its August 12, 2000 BSL instructing discontinuation of the use of the ear stick method is being followed by the regions, or to ensure that in the future, significant medical concerns can be identified earlier and more promptly addressed and corrected.

143. In this ear stick episode ARC manufactured and distributed subpotent and misbranded blood components, failed to initiate and complete thorough investigations of errors and adverse reactions, and failed to take corrective action with respect to the errors and adverse events.

ARC HAS NOT CORRECTED THE NATIONAL HEADQUARTERS OBSERVATIONS: THE RECENT INSPECTION IN SALT LAKE CITY

144. In response to FDA's February-April 2000 inspection of ARC National Headquarters, ARC sent a letter to FDA on May 15, 2000, stating that it "understands the gravity of the issues identified during the inspection and has taken a series of immediate actions to bring about prompt, comprehensive corrective action of both the inspection observations and their underlying causes . . . ." By letter dated June 21, 2000, ARC assured FDA that it had "taken aggressive action" to correct the system-wide deficiencies identified during the National Headquarters inspection. Among the actions identified by ARC were: (1) issuance of a Blood Service Letter (BSL 00-131) that asked all regions to implement, by August 1, 2000, a system for supervisory review of quarantine and inventory reconciliation reports; (2) issuance of a BSL (00-114) that asked all regions, by June 5, 2000, to implement supervisory review of returned blood products; and (3) issuance of a BSL (00-084) that asked all regions to implement, by June 16, 2000, a schedule for daily and weekly review of product disposition reports, in part to prevent loss of blood components.

145. In a July 21, 2000 letter to FDA, ARC described how it would verify that the Regions had implemented the foregoing corrective actions and that the corrections were effective. That approach included verification by regional quality

assurance personnel that the corrective actions had been implemented. See Tab 64 (August 3, 2000 Quality Assurance Letter (QAL #00.020) directing all regional quality assurance directors to verify that corrective action had been implemented properly and fully); see also Tab 65 (QAL #00.022, dated August 24, 2000, forwarding to QA staff a checklist that had to be used in verifying corrective action pursuant to QAL #00.020).

146. As discussed below, FDA's March-May 2001 inspection of the Salt Lake City facility demonstrates that despite its many promises and assurances to FDA, ARC still has not corrected the violations that FDA observed while inspecting National Headquarters in February - April 2000.

147. FDA began the inspection of the Salt Lake City facility on March 26, 2001. The inspection was completed on May 16, 2001. During the inspection, ARC's Quality Assurance Officer provided a copy of the checklist that he said he had used to verify that the corrective actions had been completed in Salt Lake City. See Tab 66.

148. FDA investigator Kelly Moore and I randomly checked three areas that Quality Assurance Officers were supposed to verify: (1) that supervisors were reviewing quarantine and inventory reconciliation reports; (2) that supervisors were reviewing returned blood products to assure that they are suitable before re-release; and (3) that Salt Lake City was

reviewing product disposition reports on a daily and weekly schedule. We found *none* of these corrective actions in place. As discussed above, these failures violate federal regulations and the Decree. See paragraphs 39, 44, and 48. When confronted with our findings, the Quality Assurance Officer admitted that the verification had not been performed for the Salt Lake City facility.

149. We observed numerous other violations in Salt Lake City demonstrating fundamental problems with quality assurance and ARC's continuing failure to monitor and exercise appropriate control over its regions. For example, under an ARC BSD (#51.110M, Tab 67 (excerpt)), personnel who interview donors about their medical history questionnaires (known as "health historians" at ARC) must fully explore all deferral categories before suitability is determined, and must document detailed explanations for all "yes" answers in those categories. Unless the "yes" in those categories has been correctly resolved to "no" using specified criteria in ARC's BSD 51.110M, the donor is prohibited from giving blood and must be placed on the Donor Deferral Registry. Our inspection showed that ARC health historians in Salt Lake City made hundreds of errors, such as failing to defer donors who answered "yes" to AIDS/high risk questions. One such question was: *"Do you have AIDS or have you ever tested positive for AIDS?"* Another such question listed

countries with a high risk of AIDS and asked: "Have you had sex with anyone who, since 1977, was born in these countries?" In each of these instances, the health historians failed to document any explanation, allowed the donors to give blood, and failed to mark the donors for deferral. They simply overlooked these "yes" answers altogether. See Tab 68 (example deviation reports of health historians overlooking "yes" answers to AIDs/high risk questions, with accompanying questionnaires (redacted)).

150. These donor suitability errors were not isolated incidents. During the investigation, we reviewed hundreds of deviation reports in which health historians overlooked problems with donor questionnaires. See Tab 69 (excerpts of Establishment Inspection Report ("EIR"); discussion of health historian errors found in Observation Nos. 12-15). Nevertheless, regional quality assurance personnel failed to investigate these errors, determine their root cause(s), and establish corrective action. See id., Observation Nos. 12 & 13. National Headquarters also failed to correct or otherwise address this obvious quality assurance failure.

151. In its response to our FDA-483 observations, ARC tried to justify these deviations, and the lack of investigation and correction by regional and national quality assurance personnel, on the grounds that ARC reviewers caught the errors

before the blood had been released for distribution. See Tab 70 (ARC's responses to Observations 12-15). ARC pointed out that blood donor records are reviewed twice for accuracy and completeness: once prior to donor registration (known as the "100%" review) and again at ARC's regional headquarters in Boise, Idaho, where donor registration is completed (the "200%" review). Id. ARC further noted that in each of the examples cited by FDA, the "100%" or the "200%" reviewer caught these errors, the donors were called on the telephone, and their "yes" answers were changed to "no," based on the conversation. Id. ARC's response is deeply troubling, on several levels.

