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July 22, 2003

ADVERSE DETERMINATION LETTER

BY FACSIMILE &
CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. Ramesh Thadani
Executive Vice President & CEO
Biomedical Services
American National Red Cross
2025 E Street, NW
Washington, D.C. 20006

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

Dear Mr. Thadani:

Paragraph IV.B.1. of the Amended Consent Decree of Permanent Injunction (Decree), entered on April 15, 2003, requires the American Red Cross (ARC) to establish and submit to the Food and Drug Administration (FDA) within 90 days of entry of the Decree standard operating procedures (SOPs) to detect, investigate, evaluate, correct, and monitor all problems, trends, and system problems. ARC submitted BSD 92.103T, "Problem Management," version 1.3, June 2003 (the SOP) on June 3, 2003. Paragraph VI.B. of the Decree requires FDA to advise ARC in writing whether each SOP submitted, pursuant to Paragraph VI.A. (including those SOPs filed pursuant to Paragraph IV.B.1.), appears to be adequate to bring ARC into compliance with the law and the Decree.

FDA has reviewed ARC's submission and has determined that the SOP is not adequate to comply with the requirements of the law and the Decree. The specific bases for FDA's determination are set forth below.

1) The SOP does not comply with Paragraph IV.B.1.a.i. of the Decree (Page 15), because it does not require that "each region and laboratory shall scrutinize, at a minimum, ARC's Clarify reports" and "compliance-related FDA correspondence" to "identify all problems that the Problem Management System must address." Problem is defined in Decree Paragraph III.B.52.

(Page 8), 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 "FDA-483s, compliance-related FDA correspondence, … ."[1] (SOP pages 7-A-1 and 7-A-2; Bates pages 028830 and 028831)

2) The SOP fails to comply with Paragraph IV.B.1.a.ii. of the Decree (Page 15), because it does not require each ARC region and laboratory to, "commensurate with the nature of the problem, promptly, thoroughly, and adequately investigate, correct, and take steps to prevent the recurrence of each problem." (emphasis added) Instead, the SOP provides instructions to classify problems and to investigate, correct, and prevent only certain problems. [See also 21 CFR 606.171(f), which states "all biological product deviations … should be investigated in accordance with the applicable provisions of parts 211, 606, and 820 of this chapter.] For example:

a) The SOP provides a guideline for ARC to classify problems based on "severity level and type." Specifically, the SOP provides that "[redacted] Page 3-4 of the SOP "summarizes the actions to take according to the type of problem." This summary requires no investigation and no corrective action plan to prevent recurrence of [redacted]" problems. (SOP pages 3-2, 3-3, and 3-4; Bates pages 028809 through 028811)

b) This same error of omission is repeated by the SOP when it states that ARC may close "events" ([redacted]) "following completion of immediate action" and "LCTs" ([redacted] "following completion of immediate actions and approval." (SOP page 4-5; Bates page 028817) However, "immediate action," as defined on page 2-4 of the SOP (Bates page 028806), does not require any investigation or development of a corrective action plan to prevent recurrence. Furthermore, BSD92.103T\JA22 (6/03), "Problem Management Timing Guidelines," which is a section of the SOP submitted under Paragraph IV.B.1. of the Decree, states that the steps, "investigate including root cause analysis" and "develop corrective action" are "NA"(not applicable) to "events" ([redacted]) and "LCTs" ([redacted]). (Bates page 028966)

c) Yet another example where the SOP fails to appropriately manage problems occurs when the SOP provides a list of "areas of concern in which any denoted problem would be

[1] In its entirety, the definition of "problem" in the Decree is "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."

