DEPARTMENT OF HEALTH AND HUMAN SERVICES

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June 3, 2008

ADVERSE DETERMINATION LETTER

BY FACSIMILE &
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. H. Chris Houdra
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. Hrouda:

In late 2007, the Food and Drug Administration (FDA) received reports from New England Region (New England) and Southern Region (Southern) of the American National Red Cross (ARC) that a total of six Washed Red Blood Cell (Washed RBCs) units had been processed improperly using hypertonic saline (1.6%), instead of sterile normal saline (0.9%), and were distributed and transfused to three recipients.[1] FDA subsequently conducted inspections limited to evaluating the investigations and corrective actions undertaken by New England and Southern following their discovery of these violations: FDA investigators inspected New England's manufacturing and distribution facilities, located at 32 North Prospect Street, Burlington, Vermont and 180 Rustcraft Road, Dedham, Massachusetts, on February 4 and 5, 2008, and on February 11 through 14, 2008, respectively, and Southern's manufacturing and distribution facility on December 3 and 4, 2007.

The inspections revealed deviations from the law, regulations, and the Amended Consent Decree of Permanent Injunction (Decree) entered on April 15, 2003. At the conclusion of the New England inspection, the investigator issued a Form FDA 483, Inspectional Observations (FDA 483), a copy of which is attached hereto. ARC responded to the FDA 483 by letter dated March 31, 2008, and FDA has reviewed that response. Pursuant to Paragraph VIII of the Decree, FDA is notifying ARC of its determination that ARC has violated the law, regulations, and the Decree. The violations are:

[1] Washed RBCs are prepared by washing red blood cells with and re-suspending them in sterile normal saline (0.9%) using automated or manual methods. This process removes approximately 99% of plasma proteins, electrolytes, antibodies, and cell debris that may predispose a patient to recurrent or severe transfusion reactions. Washed RBCs must be used within 24 hours of processing because the process is accomplished in an open system, which increases the risk of bacterial contamination. Use of hypertonic saline to wash red blood cells may cause a temporary adverse health consequence but is unlikely to cause a serious one. The potential hazard is considered temporary and reversible without medical intervention.

1. Failure to review all records pertinent to a lot or unit before the release or distribution of a lot or unit of final product, as required by 21 CFR § 606.100(c) and 21 CFR § 211.192. For example:

a. On November 17, 2007, New England reported to FDA that it had distributed two units of Washed RBCs ([redacted] and [redacted]) that had been washed in 1.6% saline, instead of the required 0.9% (normal) saline. According to ARC's system-wide SOP, [redacted] Regions not using electronic production records must record on a *Washed RBC Log* specific manufacturing information pertaining to Washed RBCs. FDA's review of New England's *Washed RBC Log* for the two units found that they were washed and distributed on November 15, 2007. However, no second party reviewed the *Washed RBC Log* until November 16, 2007.

b. On October 3, 2007, and November 7, 2007, Southern reported to FDA that it had distributed a total of four units of Washed RBCs washed in 1.6% saline, instead of the required 0.9% (normal) saline. FDA's review of Southern's *Washed RBC Logs* for the four units found the following:

i. Washed RBC [redacted] was washed and distributed on January 24, 2006. The second party review of the *Washed RBC Log* was performed on January 25, 2006.

ii. Washed RBCs [redacted], and [redacted] were washed and distributed on September 22, 2007. The second party review of the *Washed RBC Log* was performed on September 27, 2007.

2. Failure to establish and maintain written standard operating procedures (SOP) including all steps to be followed in the collection, processing, compatibility testing, storage, and distribution of blood and blood components for transfusion and further manufacturing purposes, as required by 21 CFR § 606.100(b). Specifically, ARC has no SOP requiring a second party to review processing records prior to distribution of blood or blood components, including but not limited to, the *Washed RBC Log*. For example:

a. FDA's inspection of New England revealed that ARC's system-wide SOP, [redacted] states that a supervisory review of manual records for these manufacturing processes "is performed on a routine basis." It does not state that such reviews must be performed prior to distribution of blood or blood components.

b. FDA's inspection of Southern revealed that a local SOP, [redacted] establishes "[w]ithin 10 days of end of month" as the target time frame for review of the *Washed RBC Logs.*

ARC's March 31, 2008 response to the FDA 483 indicates that New England staff responsible for performing red blood cell freezing, deglycerolizing, and washing processes and for reviewing the related records have been informed of the pre-distribution review requirement. The response also states that ARC's Biomedical Headquarters staff agrees that such logs must be reviewed prior to distribution of blood components and will issue system-wide guidance, including a training implementation plan, by

April 30, 2008. Although FDA believes these are appropriate and necessary steps, ARC should have had such procedures already in place pursuant to its obligations under FDA regulations.

