DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Baltimore District Office
Central Region
6000 Metro Drive, Suite 101
Baltimore, MD 21215
Telephone: (410) 779-5454
FAX: (410) 779-5707

November 21,2006

ADVERSE DETERMINATION LETTER

BY FACSIMILE &
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John F. McGuire
President and CEO &
Executive Vice President
Biomedical Services
American National Red Cross
2025 E Street, N.W.
Washington, D.C. 20006

RE: United States v. American National Red Cross; Civil Action No. 93-0949 (JGP)

Dear Mr. McGuire:

United States Food and Drug Administration (FDA) investigators inspected the American National Red Cross (ARC) New York Penn Region's (NYPR) Blood Services facility, located at 825 John Street, West Henrietta, NY, on 29 days between August 24 through December 16, 2005. During the inspection, FDA investigators observed many violations of the law, regulations, and the Amended Consent Decree of Permanent Injunction (Decree), entered on April 15, 2003. At the conclusion of the inspection, the investigators issued a Form FDA 483, Inspectional Observations (FDA 483), attached hereto (Attachment I). FDA is now, pursuant to Paragraph VIII of the Decree, notifying ARC of its determination that ARC has violated the Federal Food, Drug, and Cosmetic Act, FDA regulations, and the Decree, specifically Paragraph IV.B.1. of the Decree and Title 21, Code of Federal Regulations (CFR), § 211.22(d).

Paragraph IV.B.1. of the Decree requires ARC to establish and submit to FDA a problem management standard operating procedure (PM SOP) to detect, investigate, evaluate, correct, and monitor all problems, trends, and systemic problems.[1] The Decree directs that the PM SOP include specific instructions for implementation and documentation of problem management requirements at ARC's Biomedical Headquarters (BHQ) as well as at the regional and laboratory facilities. As FDA informed ARC in a July 22, 2003 Adverse Determination Letter (ADL), FDA regards the PM SOP "as a first and indispensable step to enable ARC to comply with current good manufacturing practice."

ARC subsequently developed a PM SOP consisting of [redacted] After FDA reviewed and accepted the PM SOP, ARC implemented it on October 1, 2004.

The 2005 inspection of NYPR is FDA's first comprehensive evaluation of ARC's implementation of the PM SOP. FDA investigators' review revealed 207 deviations from the PM SOP. The high number of deviations observed indicates that the NYPR has not properly implemented and does not consistently follow the PM SOP. The frequent failure of NYPR's Regional Quality Director (RQD) and Quality Assurance (QA) staff to detect, correct, and prevent these deviations demonstrates that significant deficiencies exist in the Regional QA department. It also indicates that BHQ did not exercise adequate control, in that it did not detect NYPR's widespread PM SOP deviations.[2]

FDA reviewed problem reports generated by ARC that showed significant deviations related to quality assurance, inventory management, control of non-conforming blood products, donor screening, and blood component manufacturing. FDA discovered additional deviations including failure to promptly conduct adequate investigations; failure to promptly develop and implement adequate corrective actions and effectiveness checks; failure to identify, correct, and prevent adverse trends; and failure to document problem management activities related to each problem. The NYPR QA staff also failed to ensure that all problems are properly investigated and corrected to prevent their recurrence and that all steps in such investigations and corrective actions are thoroughly documented. FDA has created a table that illustrates the approximate numbers and types of PM SOP deviations recounted in problem reports involving various functional areas (Attachment II).

Many of the deviations from the PM SOP reflect recurring or continuing problems, some of which have been previously brought to ARC's attention by FDA. The most significant of these 207 violations include, but are not limited to, the following:

1. INVENTORY **MANAGEMENT**

Paragraph IV.B.17. of the Decree requires ARC to perform specific inventory management steps to prevent distribution of unsuitable blood products.[3] ARC's SOP [redacted], provides instructions for conducting an investigation each time a unit of blood or a blood component is not in the correct inventory location and for reporting such occurrences to ARC senior management and, in certain circumstances, to FDA. ARC's PM SOP also requires that deviations from quarantine procedures undergo at least a [redacted] investigation. [redacted] from ARC's SOP, provides instructions for determining how to conduct an investigation commensurate with the nature of the problem. It states certain types of problems always require at least a [redacted] investigation, such as [redacted]." Additionally, [redacted] requires formal corrective action plans and evaluations of their effectiveness for [redacted] problems.

Failure to follow inventory management procedures related to physical and electronic quarantine of blood products presents a potential risk to public health. When blood products have been determined unsuitable for transfusion or when their suitability has not yet been determined, they must be quarantined or controlled to prevent distribution. Any failure to thoroughly investigate deviations from quarantine procedures is a serious violation of the PM SOP and Paragraph IV of the Decree, which requires ARC to implement and adhere to its PM SOP.

During the inspection, FDA investigators found that on many occasions, NYPR discovered deviations from Paragraph IV.B.17.a. of the Decree and [redacted] but failed to investigate and correct those problems, as required by the PM SOP. These deviations include the following:

FDA ***483 observations 9 through 11***

a. FDA investigators reviewed problem reports related to inventory management and quarantine procedures and found that NYPR frequently failed to conduct thorough investigations and to take corrective actions commensurate with the nature of these problems, as required by the Decree and the PM SOP.[4] After the FDA investigators identified and notified NYPR of these violations, NYPR investigated further and found an additional 72 problems that NYPR had incorrectly designated as [redacted]. None of these problems were thoroughly investigated or corrected. Additionally, some of the problem reports revealed that NYPR failed to perform even the minimum requirements for a [redacted] problem. The 72 problem reports were created between October 6,2004, and September 20,2005. For example,

i. Problem Report 2005-001-1051730 (created on August 22, 2005) includes the description, [redacted]." A plasma product that had not passed a visual inspection must be identified as a non-transfusable product and placed in a quarantine location to prevent distribution. Instead, the product was physically returned to an in-process location ([redacted]), where it was available for labeling and distribution.[5] The problem report indicates NYPR investigated this error by answering 14 questions that are listed in [redacted] as the minimum investigation required for a [redacted] problem. On August 24,2005, NYPR determined that quarantine procedures were not followed. NYPR's investigation did not determine the scope of the problem, why the staff member did not follow procedures, or whether process improvement or workflow modification was necessary to prevent recurrence. QA approved the corrective action on November 10,2005, without identifying the inadequacy of the investigation and corrective action.

ii. Problem Report 2005-001-0838736 (created on March 18,2005) includes the description, [redacted] Two bins labeled "incorrect anticoagulant volume?" and containing 16 blood components were found in an in-process location, instead of a quarantine location. A staff member was improperly instructed by her supervisor to place the components in the in-process location. The problem report indicates NYPR investigated this error by answering the [redacted] questions in [redacted]. NYPR determined that quarantine procedures were not followed and, as a corrective action, reminded staff to quarantine non-conforming products immediately. However, NYPR's investigation did not determine the scope of the problem, why both an employee and supervisor failed to follow a critical control process, and whether process improvement was necessary to prevent recurrence. QA closed the problem on April 21,2005, without identifying the inadequacy of the investigation and corrective action.

ARC responded to these FDA 483 observations on June 13,2006 (June 2006 483 response) and stated that the "region has determined there is no negative product impact as a result of conducting [redacted] investigations." The purpose of the PM SOP, which as noted requires at least a [redacted] investigation for these incidents, is to prevent recurrence of problems and distribution of unsuitable blood products. ARC may not violate its own SOPs and dismiss the violation as inconsequential. ARC missed 72

opportunities to thoroughly investigate, correct, and prevent recurrence of these serious problems, including determining whether the problems resulted in the release of unsuitable blood or blood components. Additionally, ARC's response provides no information regarding whether NYPR took steps to address each of the 72 problems, such as reopening the problems, conducting a thorough investigation to determine root causes, and implementing adequate corrective action. Furthermore, ARC stated in its response that it modified an SOP, but there is no indication of how that modification relates to the root causes of the 72 problems, and whether the corrective action will be monitored for effectiveness.