152. First, relying on "100%" or "200%" reviewers to catch and attempt to undo such donor suitability errors is improper and violates the law. Under 21 C.F.R. § 640.3, donor suitability determinations based on medical history must be made on the same day the blood is collected. One reason for this rule is to allow an opportunity for prompt, meaningful, and confidential face-to-face follow-up with the donor, ensuring that donors are truthful and that their answers are reliable. Pursuant to a BSD never submitted to FDA to review (#57.201M), ARC personnel in Salt Lake City contacted donors by phone days after their donation, repeated the questions to which the donor had answered "yes," and changed the donors' answers to "no," based solely on the telephone conversation. ARC then

distributed those blood components. ARC has no adequate procedure to ensure that the individuals contacted by phone were in fact the donors, and had no method to ensure that donor confidentiality, critical to ensuring truthful answers, was not compromised by asking the questions over the phone because, for example, other people could overhear the donors' conversation. In each of these cases when only telephone follow-up was conducted, ARC should have discarded the blood and sought a face-to-face follow-up interview under confidential conditions to determine the donors' deferral status. Moreover, National Headquarters should have investigated the causes of this violative practice, and ensured that the practice was corrected in the Salt Lake City facility and throughout its regions.

153. Second, ARC's careless attitude toward the hundreds of donor suitability errors reflects a dangerous reliance on subsequent safety checks to excuse grossly inappropriate and sloppy blood donor receiving practices. One possible explanation for why ARC health historians missed so many "yes" answers on questionnaires is that they were under pressure to work quickly and were relying on subsequent checks by others to catch any errors they made. I have observed this attitude among ARC employees on numerous other occasions. Such an attitude reveals that ARC employees and managers either do not understand the critical importance of sequential safety checks and of

ensuring that each safety measure is performed diligently, or do not care to invest the effort to adequately assure the safety of the products ARC makes and distributes. Past observations, like the observations described in paragraphs 153 and 157, have demonstrated to me that when employees believe that they can rely on other, downstream safety checks, unsuitable blood components are more likely to pass through all safety levels and be released.

154. Third, some questions, such as "Are you in good health today?" and "In the past 6 months, have you suffered from heart-related chest pains?," are intended to verify that the donor will not be adversely affected by donating blood. Verifying such information from the donor after the blood has been collected is meaningless and completely unacceptable. See, e.g., Tab 71 (third item)(summary of deviation in which blood was taken from donor who answered "yes" to Question #28 about heart-related chest pain).

155. Fourth, it is disturbing that quality assurance personnel at both the regional and National Headquarters level simply ignored hundreds of such deviations. No Quality Assurance personnel investigated the deviations, sought the root cause(s), or initiated corrective action of any kind.

156. Fifth, in at least one instance, both the "100%" and "200%" reviewers failed to prevent a blood component from an

ineligible donor from being labeled for distribution. See Tab 69 (Observation 15); see also Tab 72 (ARC's related deviation report and tracking log). Specifically, one person who was ineligible to donate due to travel in a high-risk malaria area was allowed to donate. The number of ARC recalls due to similar erroneous collections has increased over the past three years. In this case, the "100%" reviewer noted this error, but failed to write "discard" on the unit, and the unit was manufactured into components. The "200%" reviewer did not check whether the unit had been discarded or electronically quarantined, and is not even required by ARC to do so. In fact, in this instance, one of the components was labeled for distribution because it had not been electronically quarantined. Distribution of the unsuitable unit was averted only because the individual entering donor deferral information into the computer noticed the error in time. Inasmuch as ARC's SOP does not require donor deferral entry before labeling and distribution of products, mere good luck prevented distribution.

157. During the inspection, FDA observed many other violations that reflect serious quality assurance failures, breaches of commitments and assurances that ARC has made to FDA, and a failure by ARC National Headquarters to establish and document managerial control over quality assurance in all

regions, as required by the 1993 Decree. Among these violations are the following:

- The Salt Lake City facility used manual CMV labeling verification procedures that were inadequate to ensure that CMV-positive units or untested units are not labeled CMV negative. See Tab 73 (excerpt of EIR, Observation No. 26). CMV labeling problems had been prominently identified during the February – April 2000 inspection (for the significance of such problems, see paragraphs 26 through 38 above).

- The Salt Lake City facility continued to have incidents in which blood components were shipped without recording the shipment electronically, subsequent to the date that corrective action was promised by ARC to have been implemented. See Tab 74 (EIR excerpt, Observation No. 3). The result is lost products for which recall and lookback could not have been performed, if necessary. This violation had been prominently identified during the February - April 2000 inspection (for factual and legal significance of this observation, see paragraphs 45 through 50 above).

- ARC employees in Salt Lake City were permitted to perform critical tasks, such as quarantining blood, irradiating blood, performing reconciliation procedures (including reconciliation of quarantined areas), and controlling returned blood components, even though, according to the records, they had not

been adequately trained in those procedures. See Tab 75 (EIR excerpt, Observations 18-20). Such practices violate federal regulations and the Decree, which require that employees be trained in the particular operations they perform, see 21 CFR § 211.25(a), and that their successful completion of training be documented prior to their assuming any duties. See Decree, ¶ III.C.4.a. See also 21 CFR § 606.20(b); Decree, ¶¶ III.C.4.e & III.C.5; Bowers Dec., ¶¶ 39, 43 – 46 (describing prior VI.A letter citations against ARC for inadequate training); id., ¶¶ 52 – 54, 58 – 59 (other post-Decree warnings to ARC for insufficient employee training).