3. Failure to promptly, thoroughly, and adequately investigate, correct, and take steps to prevent the recurrence of each problem, as required by the Decree, Paragraph IV.B.1.a.ii.[2] Specifically, the investigations conducted by New England and Southern into the distribution of unsuitable Washed RBCs were inadequate because their root cause determination did not identify the failure to review *Washed RBC Logs*, in accordance with 21 CFR §§ 606.100(c) and 211.192, as contributing to the problems. For example:

a. Southern documented the problem involving Washed RBCs [redacted] and [redacted] in [redacted]. The [redacted] states that the problem was caused by the employee, that no supervisor was involved, that "procedure instructions" are adequate, that associated records do not "provide or suggest evidence to be considered," and that supervision is adequate. The root cause is documented as "...staff failed to verify that NaCl solutions were the correct concentration." The corrective action plan for the problem was approved by Southern's Quality Assurance Manager on November 8, 2007. Neither the investigation nor the corrective action plan addressed (1) Southern's failure to perform a second party review of the *Washed RBC Logs* before distribution of the units, and (2) ARC's failure to establish and maintain an SOP requiring such review.

b. New England documented the problem involving Washed RBCs [redacted] and [redacted] in [redacted]. The [redacted] states that the problem was caused by an employee, that no supervisor was involved, and that "procedure instructions" are adequate. In response to the pre-printed question, "Do associate records provide or suggest evidence to be considered," New England responded, "N/A." The root cause is documented as "The staff member failed to verify the lot # of the saline solution when documenting the lot # on the *Washed RBC Log* [redacted]. The lot # [redacted] for 1.6% was recorded instead of [redacted] which identifies the 0.9% solution." The investigation was approved by a Quality Assurance Associate on December 10, 2007. The investigation and the corrective action plan do not address (1) New England's failure to perform a second party review of the *Washed RBC Logs* before distribution of the units, and (2) ARC's failure to establish and maintain an SOP requiring such review. New England's March 31, 2008 FDA 483 response does not address this inadequate investigation and corrective action plan.

This list is not intended to be an all-inclusive list of deficiencies at your establishment. FDA has reviewed ARC's March 31, 2008 response to the New England FDA 483 and will verify the promised corrective actions and evaluate their effectiveness during future inspections of ARC facilities.

* * *

[2] The Decree defines "problem" 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." Decree, Paragraph III.B.52.

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 the 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 ...; then 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, or this Order."

For the reasons stated above, FDA has determined that ARC did not comply with the law, ARC SOPs, and the Decree. Therefore, FDA orders ARC to do the following:

1. Perform a gap analysis of ARC SOPs to ensure that all blood and blood components are not distributed prior to second party review of relevant records, as required by 21 CFR §§ 606.100(c) and 211.192. Within 60 days of receipt of this letter, report the results of the analysis to FDA and provide a plan to correct any detected deficiencies.

2. ARC's March 31, 2008 FDA 483 response states that, by April 30, 2008, Biomedical Headquarters will provide system-wide guidance pertaining to second party review of manufacturing logs. Please certify to FDA whether and when implementation of that guidance was completed.

3. Records related to [redacted] state that as part of its investigation, New England conducted a retrospective review of *Washed RBC Logs* that were completed by the employee responsible for using the 1.6% saline. However, FDA 483 observation 3 indicates that ARC has not provided instructions for performing the second party review of *Washed RBC Logs* and that the manner in which such reviews are to be performed may not detect inaccurate information recorded in the logs. For example, reviewers check for omission of required information and incorrect dates, but do not verify the accuracy of required information, such as the lot numbers of supplies and reagents. ARC's March 2008 FDA 483 response to observation 3 does not state that ARC will expand the retrospective review of *Washed RBC Logs* to detect whether any errors were made by other employees but were not identified during the second party reviews. Please expand the New England retrospective review of *Washed RBC Logs* to include those completed by other employees for the period January 1, 2007, through the date on which ARC implemented system-wide guidance pertaining to second party review of the *Washed RBC Logs*. Within 90 days of receipt of this letter, please report to FDA the results of that retrospective review.

4. Within 120 days of receipt of this letter, identify all Regions that have not complied with 21 CFR §§ 606.100(c) and 211.192, including New England and Southern, and expand the record review to include *Washed RBC Logs* in all such Regions for the period May 1, 2005, through the date on which those Regions implemented the system-wide guidance pertaining to second party review of manufacturing records, as described in ARC's March 31, 2008 FDA 483 response. Please report to FDA the results of the expanded review and provide copies of all problem reports opened as a result of the review.