classified as a Level 3 investigative problem, regardless of the point of discovery, severity, or safety, quality, identity, potency, or purity (SQUIPP) implication." The list includes "staff performing tasks without training" but states that "this does not include documentation problems with training records." (BSD92.103T\JA23 (6/03; Bates page 028971) (emphasis added) Not only does a training documentation problem require investigation and corrections pursuant to Paragraph IV.B.1.a.ii., but also Paragraph IV.C.5.a. of the Decree specifically requires documentation of employee training as a method of ensuring that each employee has successfully completed his or her training program prior to assuming any duties. Additionally, the October 19, 2001 letter issued to ARC, pursuant to Paragraph VI.A. of the Consent Decree of Permanent Injunction entered May 12, 1993, (VI.A. letter) as a result of inspectional observations made at ARC's Lewis and Clark Region, cites deficiencies in training documentation, as does the VI.A. letter issued to ARC on February 9, 1998, as a result of inspectional observations made at several ARC regions.

Although the Decree defines "problem" and explicitly requires investigation and correction of each problem, as noted above, this SOP provides ARC staff with instructions for exempting certain problems from the requirement to investigate and correct. FDA finds that, in this respect, this SOP is not materially different from its predecessor (which FDA also found deficient), in that it requires classification of a problem based primarily on when the problem was discovered and whether blood or blood components were distributed. The results of an adequate risk assessment are not utilized to determine the nature of the problem, nor is consideration given to the health hazard associated with the problem. Absent an adequate risk assessment and consideration of health hazard in this problem classification process, it is impossible to ensure that health hazards will be immediately identified and handled appropriately."

3) The SOP also fails to comply with Paragraph IV.B.1.a.ii. of the Decree (Page 15), because it does not require that each region and laboratory "thoroughly and contemporaneously document each step it takes to investigate, correct, and prevent recurrence of each problem" and that "such documentation shall be maintained at the appropriate region or laboratory." For example:

a) The SOP does not require ARC regions and laboratories to thoroughly and contemporaneously document investigations or to identify the quality assurance staff member(s) who reviewed and approved the investigation. (SOP page 4-3; Bates page 028815)

b) The SOP does not require ARC regions and laboratories to document each step taken to develop a corrective action. (SOP page 4-4; Bates page 028816)

c) The SOP does not require ARC's regions and laboratories to document their review and approval of corrective action plans or results of effectiveness checks. (SOP page 4-5; Bates page 028817)

d) The SOP states, "Note: Documentation should be transferred t[redacted] as soon as possible. Maintenance of the initial paper documentation is not required after all necessary information has been entered into [redacted] (SOP page 2-5; Bates page 028807) In FDA's view, this "note" is objectionable, because the records that were created contemporaneously with the steps performed may not be maintained. Paragraph IV.B.1.a.ii. of the Decree explicitly requires thorough and contemporaneous documentation and availability of such documentation for FDA review. [See also 21 CFR 606.160(a)(1), which requires that "records shall be maintained concurrently with the performance of each significant step in the collection, processing, compatibility testing, storage, and distribution of each unit of blood and blood components so that all steps can be clearly traced."]

4) The SOP fails to comply with Paragraphs IV.B.1.a.iv. and IV.B.1.a.v. of the Decree (Pages 16 and 17), because it does not require the monthly Summary Problem Report to include all elements set forth in the Decree. For example:

a) The SOP does not require the Summary Problem Reports to state "the nature of the problem(s), including, but not limited to, whether they constitute deviations from the law, ARC SOPs, or this Order;" "the frequency with which those problems have occurred in that region or laboratory since entry of this Order or the prior 24 months, whichever is shorter;" and "whether the problems may be potential system (systemic) problems." [Decree Paragraphs IV.B.1. iv.A., IV.B.1.iv.C., and IV.B.1.iv.D.]

b) The SOP does not require that the first Summary Problem Reports "shall include the categories of fully corrected problems that have been initially discovered after entry of this Order." [Decree Paragraph IV.B.1.a.iv.]