- Even though an ARC SOP (QAL #00.004; Tab 76) instructs the regional quality assurance directors and officers to review FDA 483s issued to other ARC facilities, to document as deviations similar problems that exist within their own region, and to investigate and correct those problems, ARC's Salt Lake City regional quality assurance personnel failed to investigate and correct, and in some instances even to record as deviations, observations they found to exist in their region that had been reported on 17 of 28 FDA 483s for other regions. That failure violates: 21 CFR § 211.22(d), which requires that such written quality control unit procedures be followed; 21 CFR § 211.22(a), which requires that if errors occur, they be fully investigated; and paragraph III.B.2.B of the Decree, which requires ARC to

correct and prevent recurrence of each deviation. FDA has cited ARC many times previously for quality assurance failures to correct know defects or otherwise for failing to maintain an adequate quality assurance program. See, e.g., Bowers Dec., ¶¶ 39, 41, 42, 44, 45, 47 (VI.A citations); ¶¶ 49, 56 - 59, 61 (other post-Decree warnings).

158. Based on my observations at the Salt Lake City facility, ARC continues to deploy insufficient resources in conducting its blood operations. For example, the Director of Operations informed us that supervisors were not reviewing quarantine and inventory reconciliation records because she did not have enough supervisors. See Tab 77 (EIR excerpt, p. 15, ¶ 3, 4th sentence). Similarly, ARC cited insufficient quality assurance resources as its excuse for: (a) relaxing the requirement that Salt Lake City quality assurance personnel review, on a monthly basis, Clarify case reports, to identify potential system problems and health hazards, see Tab 78 (EIR excerpt, Observation No. 8; Temporary Variance Request, approved by QA Director on Feb. 8, 2001; and (b) allowing quality assurance personnel to forego a monthly review of CGMP deviations, see Tab 79 (EIR excerpt, p. 24 (last ¶); Temporary Variance Request, approved by QA Director on Feb. 12, 2001. Indeed, in its June 18, 2001 response to the FDA 483, ARC cited a lack of quality assurance staff as a cause of the observed

quality assurance deficiencies in Salt Lake City. See Tab 80. These failures are more examples demonstrating that ARC continues to fail to invest the resources necessary to ensure compliance with the law, its own SOPs, and the Decree. See 21 CFR § 211.25(c), which requires firms to have "an adequate number of qualified personnel to perform and supervise the manufacture, processing, packing, or holding of each drug product," and paragraph III.B.3 of the Decree, which requires ARC to take actions necessary, including ensuring the availability and expenditures of monies, to achieve continuous compliance with the law, ARC SOPs, and the Decree.

159. On October 19, 2001, FDA issued to ARC a letter under paragraph VI.A of the 1993 Decree notifying ARC of the significant problems observed during the Salt Lake City inspection. See Tab 81. To date, ARC has issued only an interim response to the VI.A letter. See Tab 82. ARC's response reinforces FDA's concerns regarding ARC's apparent failure to understand the critical importance of ensuring that each safety measure is performed diligently in order to ensure the safety of the blood products it manufactures and distributes. For example, in its interim response, ARC stated that it would not, until April 2002, revise BSD 66.101M to include immediate, second-person confirmation that units are placed in quarantine, both physically and electronically. Id.,

p. 025192 (#4). Further, ARC refused to issue interim instructions to deal with the problem, stating that its subsequent reconciliation process is sufficient to catch any errors. Id. This over-reliance on subsequent safety checks ignores the critical importance of ensuring that the quarantine process takes place immediately.

160. These quality assurance failures in Salt Lake City demonstrate that in the year and a half since the National Headquarters inspection, ARC still has not exercised adequate quality assurance control over the regions. Our observations at ARC's Salt Lake City facility provide further evidence that promises and representations by ARC National Headquarters to FDA regarding corrections and compliance may not be relied upon.

CONCLUSION

161. In the nine examples from the National Headquarters inspection discussed above, ARC violated the Decree, federal regulations, and its own SOPs. Each example constitutes a significant health risk to the public and, in the cases of CMV labeling and quarantine and inventory errors, involve the release and transfusion into patients of unsuitable blood products. ARC's responses to FDA's observations, ARC's December 15, 2000 Annual Report, and subsequent ARC error and accident reports submitted to FDA show that ARC has not adequately investigated these errors to determine their underlying causes

and has not instituted sufficient corrective action to prevent their recurrence. Furthermore, and more significantly, the nine examples demonstrate serious, widespread failures on the part of ARC's Quality Assurance program. Such failures represent independent violations of the Decree and show that ARC has a pattern and practice of not identifying, investigating, and correcting CGMP problems sufficiently to ensure the safety of the blood supply.

162. The recent inspection of the Salt Lake City facility in the Lewis and Clark Region confirms that this pattern of Quality Assurance deficiencies persists despite a comprehensive FDA inspection of ARC's National Headquarters and ARC promises to address FDA's concerns.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on: _____ _____
Mary T. Carden

UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF COLUMBIA

UNITED STATES OF AMERICA, **Plaintiff,** **v.** **AMERICAN NATIONAL RED CROSS, a** Corporation, Defendant.	Civil Action No.93-0949 (JGP)

DECLARATION OF JAY S. EPSTEIN, M.D.

I, JAY S. EPSTEIN, M.D., do state and declare as follows:

Personal Background and Qualifications

1. I am currently employed as the Director, Office of Blood Research and Review, at the Center for Biologics Evaluation and Research, U. S. Food and Drug Administration (FDA). I directed the Office of Blood Research and Review on an acting basis since August 1993, and I was promoted permanently to this position in October 1995. I was the Director of the Division of Transfusion Transmitted Diseases within the Office of Blood Research and Review, from January 1993 to October 1995. I directed the Retrovirology Laboratory in the blood program from August 1986 to December 1992. (Retroviruses are a class of viruses that includes human immunodeficiency virus (HIV)). I have worked for FDA since October 1981 when I began as a Senior Staff Fellow for Research in Virology, which is the branch of microbiology concerned with viruses and viral diseases. In that role, I personally conducted and supervised research on the natural history and diagnosis of diseases caused by cytomegalovirus and HIV.