5. Ensure that each Region has evaluated the processes, equipment, supplies, and facilities used to manufacture Washed RBCs and has implemented corrective actions, as necessary, to prevent use of incorrect saline concentrations. Within 90 days of receipt of this letter, report to FDA the results of the Regions' evaluations and corrective action plans developed as a result of the evaluations.

6. Within 30 days of receipt of this letter, provide to FDA copies of problem reports and files related to the investigation and corrective action plans that address the failure of New England and Southern to adequately investigate and correct the problems, specifically, [redacted] and [redacted], respectively.

7. The Decree required ARC to complete the following assessment by mid-August 2003: "complete an assessment of the QA/QC program to ensure that it is comprehensive and that all ARC blood and blood components are collected, manufactured, processed, packed, held, and distributed in compliance with the law, ARC SOPs, and this Order and have the purity they purport or are represented to possess. The results of such assessment shall be reported, in writing, to ARC senior management pursuant to paragraph XI herein, and to the ARC Biomedical Services Committee and the Audit Committee of the Board of Governors within 10 days of completion." Decree, Paragraph IV.B.18.a. ARC was not required to furnish the assessment report to FDA at that time. Within 20 days of receipt of this letter, provide to FDA a copy of the assessment protocol and the assessment report.

* * *

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 assessing two per diem fines -- one per diem fine for one violation in each Region. More specifically, FDA is fining ARC $6,000 for each day on which a violation occurred in Southern and an additional $6,000 for each day on which a violation occurred in New England during the relevant periods described below. The relevant periods will run: (1) for the Southern fine, from November 8, 2007 (the day on which the Southern Quality Assurance Manager approved the inadequate investigation and corrective action plan for Exception Report E-0184040) through April 10, 2008, tens days after ARC's March 31, 2008 response to the FDA 483; and (2) for the New England fine, an additional $6,000 for each day from December 10, 2007 (the day on which the New England Quality Assurance Associate approved the inadequate investigation and corrective action plan for [redacted] through April 10, 2008. These fines accrue from the date of the violation, through the time it took for ARC to submit its inadequate response on March 31, 2008 to the FDA 483 issued on February 14, 2008, through April 10, 2008, which includes the first ten days that FDA had to review the March 2008 483 response.[3] The subtotal for the fine is $1,668,000 ($930,000 for Southern and $738,000 for New England). There will be an additional fine amount yet to be determined for the number of days it takes ARC to submit an adequate compliance plan. If the compliance plan is not adequate, additional penalties may be assessed.

We have assessed two per diem fines (November 8, 2007, through April 10, 2008 and December 10, 2007, through April 10, 2008, respectively) because FDA investigators documented multiple violations of the law in two Regions that resulted in distribution of six unsuitable blood components and that ARC failed to identify, investigate, and properly correct. These fines are warranted given the chronic nature of ARC's systemic quality assurance problems. Because these violations arose at different facilities, it

[3] Although ARC's March 31, 2008 response to the FDA 483 related specifically to the violations in New England, FDA will use this correspondence to terminate the fine for Southern as well, particularly given the similarities in the violations in the two regions.

appears that they represent, not isolated incidents, but a more pervasive failure to institute processes and procedures to adequately protect the public health.

The total fine assessed pursuant to this letter, while substantial, is significantly less than the maximum possible fine for these violations authorized under the Decree, because there are other methods that FDA could have used to calculate the fine. First, because multiple violations involving six blood components occurred in each Region, there were many days on which several violations occurred simultaneously. Thus, under paragraph IX.A. of the Decree, FDA could have charged "up to $10,000 for each violation and for each day described in FDA's [ADL]" instead of the single per diem charge for each Region. That fine could have been up to $15,780,000. Second, under paragraph IX.F.4 of the decree, FDA could have penalized ARC not only for two instances of inadequate problem management but also for each failure to review processing records prior to distribution of blood components and the system-wide failure to establish and maintain SOPs that ensure compliance with 21 CFR §§ 606.100(c) and 211.192. That fine could have been up to $23,420,000. FDA did not impose these cumulative per violation and per diem fines here and instead chose to impose a single per diem fine for each Region. Please also note that our decision to not cumulate the fines for these violations does not bind us in any 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 2007 and 2008: $456,000 of the fine is attributed to 2007 and $1,212,000 is attributed to 2008.

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

ATTACHMENT

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