

OLYMPUS

OLYMPUS AMERICA INC.
DIAGNOSTIC SYSTEMS DIVISION

3131 WEST ROYAL LANE
IRVING, TEXAS

75063-3104
TEL (972) 556 9697

FAX (972) 556 0365

99 DEC 22 10 42

December 21, 1999

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

RE: Requirements for Testing Human Blood for Evidence of Infection Due to Communicable Disease Agents

Dear Sir or Madam:

We are writing to comment on the "Requirements for Testing Human Blood for Evidence of Infection Due to Communicable Disease Agents", published on August 19, 1999, in the Federal Register. Specifically, we are commenting on the proposed changes to Secs. 640.5(a) and 640.65(b) relating to the requirement for a serologic test for syphilis on blood donors. We are opposed to the proposed change and strongly feel that screening for syphilis should be continued. The conclusion of the 1995 National Institutes of Health Consensus Conference Development Conference was that there was insufficient information concerning the role serologic tests for syphilis has played in preventing transfusion-transmitted syphilis. It is our contention that there is still insufficient information to make a determination.

1. The following is known about transfusion-transmitted syphilis:
 - a. Syphilis can be transmitted by blood transfusions. This is not a theoretical possibility as approximately 200 cases have been reported in the literature. Syphilis is one of the oldest recognized infectious risks of blood transfusion.
 - b. Blood donations have been screened for syphilis since 1938 using a serologic test for syphilis. Since 1990, blood donations have been screened using a treponemal based tested with greater sensitivity and specificity at all stages of the disease than reagin based screening tests. Currently 88% of the North American blood supply is tested using a treponemal based assay.
 - c. The number of reported cases of transfusion-transmitted syphilis have decreased. This is probably due to a number of causes; serology screening of blood donors for syphilis, better donor interview process, decrease in the incidence of syphilis in the general population, refrigerated storage of blood, lack of recognition of transfusion-transmitted syphilis and lack of active surveillance for transfusion-transmitted syphilis.
 - d. The spirochete can survive for up to five days in refrigerated stored blood although some studies reported survival of only 47 to 72 hours.
 - e. There is a high correlation of between syphilis and HIV infections. In 1985, the FDA considered dropping the requirement for serologic testing for syphilis in blood donors. Fortunately, this did not happen before implementation of HIV screening as many HIV infectious blood donations were coincidentally discarded due to a positive syphilis test. In retrospect, the decision to continue testing for syphilis at that time was excellent as it

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prevented many cases of transfusion-transmitted AIDS.

2. The following is unknown about transfusion-transmitted syphilis:
 - a. When does spirochetemia occur in an infected individual? References state that spirochetemia occurs in the incubation period, in primary syphilis, in secondary syphilis, and probably during latency.
 - b. When does infectivity occur? Theoretically, based on the occurrence of spirochetemia, infectivity could occur during the incubation, primary, secondary or latent stages of syphilis. Consequently, transfusion-transmitted syphilis could occur at a time when the donor is asymptomatic.
 - c. What is the dose required for infection? It is unknown how many *T. pallidum* organisms are needed for an infectious dose in humans. At the recent FDA Public Meeting on the proposed changes, it was stated during the ARC presentation that the minimal infective dose was one (1) spirochete/ 100 μ l based on rabbit infectivity testing.
 - d. How long can the spirochete survive at room temperature in platelet concentrates? There is no experimental data indicating how well *T. pallidum* survives in stored platelet concentrates. Despite the absence of data, most authorities assume that *T. pallidum* survives in platelet concentrates throughout the five day storage period.
 - e. What is the scope and effectiveness of post-transfusion syphilis surveillance?
 1. It is possible there have been no cases of post-transfusion syphilis since 1950 with the exception of the two cases reported in 1969 and 1978.
 2. It is also quite possible that cases of post-transfusion syphilis have occurred and not been recognized. Transfusion-associated cases of syphilis have no chancre, which is the diagnostic hallmark of the disease. Also the incubation period is an average of 10 weeks. Consequently, it may be difficult to recognize post-transfusion syphilis. Also the widespread use of antibiotics in hospitalized, transfused patients may obscure the diagnosis but may not prevent long-term complications of the disease.
 - f. Although the value of a serologic test for syphilis as a surrogate marker for HIV is no longer valid due to the implementation of HIV specific assays, what is the value of the syphilis test as a surrogate marker for high risk behavior and other as yet, undiscovered transfusion and sexually transmitted diseases that could threaten the blood supply.