2. I am a medical doctor with Board Certifications in Internal Medicine (1979) and in Infectious Diseases (1984). I hold a bachelor's degree from Harvard College, Cambridge, MA (1969) and a medical degree from Downstate Medical College, Brooklyn, NY (1976). My *curriculum vitae* is attached hereto as Tab 1, including a list of publications.

3. My duties at FDA include the regulation of blood, blood products, blood establishments, and devices used in blood product manufacturing. In relation to the present case involving the American National Red Cross (ARC), I am the FDA's lead scientist responsible for the federal regulation of the screening process used in blood banks to prevent the transmission of infectious diseases by the transfusion of infected blood and blood products. In my capacity as Office Director, I supervise a group of approximately 150 people who are engaged in the regulation of and scientific research on blood products, such as red cells and immune globulins; diagnostic tests used to screen blood donors, such as tests for antibodies and nucleic acids of HIV; and other blood-related products, such as cell separation machines. As a senior medical officer, I am responsible for evaluating the health hazard caused by product and processing deviations, including errors and accidents.

4. I am also responsible for policy development in all areas of blood safety, including donor deferral criteria and product standards. I have testified on numerous occasions before congressional oversight committees at hearings related to FDA oversight of the U.S. blood system. I frequently represent the FDA at international meetings, including contacts with regulatory officials of foreign governments and the World Health Organization. I am a lead spokesperson for the agency in contacts with the media concerning blood safety issues.

5. As Director of the Office of Blood Research and Review, I have been responsible on many occasions since 1993 for evaluating the risks and public health significance of numerous findings of violation made by FDA

investigators during inspections of blood centers, including ARC regional centers and National Headquarters.

Summary of Concerns Regarding ARC

6. I am familiar with the FDA–483, Lists of Observations that FDA investigators issued to ARC following the February-April 2000 inspection of ARC's National Headquarters and the March-May 2001 inspection of ARC's Salt Lake City facility in the Lewis and Clark Region. I am also familiar with the declarations of Robert Lee Bowers and Mary Carden filed in this case. Although some of the violations reflected in the FDA-483 could be regarded as having limited public health significance, in my opinion the issues raised in Ms. Carden's declaration raise significant concerns; some of the observed conditions create an imminent and serious potential for harm to blood donors and recipients. Moreover, and no less importantly, the consistently inadequate, piecemeal, and sometimes casual, manner in which senior ARC management, including its Quality Assurance unit, has responded to FDA observations and to ARC's own internal error reports, to me demonstrates that ARC officials either do not appreciate the potential public health significance of their conduct or have not properly interpreted Quality Assurance and current good manufacturing practice (CGMP) principles as they apply to the blood banking industry.

7. Examples of areas of particular concern to me include system-wide errors in donor identification (e.g improper registration), donor deferral classifications, and donor record keeping (*e.g.,* duplicate and discrepant records); collection of blood from donors with a documented history of risk factors that should be a basis for deferral; release of mislabeled, test-positive blood; inability to account for unsuitable units belonging in quarantine; and use of medically unacceptable, and potentially hazardous blood sample collection methods. These problems are too important for any blood provider to ignore. ARC supplies approximately 45% of the blood

products that are transfused annually in the United States. Release of unsuitable units for use in transfusion is a hazard to individual and public health. Additionally, a test sample collection technique that was used by ARC for several years placed blood donors at health risk.

8. I am also concerned about the combined effect of the observations made by the FDA investigators at ARC's National Headquarters in February-April 2000. The violations observed by the investigators occur at sequential stages of blood processing, thereby undermining CGMP precautions that, in some cases, are intended to be overlapping. A final point: the chronic pattern and repetitive nature of ARC's violations (many of the same type of violations occur over and over again, year after year) reflected in Mr. Bower's declaration make it impossible to assure that ARC products generally meet their intended quality and safety characteristics. This point is further illustrated by the recent findings on inspection in March-May, 2001 at the Salt Lake City facility in the Lewis and Clark Region, as described in Ms. Carden's declaration. The violations documented in that inspection persist despite ARC's assurance in a letter to FDA dated June 21, 2000 that it had "taken aggressive action" to correct the system-wide deficiencies identified during the February-April 2000 inspection of ARC National Headquarters.

Importance of Blood and Role of ARC

9. Each year, approximately 18 million units of blood, platelets, red blood cells, and other blood products are transfused into about 3.5 million patients in the United States. Blood products generally are transfused into patients who have serious medical conditions such as cancer; who undergo surgery, including obstetrical procedures; who have had traumatic accidents; and who have a variety of acute or chronic medical conditions requiring blood replacement, such as a bleeding ulcer or sickle cell anemia. Many of these patients are highly susceptible to the diseases that may be caused by

transfusion-transmitted viruses and other infectious agents because of compromises to the function of their immune system related to their condition. However, serious transfusion-transmitted diseases, such as AIDS and chronic hepatitis, also may develop in otherwise healthy blood recipients with a normal immune system.

10. Blood transfusion is often lifesaving and is necessary to permit many modern medical procedures, particularly in surgery and chemotherapy. Because they cannot independently assess the safety and quality of products, doctors and patients must rely on the blood providers to assure the quality of the blood products they use as critical elements of patient care. Nor can the medical community, the public, or even blood providers rely primarily on FDA investigators to assure the potency, purity, safety, and quality of blood products. FDA investigators can only infrequently visit, and can spend only a limited amount of time in a particular facility. Generally, they have no prior familiarity with a provider's practices and records, and on any one visit can only look at a few areas to evaluate the manner in which blood products are being made. Accordingly, the responsibility rests with the provider to self-ensure both the rigor and integrity of its processes and the ultimate safety, purity, quality and potency of its products.