FDA 483 observations 14 through 18

b. Problem report 2005-001-1019853 (created on July 27,2005) involves a red blood cell component that was missing from its assigned location. The component was electronically located in the NYPR's distributable inventory; however, during inventory reconciliation, NYPR discovered it was missing from its assigned physical location. During the inspection, FDA investigators reviewed the problem report and found that ARC failed to promptly, thoroughly, and adequately investigate and correct the problem and to document each step it took. For example,

i. The problem report states that one of the causes of this problem is that ARC's [redacted]. These conditions resulted in the red blood cell product being physically shipped to a consignee with no record of its distribution and with no final check of computer records to ensure the component's suitability for transfusion.[6] Although the problem report describes a corrective action related to staff performance, it includes no documentation of any corrective actions addressing the steps that staff must perform (work-around procedures) when [redacted] is [redacted].

In its June 2006 483 response, ARC states that it determined no additional corrective action is necessary because SOPs exist to "ensure the accuracy of shipment information as well as the handling of [redacted] issues such as [redacted]." +However,in this instance, those SOPs did not ensure the accuracy of shipping information. FDA has previously notified ARC of repeated instances where blood products were distributed with no record of final disposition.[7] ARC has repeatedly told FDA that it has corrected this problem, yet, as the foregoing instance demonstrates, it still occurs.

ii. FDA investigators observed that NYPR failed to comply with [redacted] requires development of corrective action plans within 30 days of discovery of the problem, and [redacted] requires QA approval or rejection of the plan within five days. Problem 2005-001-1019853 was discovered on July 27,2005, but QA did not approve the corrective action plan until October 3,2005, more than two months later.

iii. FDA investigators found that the problem report did not include information regarding how and when the component was found. Such information is necessary to determine the adequacy of ARC's investigation and corrective action and to assess its compliance with [redacted], and Paragraph IV.B.17.a. of the Decree, the reporting requirements for blood and blood components not located in their assigned locations. In its June 2006 483 response, ARC informed FDA that the component was located on July 27,2005, when a consignee reported to NYPR that it had

received an extra component in a shipment; however, that information was not in the problem file and was not provided to investigators during the inspection.

FDA 483 observation 8

c. FDA investigators reviewed 20 randomly selected inventory management-related problem reports dated from April 4 through August 5,2005. They found that 13 of those problem reports lacked adequate documentation of the facts surrounding each problem and of all steps taken to resolve the problems, in violation of Paragraph N.B.1.a.ii. of the Decree. That lack of documentation prevented the investigators from verifying whether the problems were thoroughly and adequately investigated and corrected and whether the final disposition of each blood product had been accurately recorded. Additionally, the FDA investigators were unable to verify whether the blood products involved in the 13 problem reports were truly missing from their assigned locations, and whether NYPR complied with [redacted], and Paragraph IV.B.17.a. of the Decree, which requires missing blood products to be reported to ARC senior management and to FDA. The inadequate documentation also prevented NYPR QA staff from performing timely verification on these matters. Only after receipt of the FDA 483, did NYPR gather information to document the problem reports and verify the actions taken. For example,

i. Problem report 2005-001-0862711 (created on April 4,2005) involves five blood components that had been placed into an electronic location for cytomegalovirus (CMV)-negative components, despite not having been tested to determine their CMV status.' A description field in the problem report states, "[redacted]" However, the report lacked the following documentation: A) a statement regarding how NYPR discovered that the blood products were missing from their assigned location; and B) a statement regarding where and when the blood products were physically located.

ii. Problem report 2005-001-0956421 (created on June 7,2005) involves three apheresis components that were placed in an electronic location for CMV-negative components without any designation in the computer system that the components had been tested and determined to be CMV-negative. A description field in the problem report states, "[redacted]". The problem report includes no documentation regarding how the problem was discovered, and where the components were physically located.

FDA has previously and repeatedly notified ARC of inventory management violations including, but not limited to, in two FDA 483s issued in April 2000 and December 2002, following inspections of BHQ, and in six letters issued to ARC, pursuant to Paragraph VI.A. of the Consent Decree entered on May 12, 1993 (the 1993 Decree). Additionally, FDA has issued two ADLs to ARC and imposed monetary penalties for blood products that ARC was not able to locate.

2. **FAILURE TO CONTROL NON-CONFORMING PRODUCT**

ARC recognizes the importance of preventing distribution of non-conforming blood and blood components in [redacted], and [redacted], by informing its staff that failure to identify or control non-conforming materials is a major risk problem. According to [redacted], a [redacted] investigation must be performed for major risk problems. Additionally, [redacted], requires that corrective

action plans for [redacted] problems be developed within 30 days of discovery of the problem and that QA approve such plans within five business days.

On July 8,2003, ARC reported to FDA, under Paragraph IV.B.2. of the Decree, the existence of a longstanding, system-wide problem involving failure to control non-conforming blood products. During an inspection of ARC's Southern California Region in July and August 2004, FDA discovered the same type of failure, which resulted in distribution of unsuitable blood components. As a result, FDA issued an ADL to ARC on March 28, 2005. In that ADL, FDA required ARC to report the status of its corrective actions to address this system problem. ARC responded in a November 30, 2005 letter, and acknowledged that its "initial assessment of its corrective action implemented in February 2005 did not indicate a satisfactory decline in the number of problems after implementation...."

Despite this history, during the inspection of the NYPR, FDA investigators reviewed reports of problems that occurred during the blood collection and the blood donor record review processes that involved the failure to control non-conforming blood products. The investigators found multiple deviations from the PM SOP and the Decree in the region's handling of these major risk problems, including inadequate investigations, inadequate and untimely corrective actions, and inadequate documentation. For example,

FDA 483 observations 128 and 129

a. The description field in problem report 2005-001-0851914 (created on March 28,2005) states, "[redacted] This problem involves two blood components that were manufactured from a whole blood unit collected on March 23, 2005, but not placed on an electronic hold upon discovery of the donor's questionable health history on the Blood Donation Record (BDR). FDA's review of this problem report revealed:

i. NYPR conducted a [redacted] investigation, instead of the required [redacted] investigation. Additionally, NYPR's investigation did not even meet the PM SOP investigation criteria, in that no probable cause(s) was determined and no corrective action was taken based on a probable cause(s). Instead, NYPR improperly voided this problem on June 16, 2005, and cross-referenced it to Problem Report 2005-001-0866868. ***[See*** item *2.e, below.]*

ii. The problem report does not include adequate information regarding when and how the BDR error was discovered and how much time elapsed before the non-conforming components were brought under control. It only states a whole blood unit "[redacted]" Although neither of the components was distributed, records show that the units were in distributable inventory locations on March 28,2005, five days after the donor's health history had been identified as questionable.

FDA 483 observations 132 and 133

b. The description field in problem report 2005-001-0853952 (created on March 29, 2005) states, "[redacted] This problem involves a unit of blood that was collected on March 26, 2005. On March 28, 2005, a reviewer discovered that quality control procedures had not been followed when the unit was collected, but the reviewer failed to immediately place an electronic hold on the unit to prevent distribution, pending a Material Review

Board (MRB) decision regarding disposition of the unit. Instead of immediately placing a hold on the unit, the reviewer sought advice regarding whether the unit should be placed on hold and a decision was not made until March 29, 2005. The unit could have been distributed during the time it took to obtain the decision. FDA investigators' review of this problem report found that NYPR conducted a [redacted] investigation, instead of the required [redacted] investigation. The investigation did not even meet the PM SOP criteria for [redacted] in that no probable cause(s) was determined and no corrective action was taken based on a probable cause(s).

FDA 483 observations 134 and 135

c. The description field in problem report 2005-001-0986261 (created on June 30, 2005) states, "[redacted]." This problem involved a unit of blood that was collected on March 29, 2005. On March 30, 2005, a reviewer discovered discrepancies on the BDR associated with that unit of blood. Based on the donor's answer to a health history question, additional information should have been obtained by the health historian, but no follow-up questions and answers were documented. The donor was inappropriately allowed to donate. Upon discovery of the error, the BDR reviewer failed to place an electronic hold on the unit to prevent distribution. FDA's review revealed the following:

i. NYPR incorrectly conducted a [redacted] investigation, instead of the required [redacted] investigation; however, the investigation did not meet the PM SOP [redacted] criteria, in that no probable cause(s) was determined and no corrective action was taken based on a probable cause(s). Instead, the problem report improperly referred to another problem report, 2005-001-0866868, for information regarding a corrective action and effectiveness check. *[See item 2.e, below.]*

ii. The problem was discovered on March 31,2005, but the problem report was not entered into ARC's [redacted] system until June 30,2005. [redacted] requires problems to be entered into that system within five working days of discovery. Timely reqording of problems is imperative because ARC regional facilities are required by the Decree and PM SOP[9] to provide monthly problem summary reports to ARC's BHQ and to perform monthly trend identification and trend analysis. This problem was not recorded for three months, thereby jeopardizing inclusion by the region for either of those purposes.