Recently ARCNET presented data regarding on-going studies to support discontinuing syphilis screening in blood donors. We feel that there are some serious deficiencies in the studies.

1. The two PCR assays used are considered to be in the research stage. Neither assay has been FDA cleared for use in screening blood donors for syphilis or for diagnostic purposes.
2. Limited field trial data has been generated to establish the performance characteristics of the assays. No data has been presented correlating the performance of the assay with clinical stage of the disease or with treatment status. With the 47KD basic membrane PCR assay, only in amniotic fluid samples was the assay sufficiently sensitive to be of diagnostic use. The second assay, the Roche Multiplex kit for *T. pallidum*, *H. ducreyi* and Herpes Simplex Virus type 1 and 2, has been used primarily with touch preparations from genital lesions. The performance of this assay has not been established as compared to rabbit infectivity testing. According to the 1998 edition of A

Manual of Tests for Syphilis (S. Larson, et al), Roche Molecular Systems had terminated further plans for marketing this test.

3. No data has been presented that validates the use of the two PCR assays for the sample source used in the study, namely, platelet concentrates. Most data on the efficacy of the PCR assay has been established using amniotic fluid, CSF, touch preparations of genital lesions or neonatal sera. Sensitivity of the PCR assay in sera is particularly poor at 60-67%. Limited and preliminary data suggests the presence of nonspecific polymerase inhibitors in serum may negatively affect sensitivity. Studies using only nine samples indicated improved sensitivity with serum after alkaline lysis. Additional testing would be necessary to validate the performance of the assay using samples obtained from platelet concentrates and subjected to alkaline lysis.
4. The sample handling conditions (sample centrifugation, freeze/thaw cycles, and shipping conditions) used in the ARCNET study have not been validated with the PCR assays.
5. Controls used in the ARCNET study were not appropriate considering the donor sample source. External controls were obtained from stock cultures of *T. pallidum*. The cultures were diluted to 50 organisms/100 μ l. The assays detect concentrations as low as 10 and 25 spirochetes/100 μ l.
6. The assays lack sufficient sensitivity to detect the minimal infective dose (1 spirochete/100 μ l) as determined by rabbit infectivity testing. One PCR assay will detect 10 spirochetes/100 μ l; the other assay detects 25 spirochetes/100 μ l.

Additional questions must be answered before a decision can be made to discontinue the syphilis screening of blood donors:

1. Even if the infectivity of platelet concentrates is disproved, it is well established that blood components are capable of transmitting syphilis. Does this mean that if syphilis testing is no longer required, that red cell products will not be available for transfusion until after storage for five days at refrigerated temperatures to assure the lack of viable spirochetes?
2. Should studies be repeated to determine the survival of the spirochete in blood stored in currently available anticoagulants, additives and plastic blood bags? Are these factors that could affect the survival of the spirochete? If additional anticoagulants, additives, and plastics be developed in the future, would survival studies need to be repeated with each one?
3. No one knows what will happen if testing were to be discontinued. We cannot be sure that the number of transfusion-transmitted syphilis cases will not increase. Is this acceptable?

Additional considerations:

1. The current tests have very good performance characteristics and are well-integrated into current blood center procedures. The assay used to test 88% of the blood supply is completely automated and requires minimal labor.
2. The cost of serologic screening for syphilis is a very small fraction of the cost of a unit of blood.
3. Approximately 13,000-26,000 units are discarded annually. The number of discarded units and the cost of testing are not very significant when one examines the total blood collections system in the US. Certainly this is insignificant compared to the lost units due to donor deferrals associated with the theoretical risk of transfusion-transmitted nvCJD.
4. Screening of blood donors provides an important public health benefit.

The proposed change to discontinue serologic testing for syphilis seems to be at odds with recent FDA policy decisions such as the newly mandated deferral of donors who have visited the UK. This policy was implemented to prevent the *theoretical* transmission of nvCJD by blood transfusions. It is estimated to reduce the blood supply by 2.2%. Transmission of syphilis by blood transfusions is well documented and reduces the blood supply by only 0.1-0.2%.

The performance of the assay is well established and insufficient data is available to determine the outcome if the assay were discontinued. We believe that the serologic testing of blood donors for syphilis should continue.

Sincerely,

A handwritten signature in black ink that reads "Candace K. Williams". The signature is written in a cursive, flowing style.

Candace K. Williams
Director, Immunohematology Systems

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