11. The safety of the blood supply is vitally important to the patients who receive transfusions of blood and blood products. The screening of donated blood for viruses such as HIV, hepatitis B, hepatitis C, and Human T-Lymphotropic Viruses (HTLV) is critical to the safety of the blood supply because of the very high likelihood of contracting the virus if a patient receives a transfusion with virally contaminated blood. It has been estimated that HIV, hepatitis C and hepatitis B will be transmitted to transfused patients by 85-90% of contaminated units. HTLV is transmitted by approximately 30% of contaminated units. The lifetime risk of serious disease or death from these infections is estimated to be 100% for HIV, 20%

for hepatitis C, 10% for hepatitis B and 4% for HTLV. Additionally, infection in a blood recipient creates the possibility for further spread of disease to others. This may occur through sexual contact, childbearing and, in the case of hepatitis B, close household contact. This can be the case even if the blood recipient remains healthy.

12. Patients generally have little or no ability to determine the source of the blood transfusions they receive. Aside from patients who are scheduled to undergo surgery and can arrange for self-donations (autologous donations) or donation of blood from close family and friends (directed donations), patients generally receive random donor blood (allogeneic donations) from whichever supplier their medical facility uses.

Safety Measures for Blood

13. Careful screening of the blood supply by the use of donor selection criteria coupled with use of laboratory tests of high sensitivity forms a cornerstone in ensuring a safe blood supply that is as free as possible from the potential to transmit infectious agents. However, to be effective, these protective measures require accurate linkage of the donor identity with all other records associated with the donor’s present and past donations, an ability to promptly identify all records associated with a particular donor, careful control of all product inventories, and accurate labeling of the blood units.

14. The safeguards that have been established by FDA to ensure a safe blood supply include: educating donors regarding risk factors that should lead to self-deferral from donation; careful screening out of unsuitable donors by the use of medical history questionnaires and a limited physical examination; maintaining an accurate list of donors who are deferred and promptly interdicting collections from such donors; controlling inventories to maintain quarantine of unsuitable units and to ensure release only of suitable units; promptly notifying consignees in circumstances where a

potentially infectious unit has been released; promptly investigating and reporting incidents involving deviations (errors or accidents) in product manufacturing; promptly and accurately determining the causes of such errors and accidents; and promptly and effectively correcting system problems identified through routine audits and the investigation of incidents.

15. Although many of the safeguards described in the preceding paragraph are partially overlapping, breaches of the safeguards at any level may result in release of infectious blood. For example, failure to defer from donation persons who provide a history of medical or behavioral risk factors for a disease transmissible by transfusion constitutes a significant hazard to blood safety. It might be assumed that laboratory testing would identify all infectious donations. This is untrue, however, because of limitations to the sensitivity of laboratory tests and the possibility of falsely negative test results through error. In particular, tests may be negative for several weeks to months after the donor becomes infected due to low levels of viruses or antibodies in the donor's blood. Additionally, even if a test result is positive on an improperly selected donor who has a history of high-risk behavior, once a unit has been collected, the unit may be released through error. Examples of such errors include inaccurate initial data collection and entry; incorrect data interpretation; improper data linkage (*e.g.,* by inadequate computer software that does not insert the correct deferral code or that erroneously de-asserts the correct deferral code); and failures of inventory management. Inadequate inventory management is a particularly dangerous condition because it may undo all the previous precautions. Thus, if unsuitable units are not carefully identified and physically controlled, they may be distributed despite proper control at the previous steps.

16. As described above, donor deferral based on a properly elicited history of high-risk behavior (*e.g.,* recent visits to an area where a

disease, such as malaria, is endemic, illicit use of intravenous drugs, exchange of sex for money or drugs, male sex with another male, etc.) serves to protect blood safety by avoiding collection of blood from persons at increased likelihood of harboring transfusion-transmissible diseases. Careful screening reduces the chance that an infectious unit will be collected, thereby preventing release of infectious units due to falsely negative screening tests and inventory management errors. Additionally, proper deferral of donors with medical and behavioral risk factors is the main line of prevention against conditions such as malaria, for which there is no current donor screening test.

Blood Safety Depends on Current Good Manufacturing Practice

17. At every step in blood collection and processing, FDA requires that blood establishments follow current good manufacturing practice (CGMP). CGMP consists not only of each of the steps that must be taken to properly manufacture the product, but also of the operational quality *controls*, such as product testing and concurrent record keeping, that are needed to ensure and document that the steps are carried out correctly. CGMP also requires quality *assurance* measures, such as routine auditing, thorough investigation of errors to determine their cause(s), implementing corrective action to prevent recurrence of the errors, and monitoring corrections to ensure continuing effectiveness. The safety, purity and potency of blood products depend on the proper performance of all manufacturing steps, controls, and quality assurance oversight. Quality must be "built into" products at each stage of their manufacture, by the foregoing measures, and cannot be added in -- or even demonstrated by -- examination and testing of the final products. Instead, quality depends on the objective, scientific demonstration that manufacturing will consistently occur as intended and that all product and process specifications will be met consistently. This last concept is referred to as “process validation.”