FDA 483 observations 138 through 140

d. The description field in problem report 2005-001-0866868 (created on April 6,2005) states [redacted]." The problem involves the failure to place an electronic hold on blood components manufactured from a unit of blood collected from a donor who gave health history information that required additional information. No additional questions or answers were documented on the BDR, and the donor was inappropriately allowed to donate blood. The BDR error was discovered on April 2,2005, but the BDR reviewer failed to place an immediate electron'ic hold on the unit of blood to prevent distribution of the blood components. The failure to place the hold was discovered on April 6,2005, but the electronic hold was not applied until April 9, 2005, after platelets manufactured from that unit of whole blood had already been distributed. FDA investigators reviewed records related to this problem and found the following deficiencies:

i. Although NYPR distributed platelets manufactured from the unit of blood, problem report 2005-001-0866868 (printed and provided to FDA investigators on August 26,2005) incorrectly indicates that no product left ARC's control and that the components were discarded. This discrepancy was not discovered and corrected prior to the FDA inspection.

ii. NYPR correctly determined that the problem required a [redacted]) investigation and corrective action plan, but records indicate that NYPR took no action to resolve this problem until June 13, 2005, 67 days after NYPR discovered the deviation, when a meeting was held to discuss the root cause. (The problem file contained no documentation of the meeting.) The report indicates NYPR did not begin an investigation until more than two months after discovery, yet there is no documentation of an approved extension of the time frame to develop a corrective action plan. [redacted] requires development of a corrective action plan within 30 days of discovery of the problem, or approval from the RQD to exceed that time frame.

iii. The problem report and associated records lack documentation that the described corrective actions were completed. NYPR determined that the root causes of this problem were the staffs lack of understanding of the requirement to immediately place an electronic hold on non-conforming blood products and a need to clarify the critical process for gaining control of such blood products. The corrective actions described in the report are: A) a decision to start immediately placing an electronic hold on all suspect products; B) an e-mail sent to specific record reviewers to inform them of the process; and C) a June 22,2005 meeting with staff to confirm the process requirements. The problem report file provided to FDA on August 26,2005, contained no documentation to show that any of those corrective actions occurred, yet the record shows that on June 17, 2005, QA indicated its approval of completed corrective actions. On October 1, 2005, FDA again requested the problem report and associated records and found that documentation of the corrective actions had been added, along with records describing two other corrective actions that were not described in the problem reports provided to FDA. ARC's June 2006 483 response states that FDA investigators reviewed the problem report before it was reviewed by QA for closure on September 22,2005. However, ARC does not explain how NYPR's QA approved the corrective actions on June 17, 2005, with no supporting documentation in the file.

iv. The effectiveness check developed by NYPR for this problem required only a 50% reduction in occurrences of this major risk problem over a two month period of monitoring. That goal is insufficient given the seriousness of the problem. QA approved the effectiveness of the corrective action on August 29, 2005, although, according to the problem report, there were two recurrences, thereby demonstrating that the measures taken were insufficient.

e. During their review of the problem reports cited in items 2.a through 2.c, FDA investigators observed that ARC closed out those problems with no investigation and corrective action, lowered the problem from [redacted] to [redacted], and cross-referenced them with problem report 2005-001-0866868('6868), which had a later discovery date. [redacted] However, that instruction does not permit-ARC to lower the level of problems and void or close investigations by linking them with a later, "master" problem. Moreover, paragraph IV.B.1.a.ii. of the Decree requires ARC to "promptly, thoroughly, and adequately investigate, correct, and takes steps to prevent the recurrence of each problem...." Failure to control non-conforming blood products

represents a potentially significant public health risk and warrants a prompt and thorough investigation and corrective action for each such problem.

According to problem report '6868, ARC attempted to justify the cross-referencing by stating that the other problems [redacted] However, the conditions for cross-referencing described in [redacted] did not exist. Because problem report '6868 was discovered after the other "linked" problems, problem report '6868 did not represent an ongoing investigation or corrective action at the time the other problems were discovered. Furthermore, probable cause(s) of the earlier problems had not been determined, and the factual consistency of the cross-referenced problems does not appear to have been fully evaluated and was not documented.

Furthermore, when NYPR lowered the assigned level of the problems in the [redacted] and in the Monthly Problem Summary Report, it misrepresented to BHQ the number of major risk problems related to recurrences of this longstanding, system-wide problem. Doing so negatively impacted the integrity of information in that database and in the Monthly Problem Summary Report. It also prevented BHQ from evaluating the region's performance and from evaluating the effectiveness of corrective actions taken to address the system-wide problem.

3. DONOR SCREENING

Donor screening is one of the recognized safeguards to ensure a safe blood supply through the use of health history questionnaires and limited physical examination. Based on information obtained during donor screening, unsuitable donors must be deferred from donation to avoid collecting blood from donors who may be infected with transfusion-transmitted diseases. Blood banks also screen donors for other specific conditions that could adversely affect the transfusion the recipient of a transfusion or the safety of the donor. [21 CFR §606.100(b)(1) & 606.100(b)(2); 21 CFR §§ 606.160(b)(1)(i) & 606.160(b)(1)(ii); 21 CFR §640.3] The FDA investigators reviewed numerous problem reports involving donor screening and found significant non-compliance with the Decree, regulations, and the PM SOP. For example,

FDA 483 observations 79 through 85

a. The description field in problem report 2004-001-0688948 (created on November 24, 2004) states, "[redacted] (Donor screening includes a test to determine hemoglobin or hematocrit levels.[11] A low test result may affect donor safety and the quality of the blood product.) The problem report was created when NYPR discovered an adverse trend (trend problem) in problems that occurred during the period February 1, 2003 through October 31, 2004.[12] FDA investigators reviewed this problem report and found inadequate and untimely corrective action, inadequate effectiveness criteria, and inadequate documentation. For example,

i. [redacted] requires development of a corrective action plan within 30 days of discovery of the problem, and it states that "[redacted]" Here, the trend problem was first identified on November 22, 2004. The first

documented action in the problem report is a December 13,2004 request for an extension for development of the corrective action plan. On January 7,2005, more than 30 days after discovery of the trend problem, QA approved the time frame extension for developing a corrective action plan to January 28,2005. The problem file contains no justification for the extension.[13] .

ii. [redacted], requires that target dates for completion of all actions to prevent recurrence of a problem be commensurate with the nature of the problem. QA repeatedly approved target date extensions for completion of the corrective action plan for this trend problem, despite the serious risk to donor safety, the length of time the trend had already existed, and the fact that the corrective action plan required only a staff meeting. The staff meeting occurred on June 16, 2005, more than six months after discovery of the trend.

iii. The problem report states that the root cause of this trend problem is [redacted] However, the investigation did not identify all root causes of the problem. For example, in order to detect errors, all BDRs are supposed to be reviewed by a second person at each donation site. NYPR's investigation and corrective action for this problem do not address the root cause of the failure of that second BDR review to detect errors.

iv. [redacted] requires effectiveness checks to [redacted] It also requires that success criteria be defined as part of the corrective action plan. NYPR's effectiveness check for this problem was to review a list of problems for the period June 14 through July 14,2005, to determine whether the corrective action (a meeting) was effective to prevent recurrence of the trend problem. The problem report indicates that NYPR defined the success criterion as a 20% decrease in the number of occurrences. The problem file contains no rationale for accepting only a 20% decrease for a problem of this serious nature. QA approved the effectiveness of the corrective action on July 18, 2005, and closed the problem report on August 5, 2005.

v. Trending data for September 2005 showed a continuation of the adverse trend in donor screening problems. NYPR opened a new trend problem report, 2005-001-1092294, on September 20,2005. This is the same trend problem that had been identified in November 2004 (2004-001-0688948) and closed on August 8, 2005. One year after discovery of the trend problem that had existed since February 2003, NYPR still had not implemented an effective corrective action to prevent recurrence of these problems. ARC's June 2006 483 response to this observation explains that the problem manager for the original trend problem only investigated one category of the donor screening problems that contributed to the donor screening trend; therefore, the other contributing categories were not investigated and corrected. ARC's response does not explain why, prior to closing the problem, NYPR QA failed to recognize these problem management deficiencies.