c) The SOP provides guidance for categorizing problems; however, the categories established in BSD92103t04.form (6/03), Appendix 1, which is part of the submitted SOP, are not sufficiently specific to enable Biomedical Headquarters (BHQ) to identify trends of particular problems, which is one of the principal objectives of this requirement. The Decree states the "categories shall be specific enough to enable ARC Biomedical Headquarters to determine whether a trend exists," but ARC has excluded significant problems from its list of categories. For example, there is no category for failure to perform inventory reconciliation, a significant problem cited by FDA in VI.A. letters issued to ARC on October 20, 1999, and August 5, 2002, as a result of inspectional observations made at ARC's Southern Region and Greater Chesapeake and Potomac Region, respectively. FDA also discovered evidence of

inventory reconciliation failures in several regions during its February-April 2000 and April-December 2002 inspections of ARC BHQ. [Decree Paragraph IV.B.1.a.iv.]

d) The SOP requires regions to submit to BHQ only one limited section ("Monthly Summary Problem Report Section 2: For Facility and BHQ Use") of the monthly Summary Problem Report and only for categories of problems that represent 1% of all regional problems. It requires laboratories to submit to BHQ that same limited section of the report and only for categories of problems that represent 10% of all laboratory problems. (SOP pages 7-A-3 and 7-A-4, BSD92103t04.frm (6/03), 7-B-4; Bates pages 028832 and 028833, 0028837, 29005 and 029006)

FDA finds that ARC's SOP does not require that regions and laboratories submit an adequate amount of information pertaining to problems that have occurred in those facilities to enable BHQ to identify trends and system (systemic) problems. The portion of the monthly Summary Problem Report intended for BHQ also excludes such significant information required by the Decree as "whether the problems could result, or have resulted, in the release for distribution of unsuitable blood or blood components, and if so, what follow-up action, such as retrieval, notification, and/or lookback has been implemented." [Decree Paragraph IV.B.1.iv.G] Additionally, ARC's exemption from the reporting requirement of problems that occur below a specific frequency, not only violates the Decree, which prohibits any violation of the law, but also may prevent BHQ from promptly identifying trends and potential system (systemic) problems. FDA has objected to ARC's practice of tolerating certain percentages of violations and has so notified ARC numerous times: in an FDA 483 issued at the conclusion of FDA's February-April 2000 inspection of ARC BHQ, in an FDA 483 issued at the conclusion of FDA's inspection of ARC's Greater Chesapeake and Potomac Region, in the August 5, 2002 VI.A. letter issued as a result of that inspection, in an FDA 483 issued at the conclusion of FDA's April-December 2002 inspection of ARC BHQ, in the VI.A. letter issued as a result of that inspection, and in compliance-related correspondence issued to ARC on March 13, 2003.

5) The SOP fails to comply with Paragraph IV.B.1.b. of the Decree (Page 17), because it does not require "a thorough analysis and investigation of each Summary Problem Report submitted by each region and laboratory to discover trends and system (systemic) problems." Nor does the SOP include all elements required under this paragraph. For example:

a) The SOP does not require ARC BHQ to analyze and investigate Summary Problem Reports.

b) The SOP does not require analysis and investigation of certain problems. As stated in item 4 above, the SOP only requires "analysis of any category of problem that constitutes one per cent of a regional facility's problems or 10 per cent of an NTRL facility's problems for the month being reported." Even if the SOP did include a requirement to thoroughly analyze

and investigate each Summary Problem Report, BHQ's reliance on incomplete Summary Problem Reports, as described in item 4 above, necessarily will result in non-compliance with Paragraph IV.B.1.b., in that BHQ cannot detect trends, potential system (systemic) problems, and system (systemic) problems by using only partial reports.

c) The SOP does not state that "information contained in a Summary Problem Report that is classified as a significant risk, according to the Problem Management SOP, shall be investigated and reported to ARC Biomedical Services senior management on an expedited basis." (SOP pages 7-B-2 through 7-B-4; Bates pages 028835 through 028837)