18. CGMP is indispensable to ensure the quality and safety of the products. For example, every blood donor must be carefully screened for high-risk behavior and tested for evidence of infection with HIV. The risk of contracting HIV from a unit of blood is very low if the donor was properly selected and tested and the other CGMP safeguards are intact. Compliance with CGMP ensures that proper screening and testing took place through controls such as accurate documentation of donor screening; verification that the provider's database system can consistently maintain proper linkage of the donor identifiers (*e.g.,* the Whole Blood number, donor name, deferral status codes) to the sample of blood that was tested to determine donor suitability; validation that the laboratory testing systems were functioning within their specifications, such as through records of equipment calibration and maintenance; and physical reconciliation of inventories with electronic inventory lists.

The Risk From Unsuitable Units

19. Violations of CGMP and of a blood center’s own standard operating procedures (SOPs) can compromise the assurance of safe blood and can significantly increase the risk that a person receiving a unit of blood will contract an infectious disease from the blood. It has been estimated that for every million members of the general population, hepatitis C is present in the blood of about 18,000 persons, hepatitis B in about 4,900 persons, and HIV in about 3,000 persons. With proper donor selection and testing, the risk of a contaminated unit per million units released is estimated to be about 10 each for hepatitis C and hepatitis B, and 2-3 for HIV. Thus, proper donor selection and testing reduce the risk by a factor of 500 to 1,000. However, in the absence of effective donor selection and testing, the risk would be expected to rise toward the level present in the general population. Thus, there is a very real and significant potential for increased risk when

donors are improperly selected, donor blood is improperly tested, or units from unsuitable collections are inappropriately released from quarantine.

20. The risks described in the preceding paragraph, as well as other known risks of transfusion, must be taken into account when physicians use blood. For the individual patient, the risk of acquiring an infection from transfusion increases in direct proportion to the number of units received. On average, a typical transfusion episode involves the use of 4-5 units of blood. The risk of infection to a typical transfusion recipient is therefore four to five times the random risk from an individual unit.

21. I understand ARC has suggested that its products are safe because no infections have been reported as being traceable to unsuitable products that it has released. This is a notoriously dangerous assumption to make. Transfusion-transmitted infections may fail to be recognized and attributed to unsuitable blood, for several reasons. First, there may be no illness associated with the initial infection, and, in sick patients, the illnesses that occur may be ascribed to other causes. Second, there is a significant delay between the time of infection and the appearance of chronic symptoms for most transfusion-transmitted diseases. For example, in the case of hepatitis C, serious liver disease may not become apparent for two to three decades following the infection. Similarly, AIDS may not become manifest for 7-10 years after the initial infection. Because of age, the seriousness of an underlying illness, or unrelated causes, the patient also may die before the infection is recognized. Third, even when the infection is diagnosed, the link to transfusion may not be discovered since transfusion-transmitted diseases also may be acquired in the community. In particular, HIV and hepatitis B often are acquired through sexual contact, and hepatitis C may be acquired through blood exposures unrelated to medical care. Fourth, even when the infection becomes manifest and is properly diagnosed and properly

attributed to the transfusion, the fact of a transfusion-acquired infection may not be reported since such reporting is not required of physicians.

22. FDA investigators discovered instances at ARC in which units from donors who tested positive for evidence of infection with cytomegalovirus (CMV) or had not been tested for CMV were mislabeled as negative and then released. Transfusion-transmitted CMV is commonly prevented by providing patients at risk with blood from donors who have a negative screening test for antibodies to the virus. Although the virus is dormant in most donors with a positive test, a small percentage of such donors will transmit the infection to blood recipients. Such transmission can be particularly devastating, as described in the next paragraph, in the settings of fetal exposure in-utero, low birth-weight premature neonates, marrow transplant recipients, organ transplant recipients, and AIDS patients. Therefore, such unsuitable units presented an imminent and serious threat to patient health. I understand that ARC National Headquarters was aware that CMV-positive units had been shipped and concluded that the incident did not present a hazard.

23. CMV is a type of herpesvirus that infects about half of the general adult population. The virus is transmitted sexually, congenitally, perinatally (during birth or by breast-feeding) and by transfusion and organ transplantation. Infections acquired congenitally or in the perinatal period may result in a devastating multi-system illness that often includes damage to the liver, the brain, and the eye. Even when mild, congenital illness often results in deafness presenting in early childhood. Infections acquired later in life typically produce a mild mononucleosis type illness with fever, lymph node swelling, and mild hepatitis. Following an infection in healthy children and adults, the virus becomes dormant, but remains present in white blood cells. Transfusion-transmitted infections typically are asymptomatic or associated with a mild hepatitis that resolves. However, in immune-compromised individuals such as fetuses in utero, low birth-weight premature

neonates, marrow transplant recipients, organ transplant recipients, and AIDS patients, a transfusion-acquired infection can cause severe illness and fatality due to hepatitis, pneumonia, encephalitis, and gastroenteritis. Also, blindness may result from retinal infection. Because these are the very types of patients for whom physicians may order CMV-negative blood, and release of such units will more likely be transfused in the patients most at risk, ARC's assessment of the risks associated with this incident is, in my view, incorrect and disturbing. Blood providers should be particularly cognizant of the risks associated with the use of their products.

Importance of Proper Procedures To Requalify Deferred Donors

24. Donors who have been deferred from future donation based on a history of high risk behavior or based on the results of a laboratory test for evidence of infection with a transfusion-transmissible infection represent a threat to blood safety unless it can be determined that they are free of infection and free of ongoing risk. For this reason, FDA regulations require that blood manufacturers maintain the names of deferred donors on a list (donor deferral registry), and take appropriate measures to prevent collection and use of their blood. However, because of the possibility for some risks to be resolved and because of the low, but significant occurrence of falsely-positive laboratory tests, FDA permits blood collection centers to requalify and “re-enter” some deferred donors, based on strict criteria. For example, donors with a record of a repeatedly reactive laboratory screening test for antibodies to HIV may be re-entered (allowed to donate again),

provided that repeat testing, including the use of a Western blot test, is performed at least six months later and is negative. The Western blot test is an additional, more specific test for antibodies to HIV that can distinguish true positive from falsely positive screening test results in most instances. In cases where the result of the Western blot test is indeterminate (neither completely negative nor positive), donors may not be re-entered because a small risk remains that the donor might harbor an HIV-related infection. Similarly, when a donor gives a history of a medical or behavioral risk factor for a disease transmissible by transfusion, the donor should be deferred appropriately, unless a suitable procedure is followed to document and override an invalid donor history.