ARC's June 2006 483 response states that on September 29,2005, QA and collections supervisors had a team meeting. This response is inadequate for several reasons. First, documentation of that meeting was not added to the problem file until after the FDA investigators reviewed the records. Second, ARC's response does not state what was discussed or decided at that meeting, such as root causes, corrective actions, or QA approval of time frame extensions. Third, the June 2006 483 response includes no evidence indicating the results of that meeting, other than the QA approval of the timeframe extension.

As noted above, this problem, involving determination of donor hemoglobin or hematocrit, potentially affects donor safety, as well as blood product quality. FDA has previously notified ARC of violations related to donor safety, including in an April 2000 FDA 483 issued at the conclusion of an inspection of BHQ, and in an August 8,2002 letter issued under Paragraph VI.A. of the 1993 Decree.

FDA 483 observation 63

b. NYPR created problem report 2005-001-1092323(on September 14,2005) when it identified, during its review of tracking and trending data for the period September 1,2004 through July 31,2005, an adverse trend in the acceptance of ineligible donors. The description field in the problem report states, [redacted] The FDA investigators determined by interviewing the NYPR RQD that, during its review of tracking and trending data, NYPR found that one of the trend criteria in [redacted], had been met. However, when the FDA investigators reviewed the same data, they determined that the trend existed as early as March 2005, but NYPR failed to identify it until September 2005. [redacted], requires monthly problem reporting by regions to BHQ. [redacted] requires regions to determine whether the region has any trends in each category of problems.

FDA 483 observations 177 through 186

c. The description field in problem report 2005-001-0929081 (created on May 13,2005) states, [redacted]." The problem report further states that collection staff documented the first occurrence day for an event requiring donor deferral using the last day of the month instead of the first day of the month, as required by ARC's SOP. (Donation deferral periods are determined and documentedon BDRs by ARC collection staff who interview donors at collection sites to assess their eligibility for donation. When a donor reports to collection staff an event or condition that meets deferral criteria. but does not provide the specific day of first occurrence, the staff member [redacted] the day on'the BDR as the first day of the month of occurrence, in accordance with [redacted], and [redacted]. The first date of occurrence documented on the BDR is the basis for determining the beginning and the end of the donor's deferral period. It is also the basis for determining the period of time for which any of the donor's previous donations require evaluation and a determination of the suitability of associated components that are in ARC's inventory or that have been distributed.) This problem report indicates the problem is a [redacted] problem and was closed on July 28,2005. The FDA investigators reviewed the report and related records and found multiple deviations from the PM SOP. For example,

i. [redacted] requires that corrective action plans include effectiveness checks for [redacted] problems. Effectiveness checks are necessary to determine whether corrective actions actually and effectively corrected the problem, as intended. The problem file for 2005-001-0929081 includes an activity log that indicates the proposed effectiveness check was to interview a sampling of collection staff -- after NYPR issued a May 13, 2005 memorandum to reiterate the requirements of [redacted] and [redacted] -- to confirm their understanding of the deferral procedure. However, on July 13, 2005, the Quality Assurance

Director said no effectiveness check was required for this problem. The problem file contains no documented justification for this decision, which is contrary to the PM SOP.[15]

ARC's June 2006 483 response also provides no explanation for the RQD's decision that no effectiveness check was required for this problem. Instead, ARC states that NYPR conducted an initial assessment of selected staff in June 2005 and a second assessment in February 2006, and then placed the relevant documentation in the file. It further states that "staff members evaluated in the June assessment understood the requirements for documenting the date of the FO. In the February assessment, certain staff members [redacted]"

ARC provided different information to FDA on June 16,2006 when, in accordance with Paragraph XIX of the Decree, it submitted a significant corrective action to report that NYPR opened another problem report to address the FDA 483 observation regarding QA's failure to require an effectiveness check, but did not properly manage that new problem. Specifically, ARC explained that NYPR's June 2005 assessment involved 20 collection staff members, and [redacted] NYPR took no action to address that [redacted]. At the second assessment in February 2006, [redacted] NYPR, again, took no further corrective action. BHQ discovered that NYPR took no further action and mandated it to do so but not until more than three months after the failed effectiveness check.

ii. [redacted] Problem report 2005-001-09219081 did not comply with this directive in that it lacks documentation of each step taken to address the problem. The report states that the region's immediate action in response to the problem was to convene a meeting and develop a strategy to review all BDRs containing deferral information; however, the problem file included no documentation of the meeting or a strategy for BDR review. Additionally, the activity log associated with this problem report includes a statement that NYPR's QA requested that the problem manager consider additional steps to confirm that collection staff understand the first occurrence date requirement; however, the problem file contains no documentation that any additional steps were taken. During the inspection, as the FDA investigators asked questions, QA had to gather records from staff members to provide evidence of problem management activities. Although QA did not have all related records assembled in a problem file at the time of this inspection, QA approved the problem management activities and closed the problem on July 28, 2005.

iii. The problem report describes one corrective action as a review of BDRs involving deferrals for a specific period. Through the review, NYPR identified six donors with donations that were potentially affected by using the wrong dates to determine appropriate deferral periods. The report further states that the region "gained control of these products." However, the FDA investigators found no evidence in the problem file to verify that steps were taken to quarantine products, in accordance with [redacted]. ARC's June 2006483 response states that no donations were accepted from the affected donors during their deferral periods. The response does not explain the discrepancy between the problem report statement that the region "gained control of these products" and its new conclusion that there were "no implicated products." It does not explain why NYPR failed to

address the discrepant statement regarding control of the products, prior to closing the problem. At the time of the FDA inspection, the problem was closed with no documentation in the problem file to verify the BDR review and its results.

iv. Problem report 2005-001-0929081 ('9081) refers to problem report 2005-001-0929375 ('9375) as having been opened to obtain an MRB decision for products collected from the six donors associated with the BDR deferral date deviations. However, report '9375 states that no MRB decision was required. It refers to a related report, 2005-001-0929431 ('9431), which says no blood components retrievals are required. Yet, report '9431 has no documentation of who made the decision or of the basis for that decision. Additionally, report '9375 states, "[redacted]," indicating no records were provided to the MRB for review and determination of the appropriate disposition for affected blood products. In spite of these deficiencies and inconsistencies, NYPR closed report '9375 on August 9, 2005, with no MRB decision.

The problem report activity log for '9375 shows that report '9375 was reopened, modified, and closed on August 11, 2005, but there is no documentation of the reason for that activity and of what was modified. ARC's June 2006 483 response states that [redacted] "does not document changes that are made in entries...; therefore, there is no way to determine what, if anything, was changed on August 11, 2005 in this problem record."[16]

FDA has repeatedly informed ARC of violations related to donor screening, specifically in six letters issued pursuant to Paragraph VI.A. of the 1993 Decree, and in an FDA 483 issued in April 2000 at the conclusion of an inspection of BHQ.

4. **COMPONENT MANUFACTURING**

After whole blood is collected from donors, it is subject to numerous manufacturing steps, such as preparation of whole blood components, component modification, product quality control procedures, labeling, and storage. According to 21 CFR §606.100(b) and 21 CFR § 211.100(b), blood banks must establish and follow written procedures for all manufacturing steps performed. Additionally, 21 CFR § 606.65(e) requires blood banks to use supplies and reagents in a manner consistent with instructions for use provided by the manufacturer of that supply or reagent. During this inspection, the FDA investigators reviewed problem reports related to component manufacturing and found significant failures to comply with the Decree and the PM SOP. These deviations include the following:

FDA 483 observations 144 through 152

a. NYPR created problem report 2005-001-0738807 (on January 3, 2005) to address its failure to control blood components that were not manufactured in accordance with ARC's [redacted], and the manufacturer's instruction for use (FU) of leukocyte reduction filters in October and November 2004. The [redacted] and IFU provide timeframes and temperature requirements for the red blood cell leukocyte reduction process and for the addition of an additive solution to extend the expiration date of red blood cells." On December 30, 2004, NYPR discovered that on October 27 and November 26,2004, it had not complied with these requirements when processing 10 red blood cell components. Instead of being discarded, as directed by [redacted], the components were distributed to consignees "[redacted]