6) The SOP fails to comply with Paragraphs IV.B.1.b.i. and IV.B.1.b.ii. of the Decree (Pages 17 and 18) because it does not include any of the required elements that must be included in each Analysis and Investigation Report for each trend discovered. The Decree states that " for each trend that the Analysis and Investigation Group discovers, the Analysis and Investigation Report shall, at a minimum, state: (A) the nature of the trend; (B) the scope of the same or similar trends (number of regions and laboratories in which the same or similar trends have been reported and the number of same or similar trends within each region and laboratory); (C) the probable or actual cause of each trend; (D) for each trend, whether it or any of its causes poses a health risk such that the time frames related to the Corrective Action Plan and the Corrective Action Monitoring Reports should be shortened; (E) the steps taken to determine whether the trend may result or has resulted in the release for distribution of unsuitable blood or blood components; (F) whether the trend resulted in release for distribution of unsuitable blood or blood components, and if so, whether appropriate follow-up action, such as retrieval, notification, and/or lookback, is required; and (G) for each trend, whether it or any of its causes is a system (systemic) problem." The Decree further requires that "if the Analysis and Investigation Group determines that a trend, or any of its causes is a system (systemic) problem, the Analysis and Investigation Report shall identify all systems that potentially or actually contributed to the system (systemic) problem, shall follow the established risk assessment procedures, and shall assign a risk factor to each system (systemic) problem." ARC has addressed none of these Decree requirements in the SOP. (SOP page 7-B-5; Bates page 028838) These omissions are particularly disturbing to FDA because these analytical elements are all indispensable to fulfilling the quality assurance functions and complying with the law and are explicitly called for by the Decree itself.

7) The SOP fails to comply with Paragraph IV.B.1.c. of the Decree (Pages 18 and 19), as follows:

a) The SOP does not require that "specific persons (to be identified by ARC in writing by position), including, but not limited to, a representative from the Quality Assurance unit and operations staff at ARC Biomedical Headquarters and at least one person from an ARC region or laboratory (representing the regions and laboratories, collectively), shall be

responsible, within specific time frames not to exceed the due date for the next Analysis and Investigation Report, for reviewing and evaluating the Analysis and Investigation Report, and preparing a written Corrective Action Plan to address the findings set forth in the Analysis and Investigation Report."

b) The SOP is also deficient because it does not state that the Analysis and Investigation Reports, which as noted in item 6 above, are deficient, are to be used to develop Corrective Action Plans.

c) The SOP also fails to distinguish between specific procedures to develop corrective action plans at the region and laboratory level and the specific procedures to develop Corrective Action Plans at the BHQ level to address findings set forth in Analysis and Investigation Reports. (SOP page 4-4, BSD92.103T\JA15 (6/03); Bates pages 028816 and 028931)

8) The SOP fails to comply with Paragraphs IV.B.1.c.i. and IV.B.1.c.ii. of the Decree (Page 19), because the SOP does not address specific elements that the Decree requires ARC to include in Corrective Action Plans. For example, the SOP does not require Corrective Action Plans to:

a) state "whether all regions and laboratories have been notified in writing of system (systemic) problem;" [IV.B.1.c.i.B.]

b) state "the precise time frame, based on the assigned risk factor, for completing each action;" [IV.b.1.c.i.D.]

c) "confirm or correct the determination in the Analysis and Investigation Report with regard to the retrieval of unsuitable blood or blood components, including expanding the scope of the retrieval, if necessary;" [IV.B.1.c.ii.] and

d) "designate specific persons to monitor, at specific time intervals, ARC's plans, at the region and/or at ARC Biomedical Headquarters, to retrieve unsuitable blood or blood components from the marketplace." [IV.b.1.c.ii.] (SOP page 4-4, BSD92.103T\JA 15 (6/03), pages 1 through 3; Bates pages 028816, 028931 through 028933)