Importance of "Lookback" Procedures and Product Tracking

25. In addition to CGMP requirements for donor selection and testing, FDA regulations and ARC standard operating procedures (SOPs) impose requirements for tracing and notification of prior blood recipients in the event that a donor is found to have a positive test for HIV after earlier donations were made. (Similar procedures are recommended for hepatitis C.) This notification is called “lookback.” The public health importance of performing lookback is that the prior, test-negative collections from a donor later found positive for antibodies to HIV (or hepatitis C) may have been infectious. This situation arises when the donor had only recently acquired the infection, and antibodies, which develop over a period of about a month after infection, were not yet detectable. The period of time between infection and a positive test is called the “window period.” Although advancements in test technology, including investigational use of direct tests for viral nucleic acids, have shortened the window period, it remains possible

for infectious blood to be collected from donors with negative screening tests. Notification of the recipients of such units is essential to protect the public health because the recipients may be unaware that they may have contracted a transfusion-transmitted infection, and may need treatment. Also, such an infection may have been, or may yet be, transmitted to the recipient's intimate partners, or in some cases, other close contacts, who may benefit from preventive measures or treatment.

26. Whenever a blood establishment discovers problems that may affect the safety, purity or potency of blood products, FDA regulations and ARC SOPs dictate that prompt action should be taken to investigate the problem and determine the need for corrective action. (Additionally, current regulations, which became effective on May 7, 2001, require that a report be filed with FDA within 45 days if the product was distributed.) The need for prompt action, including corrective measures, is driven by the fact that some potentially hazardous products may be retrievable due to their long shelf-life, and the fact that system-wide problems, if they exist, virtually assure that the same hazardous conditions will recur either at the same, or at other collection and processing sites. It is self-evident that recognized deficiencies that may permit the release of unsuitable units should be addressed promptly, since these represent the greatest threat to public health.

27. Many of the deficiencies discussed in Ms. Carden's declaration, individually and collectively, compromise ARC's ability to perform effective lookback checks (product retrievals, and consignee and recipient notifications). These observations include inaccurate donor registration; uncorrected duplicate and discrepant donor records; deficient donor hold systems; unreliable donor deferral classification and declassification; blood collection in the face of documented risk factors; and a grossly inadequate quarantine and inventory system. Because these same deficiencies compromise

ARC's ability to locate and track unsuitable products, FDA cannot be assured that ARC can effectively conduct product recalls, when they are necessary.

Importance of an Accurate Hematocrit Determination

28. Ms. Carden’s declaration notes the finding made on inspection that ARC failed to promptly discontinue use of an earlobe puncture to obtain a blood sample for determination of the donor hematocrit. This failure inexplicably was allowed to continue at ARC despite evidence from studies conducted by ARC that the earlobe stick procedure overestimated the hematocrit in a high proportion of donors. Some donors who would have been deferred based on an accurately measured low hematocrit suffered adverse events as a result of blood collection. As part of the suitability determination prior to blood donation, FDA regulations require a test for hemoglobin, which is the substance within red blood cells that carries oxygen. The requirement can be met either by a direct test for hemoglobin, or by a test for hematocrit, which is the percent of the volume of a whole blood sample that is attributable to the red cells. The standard is met when the test demonstrates a hemoglobin level (concentration) of at least 12.5 grams per 100 milliliters of blood, or the equivalent hematocrit of 38 percent.

29. The primary purpose of the hemoglobin (or hematocrit) requirement is to ensure that donation of blood will not create a threat to health in the donor. Additionally, the hematocrit of 38% assures that the red cell content of a blood donation will be adequate for clinical use of the red cell product. In a normal person, symptoms of anemia are likely to become manifest when the hematocrit falls below 30%. On average, removal of a unit of blood lowers the hematocrit value by about 3%. Thus, this amount of blood loss is sufficient to provoke significant physiologic stress in a person whose pre-donation hematocrit is 33% or less. For this reason, a procedure that may overestimate the donor’s hematocrit by 5% or more should not be

used. Persons made anemic by donation may experience mild symptoms including fatigue, palpitations, shortness of breath and light-headedness. Some persons also may faint, have heart attacks or have strokes. These complications may be avoided by an accurate determination of the hemoglobin or hematocrit to prevent an inappropriate donation by a donor with a low blood count.

Conclusion

30. In my opinion as a senior regulator and as a physician, ARC has been unusually and chronically resistant to taking a responsible approach to correction of deviations from CGMP. Given the large role that ARC plays as a provider of blood products, and the need and reasonable expectation of the public health community for confidence in the safety of the blood supply, ARC's lack of effective management commitment to quality is inexcusable. It has been a matter of great frustration to FDA to witness ARC's historic and continuing failure to correct its inadequacies despite more than a decade of enforcement efforts by the FDA, including warning correspondence, a voluntary agreement, license suspensions, tens of thousands of hours spent by FDA staff on inspections, countless meetings with ARC officials, and an injunction resulting in a consent decree.