The FDA investigators reviewed the problem report and found numerous deviations from the PM SOP. For example,

i. [redacted], requires development of corrective action plans within 30 days of discovery after the problem. QA must review and approve or reject corrective action plans within five business days of development. However, QA did not approve a corrective action plan for this problem until March 21,2005, more than two months after discovery. The problem report shows that, without any documented justification, QA granted multiple extensions to develop the plan and multiple extensions to implement the plan and to perform the effectiveness check. The corrective action plan required training two staff members to perform tasks described in [redacted] which was completed on April 15,2005. Although the approved effectiveness check was to conduct interviews of the two staff members to ensure their understanding of the procedure, the QA–approved effectiveness check was not completed until May 12,2005, more than four months after discovery of the problem.

ii. The problem description states that a [redacted] determined the components were acceptable based on a prior MRB decision. [redacted], however, did not follow the PM SOP once he discovered the deviations [redacted]. When NYPR eventually identified the deviations and investigated, the staff responsible for the investigation did not identify, investigate, and correct the [redacted] failure to follow the PM SOP. The problem report should have addressed the [redacted] failure to manage the manufacturing errors as a 'problem,' as defined by the Decree, and to follow the PM SOP. Additionally, NYPR took no corrective action to address the [redacted] failure to properly manage the staff in following [redacted], and the IFU.

iii. The FDA investigators found no documentation indicating that NYPR followed [redacted], in order to prevent further distribution of unexpired blood products associated with problem 2005-001-0738807, or to notify consignees to place the blood products on hold. Two red blood cell components had been distributed and had not expired at the time of discovery.

iv. On January 3,2005, NYPR opened an MRB problem report to determine the appropriate disposition of the non-conforming blood products. The MRB decided on March 9,2005, more than four months after discovery of the problem, not to require retrieval of the affected components. FDA's review of the MRB problem report found the following deficiencies: A) no documented justification for the MRB's decision not to recall blood components that were manufactured in violation of 21 CFR § 211.110(b), 21 CFR § 606.100(b), and 21 CFR § 606.65(e); B) no documentation in the problem file indicating that the MRB considered the effect on expiration dating of adding the AS-3 additive to the components beyond the time frame established in the [redacted] and the IFU; and C) no documentation that the MRB considered BHQ's February 7,2005 instructions to NYPR to follow [redacted] which requires components that have not been manufactured in accordance with that [redacted] to be discarded. QA closed the MRB problem report on March 15,2005.

ARC's June 2006 483 response cites an undocumented conversation with the filter manufacturer as the basis for the MRB's decision not to retrieve the components. NYPR contacted the manufacturer to obtain documentation of this conversation during the inspection. The statements contained in that

document are not consistent with requirements in the manufacturer's IFU. As stated above, 21 CFR § 606.65(e) requires blood banks to follow manufacturers' IFUs for supplies and equipment such as filters. Licensed blood banks may request that FDA grant a variance for alternative procedures, in accordance with 21 CFR § 640.120, but no such variance was requested by ARC for this occurrence.

FDA 483 observations 169 and 170

b. The description field in problem report 2005-001-0845591 (created on March 23, 2005) states, [redacted] The problem involves distribution of a double red blood cell unit[18] that was collected on an apheresis instrument, but was not subjected to the quality control testing required by the instrument manufacturer's IFU and by ARC's [redacted] In this instance, one of the red blood cell products required a quality control check to ensure that its hemoglobin/hematocrit levels met acceptance criteria. The FDA investigators' review of the problem report found multiple deviations from the PM SOP. For example,

i. According to the problem report, one root cause of this problem indicates that the Quarantine and Labeling (Q&L) staff released the product without verifying that all procedures listed in a "special handling" tie tag attached to the blood product had been performed. The effectiveness check for this problem states that a sample of the Q&L staff was interviewed regarding their understanding of the process of reviewing and releasing blood products that have "special handling" tie tags. Although the problem file includes no documentation of those staff interviews, QA approved the effectiveness check on May 11,2005.

ii. [redacted] requires QA to review a corrective action plan and final effectiveness check within five business days of completion. The final effectiveness check was completed on July 2,2005, but as of September 11, 2005, QA had not reviewed and approved the corrective action plan for effectiveness.

iii. On March 23,2005, NYPR convened an MRB to determine the appropriate disposition of the affected blood products. The MRB required retrieval of the red blood cell unit that had been distributed; however, the required electronic hold was not applied to the computer record for that product to prevent redistribution if successfully retrieved.[19] The hold was not applied until March 28,2005, five days after the MRB decision, and the region learned on March 27, 2005, that the product had been transfused. QA reviewed and closed the MRB records, yet failed to detect this significant error. (The failure to immediately apply an electronic hold is related to the longstanding systemic problem that is described in item 2 of this letter.)

iv. On October 3, 2005, NYPR opened a problem report to address the failure to apply the electronic hold. FDA investigators reviewed that problem report and found no documentation of the corrective action for that failure. Additionally, the investigators found no investigation and corrective action to address NYPR QA's failure to detect, investigate, and correct the electronic hold error until FDA discovered it.

FDA subsequently learned from ARC, on June 15,2006, that BHQ found NYPR's investigation and corrective action for these FDA 483 observations to be inadequate and recommended that the region

conduct a retrospective review of its MRB decisions "to ensure that electronic holds on involved products were placed in a timely manner."

* * *

FDA investigators observed significant inventory management deviations that were not investigated and corrected in accordance with the PM SOP, but which are time-barred by Paragraph IX.F. of the Decree. Although FDA has not assessed a penalty for these violations, they are included below for informational completeness about inventory management:

1. Problem report 2004-001-0639068 (created on October 25,2004) includes the description, "[redacted] A red blood cell component that was marked "contaminated" was found in a bin designated for products suitable for labeling and distribution. The problem report indicates that NYPR investigated the error by answering the [redacted] questions in [redacted] and determined that procedures were not followed. NYPR directed, as the corrective action, a review of the procedures with the involved staff member. NYPR's investigation did not determine the scope of the problem, why the employee did not follow the procedure, and whether process improvement was necessary to prevent recurrence. QA closed the problem on November 17,2004, without identifying the inadequacy of the investigation and corrective action.

2. Problem report 2004-001-0647817 (created on October 24,2004) involves 65 platelet units that were assigned the wrong electronic location, which can lead to distribution without the required final status check. The report recounted that [redacted]) Distributing blood products from [redacted], instead of [redacted], presents a potentially significant risk because there is no assurance the final component status check is performed.. (The final component status check is the last opportunity prior to distribution to ensure the component is suitable.) Here, 33 of the 65 platelet units were ultimately distributed with no final component status checks. FDA investigators reviewed the problem report and found NYPR failed to adequately investigate and correct the problem, and failed to follow its own procedures for determining the disposition of non-conforming blood products. [FDA ***483 observations 27 through 30***] For example,

1. NYPR did not follow [redacted] and [redacted] which provide instructions for assessing risk and determining the appropriate level of investigation for problems. NYPR conducted a [redacted] investigation, even though this problem involved distribution of 33 non-conforming blood products.[20] The products met ARC's definition of non-conforming blood products because procedures were not followed to ensure product suitability for distribution. Specifically, the components were not subjected to the final component status check that takes place in [redacted] when blood products are properly distributed from [redacted]

ARC's June 2006 483 response states that no additional corrective actions are necessary, because a [redacted] investigation was appropriate based on Biological Product Deviation (BPD) code 0C-96-01-23, which is a minor risk problem, according to [redacted] ARC's response shows a disregard for the serious consequences of this problem: 33 non-conforming blood components were distributed as a result of this occurrence. ARC is required to consider the seriousness

of the problem in determining its appropriate course of action. [redacted] requires ARC to "[redacted] Indeed, FDA believes that any erroneous distribution warrants at least a [redacted] investigation and corrective action.

ii. [redacted] which provides instructions for managing and determining the appropriate disposition of non-conforming materials, supplies, or products. The instructions state, "[redacted]" NYPR disregarded that requirement and failed to convene an MRB to determine the appropriate disposition of the 65 electronically misdirected platelet units. 33 of which had been distributed. Additionally, NYPR failed to follow [redacted] to gain control of in-date (not-expired) components located in-house or previously distributed. That process is necessary to prevent distribution of components located in-house or, if the product has already been distributed, to notify consignees to prevent further distribution of implicated components that are unexpired.