9) The SOP fails to comply with Paragraph IV.B.1.d.i.A. of the Decree (Page 20), because it does not require Corrective Action Monitoring Reports to include "details of retrieval, notification of consignee(s) and/or, if necessary, lookback investigation" that may have been part of the Corrective Action Plan. When unsuitable blood and blood components have been distributed, retrieval, consignee notifications, and lookback investigations are necessary to protect the public health and are critical elements of a Corrective Action Plan. Accordingly, these factors must be monitored to ensure their completeness and effectiveness. The Decree

requires ARC to monitor those activities, but ARC's SOP does not. (SOP page 7-B-4, Bates page 028837)

10) The SOP fails to comply with Paragraphs IV.B.1.e., IV.B.1.e.i., IV.B.1.e.ii., IV.B.1.e.iii., IV.B.1.e.iv., and IV.B.1.e.v. of the Decree (Pages 20 and 21), because it does not require ARC to perform all of the quality assurance steps listed in the Decree. The Decree requires specific persons at BHQ, including the quality assurance director, every 90 days to review "all Summary Problem Reports, Analysis and Investigation Reports, Corrective Action Plans, Corrective Action Monitoring Reports, ARC internal and external audit reports, FDA-483 observations, and compliance-related FDA correspondence to identify any problems, trends, and system (systemic) problems that have not been detected, investigated, and effectively corrected within established time frames." For example, the SOP does not require:

a) any such review by "specific persons at ARC Biomedical Headquarters …, including the quality assurance director;" [Decree Paragraphs IV.B.1.e. and IV.B.1.e.i.]

b) such review to include an assessment of "the public health risk of all unresolved problems, trends, and system (systemic) problems identified during this review;" [Decree Paragraph IV.B.1.e.ii.]

c) "ensuring that all problems, trends, and system (systemic) problems identified during this review are promptly resolved;" [Decree Paragraph IV.B.1.e.iii]

d) "ensuring that all ARC regions and laboratories have been notified in writing of system (systemic) problems;" [Decree Paragraph IV.B.1.e.iv.] and

e) "reporting the result of the review in the quarterly quality assurance report as described in Paragraph IV.A.2.b. to ARC senior management and ARC Biomedical Services senior management pursuant to paragraph IX herein." [Decree Paragraph IV.B.1.e.v.]

Review of these reports and plans presents an important opportunity for those most responsible for quality assurance to ensure that ARC is operating in compliance with the law, ARC's SOPs, and the Decree. But the SOP does not even address this review. Even if the SOP had addressed this BHQ review, FDA notes that the cumulative effect of ARC's failure to comply with the Decree requirements, as described in paragraphs 1 through 11 of this letter, would be fruitless because of the numerous deficiencies in the reports and plan.

11) The SOP fails to comply with Paragraph IV.B.1. of the Decree (Page14), because the risk assessment procedure, included in the submitted SOP, will not ensure that ARC properly prioritizes problems to ensure those that are a significant risk problem are corrected expeditiously. The Decree requires ARC to establish a risk assessment procedure. The Decree

states: 1) that "information contained in a Summary Problem Report that is classified as a significant risk, according to the Problem Management SOPs, shall be investigated and reported to ARC Biomedical Services senior management on an expedited basis" [Decree Paragraph IV.B.1.b.]; 2) that "for each trend, whether it or any of its causes pose a health risk such that time frames related to the Corrective Action Plan and the Corrective Action Monitoring Reports should be shortened" [Decree Paragraph IV.B.1.b.i.D.]; 3) that "if the Analysis and Investigation Group determines that a trend … is a system (systemic) problem, the Analysis and Investigation Group … shall follow the established risk assessment procedures, and shall assign a risk factor to each system (systemic) problem" [Decree Paragraph IV.B.1.b.ii.]; and 4) that "the Corrective Action Plan shall, at a minimum, state … the precise time frame, based on the assigned risk factor, for completing each action." [Decree Paragraph IV.B.1.c.i.D.] Despite the foregoing, the risk assessment procedure ARC included in the SOP:

a) excludes problems related to donor safety. Although the SOP requires use of a [redacted] and a [redacted] to determine a risk factor, the SOP states those factors "represent the potential risk to the recipient of a blood product." (emphasis added) The Decree requires ARC to establish an SOP to "detect, investigate, evaluate, correct, and monitor all problems, trends, and system (systemic) problems." The Decree defines "problem" as "any deviation from the law, ARC SOPs, or this Order." [Decree Paragraph III.B.52.] Donor Safety is governed by the law, ARC SOPs, and the Decree, and thus falls under that definition and must be carefully managed by ARC. [See also Decree Paragraph IV.B.14 (Page 38) and 21 CFR 640.3, which address donor safety.] (SOP pages 8-2 through 8-5; Bates pages 028840 through 028843)

b) does not clearly describe the use of risk factors in ARC problem management process, such as how BHQ will use risk factors assigned to problems to comply with BPD reports, Quality & Regulatory Affairs (Q&RA) audit observations, and "trend problems" or how ARC will ensure that significant risk problems, BPD reports, Q&RA audit observations, and "trend problems" are corrected promptly. (Pages 7-A-3, 92103t04.frm (6/03); Bates pages 028832, 029005, and 029006)

c) includes Job Aid, BSD92.103T\JA15 (6/03), "Problem Solving at Biomedical Services Headquarters," that describes steps to be taken "when assessing potential system problems, trends in problems that were submitted on the Analysis Investigation Report, or escalated problems," and includes one step related to risk. However, the procedure is not consistent with the risk assessment procedure, in that it defines "significant risk" as a "hazard or recall that involves more than 100 WBN units." The risk assessment procedure does not define the term hazard or refer to the number of recalled Whole Blood Number units as a factor in determining risk. Additionally, the Job Aid does not instruct ARC staff to refer to the risk categories defined in Chapter 8. (BSD92.103T\JA15 (6/03); Bates page 028931)

d) does not require use of the risk assessment procedure to classify problems. Specifically, Chapter 3 requires classification of problems [redacted] and refers to Chapter 8 and BSD 92.103T\JA03, "Biological Product Deviation Codes." However, Chapter 3 does not state how to apply Chapter 8 and BSD92.103T\JA03s to the classification procedures. (SOP pages 3-1 through 3-4; Bates pages 028808 through 028811)

e) includes Job Aid, BSD92.103T\JA03, "Biological Product Deviation Codes," which includes pre-determined risk factors for specific categories of BPDs. However, it does not state the basis for those factors, the manner in which ARC uses those factors, or when use of pre-determined risk factors is appropriate. (BSD92.103T\JA03 (5/03); Bates pages 028853 through 028908)

f) does not require documentation of risk assessment for each problem.

In addition to the deficiencies discussed in items 1 through 11 above, FDA's review of ARC's SOP revealed additional problems that make the SOP inadequate to accomplish its intended purpose, as follows:

1) The manner in which the SOP is organized and the grossly insufficient level of detail make it difficult for ARC staff to follow or assure consistency among staff and regions and, therefore, to ensure compliance with the law and the Decree. For example:

a) Many significant parts of the SOP exist in Job Aids that are not referenced in the body of the SOP.

b) The work flow is not completely described. As a result, the problem management process described in the SOP is difficult to follow from beginning to end.

c) The SOP does not adequately address the immediate handling of urgent health hazards.

d) The SOP does not state whether the regions and laboratories are required to transfer Clarify cases into the [redacted] or whether the regions and laboratories are required to analyze the problems in Clarify and [redacted] separately for inclusion on the Facility Monthly Summary Problem Reports.

e) The SOP does not address the implementation of Corrective Action Plans for system problems and trends identified by BHQ during its review of the Facility Monthly Summary Problem Report.