31. I understand that ARC does not deny FDA's findings of violation or their significance. Generally, firms that recognize and accept their regulatory deficiencies move quickly and effectively to make the necessary corrections. Although ARC has made efforts in this direction, it is my observation that progress has been episodic, slow, and incomplete, reflecting an attitude of disregard for the public's interest.

32. FDA remains of the view that ARC possesses the resources and expert knowledge to come into compliance with regulatory standards. Reluctantly, FDA has also come to the view that additional incentives,

including court-ordered prospective money penalties, must be imposed on ARC to induce the organization to comply fully with regulatory requirements.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on _____, 2001. _____

Jay S. Epstein, M.D.
Director
Office of Blood Research
and Review
Center for Biologics
Evaluation and Research
Food and Drug Administration

IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF COLUMBIA

)

UNITED STATES OF AMERICA,)
)
Plaintiff,)
)
V)
) Civil Action No. 93-0949
The AMERICAN NATIONAL RED)
CROSS, a corporation,)
)
Defendant)
_____)

DECLARATION OF DANA DELMAN

1. My name is Dana Delman. I am a Policy Analyst employed in FDA's Office of Executive Secretariat. I have held this position since January 23, 1994.

2. On August 14, 2000, I attended a meeting between representatives of the American Red Cross (ARC) and FDA. The meeting had been requested by ARC. In attendance were Jane Henney (Commissioner), Dennis Baker (Associate Commissioner for Regulatory Affairs), Rick Blumberg (Office of the Chief Counsel), Mark Elengold (Deputy Director, Center for Biologics Evaluation and Research), and Dana Delman from FDA, and Bernadine Healy (President), Jackie Fredrick (Chief Operating Officer, Blood Services), Ron Lund (General Counsel), and Catherine Miller (Chair, Consent Decree Oversight Committee) from ARC.

3. During that meeting, Dr. Bernadine Healy said that ARC had no disagreements with the findings made by FDA investigators during the recent inspection of ARC's headquarters, and that she found those findings alarming. Dr. Healy further stated that ARC management had been unaware of the seriousness of the problems, that she had uncovered both a willfulness and a lack of urgency on the part of some ARC staff in not responding to FDA, and that there were widespread infrastructure, quality, and auditor problems at ARC. She also said that the "severity" of the issues held the potential for "grave impact" to patients. Near the end of the meeting, Dr. Healy stated that the ARC headquarters computer system had periodically "lost functionality," and that ARC had a long way to go to clean up the system.

She also expressed surprise at the evident lack of concern for patients in some ARC employees. She noted problems with interactions between ARC field offices and ARC headquarters, particularly the lack of timely responses by headquarters to field reports. She stated that she was especially concerned about ARC's shipment of quarantined units.

4. A true and accurate copy of the minutes of this meeting, which I prepared on August 14, 2000, directly after the meeting, is attached hereto as Tab 1.

5. A true and accurate copy of a memorandum of telephone conversation between Dr. Henney and Dr. Healy, dated November 20, 2000, is also attached hereto as Tab 2.

I declare under penalty of perjury that the above statement is true and correct.

Executed on:_____ _____
Date Dana Delman

MEMORANDUM OF MEETING

August 14, 2000

Attendees: FDA: Jane Henney, Dennis Baker, Rick Blumberg, Mark Elengold, Dana Delman

American Red Cross (ARC): Bernadine Healy, President
Jackie Fredrick, C.O.O., Blood Services
Ron Lund, General Counsel
Catherine Miller, Chair, Consent Decree Oversight Subcommittee

Subject: Courtesy Visit

Dr. Healy began by stating that the most recent headquarters inspection was alarming, but that it was a service to the organization and ARC had no disagreements with the FDA-483 findings. She said that top ARC management had been unaware of the seriousness of the problems and had been told that difficulties in the Atlanta Region were an aberration. She admitted to uncovering both a willfulness and a lack of urgency on the part of some ARC staff in not responding to FDA, and said that strategic and structural changes to the organization are needed. She listed several changes to the ARC management team. Despite the existence of some great components, such as the St. Louis National Testing Lab, she acknowledged widespread infrastructure, quality, and auditor problems.

Dr. Healy emphasized that ARC was not concerned with market share and may eliminate some activities. She said that only the plasma business held any appeal to for-profit firms. Dr. Healy stated her belief that ARC, as a unique non-profit organization, was best equipped to deal with the complex problems it faces.

Ron Lund is heading the ARC President's Task Force, which will examine a wide range of issues, including those identified by FDA. Its first meeting is on August 25. Mr. Lund concurred with the need for strategic initiatives, a change in the governance process of ARC, and for the legal function to be more actively engaged.

Ms. Fredrick discussed the need for some consolidation of the 36 blood centers, in the same way as the number of laboratories have been consolidated. She wants to examine the applicability of aspects of FDA's MedWatch program to the analysis of deviations reported to ARC headquarters.

Dr. Henney expressed appreciation for the forthrightness in Dr. Healy's presentation, and noted that FDA inspectors had also appreciated her involvement in the exit interview following the headquarters inspection. Dr. Henney pledged to work together to improve ARC compliance, utilizing the tools of both organizations. She stated that some modifications to the Consent Decree were in order and that Rick Blumberg would be in contact with Ron Lund about those modifications. Mr. Lund expressed concern that such modifications may affect the public's confidence in ARC, and may have an effect on voluntary donations.

Dr. Healy admitted that ARC headquarters was at fault regarding problems with its centralized computer system that had periodically "lost functionality." She also noted the need for a systematic analysis of errors reported to headquarters and problems in field/headquarters interactions, particularly in the response time of headquarters to field reports. Dr. Healy said that preventing the shipment of quarantined units was her top priority.

Dana Delman
Policy Analyst
FDA Executive Secretariat