ARC's June 2006 483 response states that an MRB, convened in April 2006, verified NYPR's rationale for accepting the components in 2004. Obtaining an MRB decision more than one year after the components were distributed is not acceptable. Also, the response provides no explanation why NYPR staff failed to follow [redacted] and made the unauthorized decision to leave non-conforming blood products on the market. The response also does not address how many other times NYPR has circumvented ARC's requirement to obtain MRB decisions regarding non-conforming blood products.

iii. The corrective action described in the problem report is inadequate because it focuses only on one probable cause, i.e., staff performance. The report says the staff was [redacted] and not following [redacted] NYPR's corrective action is described as [redacted] FDA investigators observed that NYPR performed no process review to determine whether any additional verification was necessary, such a review by another person.

iv. NYPR's QA staff closed the problem on November 4,2004, without detecting any of these violations of the PM SOP and the Decree.

* * *

These foregoing violations are not intended to be an all-inclusive list of violations at ARC facilities. It is ARC's responsibility to ensure compliance with all requirements of the law and the Decree.

Since entry of the 1993 Decree, FDA has repeatedly notified ARC of deficiencies in its quality assurance program, including but not limited to, in six VI.A. letters and two ADLs. Additionally, since implementation of the PM SOP, FDA investigators have observed significant violations of the PM SOP in four other ARC Regions, including Greater Chesapeake and Potomac, Greater Alleghenies, Southern California, and North Central.

ARC'S RESPONSE TO THE FDA 483

ARC responded to the FDA 483 in four letters dated February 2, March 30, June 13, and October 9, 2006. FDA has reviewed those letters and has commented on specific matters elsewhere in this letter. However, FDA has the following additional comments on the responses:

1) ARC's March 30,2006 response summarizes the FDA 483 observations in one statement: "The NY Penn Region did not implement the Problem Management System effectively." The response indicates ARC identified seven root causes of that problem and listed them, as follows: a) "resources were inadequate or not used effectively to support Problem Management requirements;" b) "PM SOPs were not being consistently followed because it was not recognized that key elements were not included in the local process map;" c) "The skills required to successfully perform the Problem Manager role were not adequately defined to ensure the selection of appropriate staff;" d) "Operational Management did not have or effectively use information to manage ongoing compliance with problem management SOPs;" e) "Quality did not have or effectively use information to manage on-going compliance with problem management SOPs;" f) "PM/QA staff did not establish required content for regional problem files [redacted] and hard copy;" and g) "Staff developing effectiveness checks lacked adequate guidance for determining success criteria and duration for monitoring."

These root causes seem to address only the failures of lower level problem managers and QA staff, but not of ARC's management and the NYPR RQD. For example, ARC's response does not describe any investigation to address whether the NYPR RQD recognized the existence of the deficiencies identified in the seven listed root causes and brought those to the attention of ARC management. It also does not state whether these deficiencies were identified during NYPR regional audits and, if not, why not.

2) ARC's June 13,2006 response states that ARC will increase management oversight at NYPR and it will create a new centralized department for problem management activities in NYPR. It further states that "Regional Quality Assurance will work closely and collaboratively with this new department and will provide guidance, oversight and support to ensure compliance with all aspects of the Problem Management System."

The response provides no specific information regarding increased management oversight, and no information regarding how ARC expects the same Regional Quality Assurance, responsible for not identifying and addressing the conditions observed during the inspection, to provide guidance, oversight, and support to ensure the new department complies with the PM SOP.

Additionally, the response states that the new department was scheduled to start its operations at the end of June 2006. The response does not state what ARC did to ensure compliance with the PM SOP in NYPR until the new department became operational.

3) The February 2, 2006 letter describes, among other activities to address the FDA 483 observations, ARC's plan to send audit teams to selected facilities to perform qualitative assessments of PM SOP implementation. In its March 30, 2006 response, ARC describes the results of its assessments and "areas for improvement, including, but not limited to improvement in management involvement and accountability, staffing levels, problem management and writing skills, and clear accountability for problem management tasks." Of six regions audited, "all the regions had some issues...." Three regions "had the most successful implementation with some opportunities for improvement." Two regions

"ranked in the middle of the assessed regions and each required some improvements." In one region, the River Valley Region, ARC's auditors found that "implementation challenges were similar to those of the NY-Penn Region." To correct the problems identified in the River Valley Region, ARC plans to create a small problem management group that reports to "the Quality Assurance Department." The response further states that staff from another region will provide interim support for managing [redacted] problems until River Valley is self-sufficient. However, because the region assisting River Valley was not subject to the qualitative assessment to ensure it had adequately implemented and complies with the PM SOP, ARC does not explain why it believes that region is qualified to provide assistance to the River Valley Region.

4) The February 2,2006 letter states that ARC intends to address potential system-wide problems (PSPs) identified in the FDA 483. The March 30, 2006 letter states that of eight PSPs it identified within the FDA 483 observations, five were facility performance problems, and three were already being addressed by BHQ changes to the PM SOP. ARC's response describes its investigation and rationale for concluding that none of the eight PSPs is a system-wide problem. However, FDA notes the information provided in the response is limited only to ARC's investigation related to NYPR. There is no information regarding any assessment ARC has performed to determine that the PSPs were not present in other facilities.

5) In response to numerous FDA 483 observations, ARC's June 2006 483 response refers to records that were added to problem files after the FDA investigators reviewed the files. ARC does not address how NYPR QA was able to monitor problem management activities related to those problems, when all relevant records were not in problem files, and QA did not identify and provide those records to FDA investigators during the inspection. For example, ARC's response to FDA 483 items 1 through 7 refers to relevant records found after the inspection, but it provides no explanation of how, without those records in their respective problem files, QA was able to monitor and approve problem management activities and ensure compliance with inventory management documentation and reporting requirements.

6) ARC's response does not indicate whether it investigated and took additional corrective actions for each problem report that is the subject of an FDA 483 observation. For example, the June 2006 483 response does not state whether ARC conducted investigations commensurate with the nature of the 72 problems described in FDA 483 observation 9. [Observation *9* is described in item *1.a* of this letter.]

7) Finally, ARC's four responses provide no insight into why BHQ was unaware of the conditions in NYPR until the FDA inspection. As stated above in this letter, FDA considers the PM SOP a critical step for ARC to achieve compliance with cGMP.

FDA will further evaluate the adequacy of ARC's promised corrective actions during future inspections of ARC facilities.

ORDERS

Paragraph VIII of the Decree provides that "[i]n the event that FDA determines, based upon inspection... review of ARC records, or other information that comes to FDA's attention … that ARC is not following any SOP that may affect donor safety or purity or labeling of blood or any blood component … has violated the law; has failed to fully comply with any time frame, term or provision of

this Order … FDA may order ARC to come into compliance with the law, ARC SOPs, or this Order, assess penalties, and/or take any step that FDA deems necessary to bring ARC into compliance with the law, ARC SOPs, and this Order." FDA orders ARC to do the following:

1) Ensure that the PM SOP has been adequately implemented in NYPR and all other ARC facilities and is continuously followed.

2) Within 20 days of receipt of this letter, provide FDA with detailed information regarding NYPR's current organizational structure, including the structure and responsibility of the problem management and quality assurance departments, and identify by name all NYPR senior management, as defined in Decree paragraph III.B.10. Additionally, the June 2006 483 response to observation 12 refers to weekly problem management meetings attended by QA and problem managers and regulatory review meetings attended by senior management. Please identify to FDA the senior management who attend the regulatory review meetings and provide copies of all minutes of both meetings and reports reviewed at the meetings or provided to staff prior to the meetings.

3) Within 20 days of receipt of this letter, provide to FDA the qualitative assessment protocol and results from that assessment of the Carolinas Region and the River Valley Region. (FDA may request additional records related to the qualitative assessment at a later date.)

4) Within 60 days of receipt of this letter, provide problem reports and problem files opened in response to the following FDA 483 observations: 8 through 11, 14 through 18, 27 through 30, 45, 49, 60, 63, 79 through 85, 94, 101, 108, 125 through 129,132 through 135,138 through 140,144 through 152, 160,169 through 171, 177 through 186,205. Also provide problem reports and problem files related to the following problem numbers that are referenced in ARC's FDA 483 response letters: 2005-001-0922447, 2005-001-1077907, 2006-001-1325895, 2006-001-1325895, 2005-001-0983539, 2005-001-1092323,2004-001-0688948,2006-001-1231033,2006-001-1325895; 2006-001-1231022,2005-001-1064285, 2005-001-0923276, 2005-001-1110676, 2005-001-1211805, and 2005-001-1211805.