2) The SOP requires each region and laboratory to establish local procedures "describing how the Problem Management system is managed in accordance with policies contained within this BSD," as opposed to implementing one SOP to govern problem management in each region and laboratory, as well as in BHQ. The lack of detail and the organization of the SOP will likely result in various interpretations and inconsistent applications across the regions and laboratories. The requirement to establish local procedures will also result in a major part of ARC's problem-solving system not being reviewed by FDA prior to implementation as required by the Decree.

3) The instructions in Chapter 4, "Managing Investigative Problems," are only brief summaries of the intricate processes of determining root cause and developing corrective actions.

4) The risk assessment procedure in the SOP does not state the manner in which ARC intends to use these procedures throughout its problem-solving process, or how ARC intends to control the uniformity of risk factor evaluations.

5) BSD92.103T\JA03 (5/03), "Biological Product Deviation Codes," which is part of the SOP, includes pre-determined risk factors for biological product deviations. To further ensure that similar BPDs are scored uniformly for risk assessment, the Job Aid must state the [redacted] scores, as well as the final score. Because the Job Aid lacks those rating scores, FDA has not performed a comprehensive evaluation of the validity of predetermined risk factors assigned to specific BPD report codes listed in that Job Aid.

6) The zip code for FDA's Baltimore District Office must be corrected on Bates page 028825. The correct zip code is 21215.

Although FDA has made an effort to identify major deficiencies in BSD 92.103T, "Problem Management," this letter is not intended to be an all-inclusive list of FDA's concerns with BSD 92.103T. Indeed, because the BSD establishes and then builds on fundamental elements which do not include all of those required in Paragraph IV.B.1. of the Decree, FDA cannot provide a comprehensive review of the BSD at this time. Additionally, FDA did not review BSD92.103T\JA02 (7/02), "Non-Reportable Biological Product Deviations," because that portion of ARC's submission is not relevant to Paragraph IV.B.1. of the Decree.

* * *

Paragraph VI of the Decree provides that if FDA determines that any SOP, report, or plan submitted under specified paragraphs of the Decree, including Paragraph IV.B1., "appears inadequate, FDA shall state the specific basis for its determination in writing, and the penalty, review, and appeal procedures set forth in Paragraph IX below shall be followed until ARC obtains a favorable determination from FDA or the Court as to the apparent adequacy of that SOP, report, or plan." Paragraph VIII of the Decree provides that if FDA determines that ARC

"has failed to fully comply with any … term, or provision of this Order" or "that any report, plan, SOP, or other measure implemented by ARC to comply with this Order is inadequate to comply with the law, … , or this Order . . . then FDA may order ARC to come into compliance with the law, … , or this Order, assess penalties, and/or to 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's BSD 92.103T, "Problem Management," which ARC submitted to FDA pursuant to Paragraph IV.B.1. of the Decree, is wholly inadequate to comply with the law and the Decree and that the violations are severe enough that it should invoke the penalty provisions of the Decree. Indeed, as expalined elsewhere in this letter, the omissions in ARC's SOP are, in most cases, explicitly required by specific language in the Decree. In other cases, FDA has brought the particular deficiencies to ARC's attention in previous FDA 483s and VI.A. letters. Finally, ARC has been on notice for several years, not only as to many of the specific deficiencies in this SOP, but also that FDA regards this SOP as a first and indispensable step to enable ARC to comply with current good manufacturing practice.

FDA hereby orders ARC to revise the Problem Management SOP in a manner that will address the violations discussed above and otherwise comply with the law and the Decree. For the reasons stated in the preceding paragraph, pursuant to Paragraph IX of the Decree, FDA intends to fine ARC up to $10,000 for each day from June 3, 2003, the date that ARC submitted the inadequate SOP to FDA, until the date ARC submits to FDA a plan to revise the Problem Management SOP that addresses the violations discussed above and otherwise complies with the law and the Decree.

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., Director, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852.

Sincerely,

Nathaniel R. Evans for Lee Bowers

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