5) Within 20 days of receipt of this letter, state when, since October 1,2004, regional and BHQ audits of NYPR and River Valley were performed. Explain why the violations observed during FDA's inspection of the NYPR and during ARC's qualitative assessment of the River Valley Region were not detected sooner by ARC's internal audit program.

6) Within 60 days of receipt of this letter, increase the frequency of internal regional audits and BHQ audits of facility implementation and compliance with the PM SOP.[21]

7) ARC's June 2006 483 response states that the [redacted]"does not document changes that are made in entries...; therefore, there is no way to determine what, if anything was changed on August 11,2005 in this problem record." [See Donor Screening item 3.c, above.] The FDA investigators found instances in which changes to problem records were undocumented and it was not possible to determine what the changes were and what was originally documented in those problem records. Within 60 days of receipt of this letter, implement a recordkeeping system that permits examination of each change made to problem records.

8) Within 30 days of receipt of this letter, ensure that all facilities understand and follow [redacted] Specifically, investigate each problem in accordance with [redacted]

and only cross-reference after the investigation reveals that a problem is closely related to an existing investigation or trend. [FDA 483 ***observations 79 through*** *85* ***and item*** *3.a, above]*

9) Within 60 days of receipt of this letter, provide a copy to FDA of [redacted], revised and implemented October 20,2005, and [redacted] implemented on April 14,2006.

10) Within 60 days of receipt of this letter, provide copies to FDA of all NYPR's Monthly Summary Problem Reports for each month since the close of the FDA inspection on December 16,2005.

11) The June 2006 483 response to FDA 483 observation 52 states "The [redacted] software that is used for inventory management of plasma for further manufacture does not have a 'gain control' capability." The corrective action described in the response states, "Biomedical Headquarters will enhance the process for notification to the plasma derivative manufacturer when a unit of plasma must be controlled. Red Cross anticipates this process will be in place by the end of the fourth quarter 2006." Within 60 days of receipt of this letter, provide detailed information regarding the enhanced notification process and state what interim steps ARC has taken to ensure non-conforming plasma units are controlled.

12) The June 2006 483 response states, "Effective March 6,2006, Senior Management allocated Quality Assurance (QA) staff from [redacted] to perform monthly tracking and trending activities for both the NY-Penn and Northeastern Pennsylvania (NEPA) Regions." Within 60 days of receipt of this letter, provide details regarding [redacted]" and how use of those resources will correct NYPR's tracking and trending deficiencies. State whether the use of staff for the [redacted] is permanent. If not permanent, state what other steps have been taken to ensure NYPR's tracking and trending deficiencies have been corrected. Please provide records related to any effectiveness checks for this corrective action.

13) FDA has reviewed evidence related to problem report 2005-001-0738807 and has determined that the 10 distributed red blood cell units were unsuitable.. Paragraph X.E. of the Decree requires ARC to notify consignees within 48 hours of learning that an unsuitable blood component[22] has been distributed and, when the component has not been used, to initiate retrieval. Paragraph X.G. of the Decree states that "In the event FDA notifies ARC in writing to notify consignees and retrieve blood or blood components from the market, and ARC agrees with FDA's notification, ARC shall take steps to notify consignees and retrieve the blood or blood components within 24 hours of receiving FDA's notification." Promptly notify the consignees to whom those 10 blood products were distributed and report to FDA when such notification has been completed.

14) The June 2006 483 response states that ARC will complete a retrospective review of MRB cases in NYPR by July 31, 2006. [FDA 483 ***observation*** *171*] Within 90 days of receipt of this.letter, report the results of that review to FDA. Additionally, ensure that NYPR's MRB decisions resulted in appropriate disposition of blood components affected by non-conformances similar to those described in problem report 2005-001-0738807. [See Component Manufacturing item 4.a, in this letter.]

For the reasons stated above, FDA has determined that ARC did not comply with the law, ARC SOPs, and the Decree. Pursuant to Paragraph IX of the Decree, FDA is fining ARC $10,000 for each day from November 27,2004 through June 23,2006. This period begins on the date that is 270 days before

investigators issued an FDA 482 Notice of Inspection, continues through the FDA inspection (which concluded on December 16,2005 when FDA issued the FDA 483 regarding the inspection and thereby notified ARC about its inadequate implementation of and compliance with the PM SOP), continues through the time it took for ARC to submit its response on June 13,2006 to the individual 483 observations (which response FDA later found to be inadequate), and ends after the first ten days that FDA had to review the June 2006 483 response. The subtotal for the fine, before including a fine amount yet to be determined for the number of days it takes ARC to submit its compliance plan, is $5,740,000. If the compliance plan is not adequate, additional penalties may be assessed.

We have fined ARC $10,000 for each day during the relevant period described above (November 27, 2004 to June 23,2006) because FDA investigators documented that ARC was significantly and consistently violating the PM SOP before November 27, 2004, as shown by the violations discussed on pages 14 through 16 of our letter, up to and including June 13,2006, the date on which ARC filed its last response to the FDA 483. In addition, we are fining ARC for the first ten days of FDA's response period.[23] Under the Decree, however, there are other methods of calculating the fine. First, because many of the violations continued for an extended period of time, there were many days on which several violations occurred simultaneously. Thus, FDA could have charged for more than one violation on a single day instead of the single per diem charge. Second, under paragraph IX.A. of the decree, FDA could have penalized ARC "up to $10,000 for each violation and (emphasis added) for each day described in FDA's [ADL]." Third, under paragraph IX.F.4 of the decree, FDA could have penalized ARC not only for the initial violations of each line employee but also for each subsequent ARC failure to detect and correct the violations (e.g., by downstream supervisors and BHQ). FDA did not impose these cumulative fines here and instead chose to impose a single per diem fine. We are confident that if FDA had chosen to cumulate the fines, the total amount would have been far more than $5,740,000. Please also note that our decision to not cumulate the fines for this inspection may not be followed in subsequent ADLs.

Paragraph IX.F.5. of the Decree states that "All penalties assessed under this Order shall be based on the year in which the violative conduct occurred. The annual cap amounts described in paragraph IX.F.1. of this Order shall also be attributed solely to the year in which the violative conduct occurred." The penalty period described in this letter includes violations that occurred in 2004, 2005, and 2006. The penalty amounts assessed as a result of the violations for each of those years is $350,000 in 2004, $3,650,000 in 2005, and $1,740,000 in 2006.

As provided in the Decree, if ARC agrees with this adverse determination, it shall within 20 days of receipt of this letter, notify FDA of its intent to come into compliance with the Decree and submit a plan to do so. If ARC disagrees with FDA's adverse determination, it shall respond in writing within 20 days of receipt of this letter, explaining its reason for disagreeing with FDA's determination. Your response

must be submitted to me at the Food and Drug Administration, Baltimore District Office, 6000 Metro Drive, Suite 101, Baltimore, Maryland 21215, with a copy to Jesse Goodman, M.D., M.P.H., Director, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852.

Sincerely yours,

Evelyn Bonnin
Director, Baltimore District

ATTACHMENTS

cc: C. William Cherry
Senior Vice President for Quality
and Regulatory Affairs
American National Red Cross
2025 E Street, N.W.
Washington, D.C. 20006

Mary Elcano
General Counsel
American National Red Cross
2025 E Street, N.W.
Washington, D.C. 20006

Bonnie McElveen-Hunter
Chairman, Board of Governors
American National Red Cross
2025 E Street, N.W.
Washington, D.C. 20006

[1] "Problem" is defined in Paragraph III.B.52. of the Decree as "any deviation from *the* law, *ARC SOPs*, or this Order, however discovered, recorded, or reported, including, but not limited to deviations reported in ARC Clarify reports (and/or in any other successor or similar deviation-reporting systems and/or reports), biological product deviation reports, internal deviation reports, trends, adverse reaction reports, *lookback* cases, cases of suspected *transfusion-transmitted disease*, *potential* system (systemic) problems, system (systemic) problems, supply and equipment problem reports, *FDA-483s*, compliance-related FDA correspondence, internal and external audit reports, and retrievals."
"Trend is defined in Paragraph III.B.64.of the Decree as "the recurrence or multiple contemporaneous occurrences of the same or similar *problems* in one or more than one ARC region and/or laboratory."
"System (systemic) problem" is defined in Paragraph III.B.63. of the Decree as "aproblem that results from a defect in *ARC* policies, procedures, equipment, or supplies, and affects either more than one *ARC region* and/or laboratory, or warrants corrective action which, when implemented, could affect more than one ARC region and/or laboratory."
Paragraph IV.B.1.a.ii. requires that "[e]ach *ARC region* and laboratory shall, commensurate with the nature of the *problem*, promptly, thoroughly and adequately investigate, correct, and take steps to prevent the recurrence of each *problem*, and shall determine whether the problem resulted in the release for distribution of any unsuitable blood or blood components and, if so, whether consignees were notified. Each region and laboratory shall thoroughly and contemporaneously document each step it takes to investigate, correct, and prevent recurrence of each problem, and to determine if theproblem resulted in the release for distribution of any unsuitable blood or blood components. Such documentation shall be maintained at the appropriate region or laboratory, shall reflect the identity of the regional or laboratory quality assurance staff member who reviewed and approved the problem investigation and the date on which that approval occurred, and shall be available for review by ARC Biomedical Headquarters and FDA."

[2] Paragraph N.A.2 of the Decree requires ARC to establish and continuously maintain managerial control over quality assurance in all regional facilities.

[3] Paragraph IV.B.17.a. requires that "Within 30 days of entry of this Order, *ARC* shall review, modify if necessary, and thereafter continuously maintain *SOPs* requiring the regions to ...(iv) document each time a unit ofbloodor a bloodcomponent is not found or is found in a location other than its assigned location;... and (vi) notify FDA in writing within 5 business days after a region has failed to locate any blood or blood component within 72 hours of the time that the region initially learned that such blood or blood component was not in its assigned location...In addition, FDA may assess a penalty of up to $1,000 for each unit of blood and each blood component that ARC fails to locate within 72 hours after a region initially learned that such blood or blood component was not in its assigned location. Within 5 business days thereafter, *ARC* shall notify FDA in writing of each such lost unit of blood or blood component and if such timely notification is not made, FDA may assess a penalty of up to $10,000 for each such notification failure."

[4] Paragraph IV.B.1. of the Decree requires ARC to investigate and develop and implement corrective action commensurate with the nature of the problem.

[redacted]

[5] ARC's inventory management system [redacted]. Blood centers simultaneously collect, [redacted] blood compo[redacted] move components from one location to another, based on processing and testing information received. Inventory control is essential to prevent release of unsuitable blood comoonents. Adequate quarantine and inventory control 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 tracked and located. [21 CFR 211.82(b), 606.40(a)(3)-(6), 606.165]

[6] [redacted]

[7] 21 CFR§ 606.165 requires blood banks to have distribut[redacted] and receipt procedures, including a system by which the distribution or receipt of each unit can be readily determined to facilitate its recall, if necessary. Additionally, distribution records shall contain information to readily facilitate the identification of the name and address of the consignee, the date and quantity delivered, the lot number of the unit(s), the date of expiration or the date of collection, whichever is applicable, or for crossmatched blood and blood cornponents, the name of the recipient.

[8] Cytomegalovirus is a virus that can be transmitted through a blood transfusion and may cause disease in the recipient. It presents a significant risk to immunocompromised individuals and to babies born to CMV-negative mothers. Physicians may specifically request CMV-negative blood components for use in low birth weight infants born to CMV-negative mothers and for immunocompromised individuals who are CMV-negative. CMV-positive or untested blood components may not be safely used in such patients. [21 CFR § 211.130 and 21 CFR § 606.122(h)] FDA has repeatedly notified ARC of deficiencies observed in its handling of blood components labeled as CMV-negative. Specifically, FDA 483s issue at the conclusion of inspections of BHQ in April 2000 and in December 2002 included observations related to CMV-negative blood components. Additionally, FDA notified ARC of such deficiencies in an April 14,2003 letter pursuant to Paragraph VI.A. of the 1993 Decree. Decree Paragraph N.B.15 requires accurate product labeling, including CMV labeling.

Paragraph N.B.I. requires ARC to identify, investigate, and correct adverse problem trends. To that end, it requires ARC regions to report to BHQ each month regarding categories of problems to determine whether trends exist. BHQ is requ[redacted] to anal[redacted] and investigate those reports to discover trends and system-wide problems [redacted]

[10] [redacted]

[11] As part of donor screening, 21 CFR § 640.3 requires a test for the donor's hemoglobin or hematocrit level. Hemoglobin is a substance in red blood cells that carries oxygen. The purpose of the test is to ensure that donation of blood will not create a risk to the health of the donor. It also assures that the red cell content of the blood donation will be adequate for clinical use of the red cell product. Donors with low hemoglobin or hematocrit may be made anemic by donation and may experience mild symptoms, such as fatigue, palpitations, shortness of breath and light-headedness. Such donors may also experience more severe complications, such as fainting, heart attacks or strokes. Such reactions can be avoided by accurate determination of hemoglobin or hematocrit.

[12] Paragraph III.B.64 of the Decree defines 'trend' as "the recurrence or multiple contemporaneous occurrences of the same or similar problems in one or more than one ARC region and/or laboratory." Paragraph IV.B.1. requires ARC to establish "SOPs to detect, investigate, evaluate, correct, and monitor all problems, trends, and system (systemic) problems." Paragraph N.B.1.a.i. requires BHQ to ensure that each region has a Problem Management System for tracking and bending ail problems and that each region shall scrutinize multiple sources of quality data, including trends. The Decree definition of problem at Paragraph III.B.52 includes trends. [redacted]

[13] Decree Paragraph IV.B.1.a.ii. requires thorough documentation of each step to investigate, correct, prevent. [redacted]

[14] Malarial infection can result from transfusion of blood donated by an infected donor. Presently, there are no practical serological tests to detect transmissible malaria in asymptomatic donors. Therefore, transfusion-transmitted infection is prevented by deferral of donors with increased risk of infection based on their medical and travel history.

[15] The Decree requires thorough documentation of each step to investigate, correct, and prevent. [redacted] Effectiveness checks are not optional, yet the problem file has documentation showing QA said no effectiveness check was necessary for the corrective action for problem report 2005-001-092908. The rationale is not documented, so FDA cannot determine why QA made the decision.

[16] Decree Paragraph IV.B.1.a.ii. requires thorough documentation of each step to investigate, correct, and prevent problems. [redacted] In this instance, records were modified, but cannot be audited to determine what was modified. There is potential for record integrity problems.

[17] a) Leukoreduced red blood cells are prepared by reducing the total white cell count to less than $5x10^6$ and retaining 85% of the original red cells. Leukocyte removal efficiency increases as the time between collection and depletion is shortened. Leukoreduced components may be indicated for patients with recurrent febrile non-hemolytic transfusion reactions; patients at risk for alloimunization to HLA antigen, and patients at risk for CMV infection. (AABB Technical Manual 13)

b) Additive red cell preservative solutions consist of an anticoagulant-preservative that must be added to red cells within a specified number of hours of phlebotomy to prevent clotting and to maintain cell viability and function during storage.

[18] Double red blood cell units are collected using apheresis, which is the process of removing whole blood from a donor, separating selected components, and returning the unharvested portion to the donor. Blood banks use instruments manufactured for apheresis procedures. Those instruments may provide alarms indicating that the blood bank must perform certain quality control tests. Double red cell bags are labeled in order of collection to ensure the correct bag is quality control tested.

[19] According to problem report 2005-001-0845684, the NYPR MRB justification for requiring that the affected blood components be retrieved is that the message "[redacted]

[20] ARC's PM SOP [redacted] paragraph III.B.65. of the Decree defines 'unsuitable blood or blood components' as those "for which the actual or purported purity has or may have been compromised."

[21] Paragraph IV.B. 3.a. of the Decree permits FDA to order ARC to increase the frequency of internal audits.

[22] Paragraph III.B.65. of the Decree defines 'unsuitable blood or blood components' as those "for which the actual or purported purity has or may have been compromised."

[23] Paragraph IX.A. provides that "Commencing with the date of the ARC violation(s) that gave rise to FDA's determination, and subject to the limitations of paragraph IX.F.2., FDA may assess a penalty of up to $10,000 for each violation and for each day described in FDA's determination until the day that ARC submits its plan and, when applicable, interim plan."