

July 29, 2004

Division of Dockets Management (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 02852

Re: Docket 04N-0181, "Critical Path Initiative"

Dear Dockets Manager:

AABB is an international association dedicated to advancing transfusion and cellular therapies worldwide. Our members include more than 1,800 hospital and community blood centers and transfusion and transplantation services, as well as approximately 8,000 individuals involved in activities related to transfusion, cellular therapies and transplantation medicine. For over 50 years, AABB has established voluntary standards for, and accredited institutions involved in, these activities. AABB is focused on improving health through the advancement of science and the practice of transfusion medicine and related biological therapies, developing and delivering programs and services to optimize patient and donor care and safety.

AABB appreciates the opportunity to provide comments to the Critical Path Initiative. It is not possible to utilize the format requested for comments to the docket to provide our critical concerns and initiatives. However, AABB believes that the initiative is very important to our membership and has elected to provide comments in a narrative format.

In recent years, the Food and Drug Administration (FDA) worked successfully with members of the blood community to support rapid development of nucleic acid amplification testing (NAT) for the purpose of detecting West Nile virus (WNV) in apparently healthy blood donors. FDA actively participated in the AABB Interorganizational West Nile Virus Task Force, which also included members of the major blood collecting organizations, as well as the Department of Defense, and staff from the Centers for Disease Control and Prevention. Two public meetings were held, and much progress has been made in this very critical area. Due to the cooperative effort of all involved, WNV NAT testing is currently in the second year of testing under IND protocols. The first year of testing resulted in the removal from the blood supply of approximately 1,000 units of blood that tested positive.

The WNV NAT project set an achievable standard for cooperation between FDA and the blood community, and that model should be utilized to achieve further progress on several initiatives of critical importance to an adequate and safe blood supply. It is essential that FDA interact and communicate with the blood banking community. This

action will make it possible for FDA to be informed about not only the scientific issues under consideration, but also the feasibility and practicality of potential solutions.

Specific areas in which the Critical Path Initiative should be applied and where improved FDA understanding of the blood banking community's concerns and more timely agency action would clearly benefit transfusion patients are outlined below. :

Detection of Bacterially Contaminated Platelets

The most common transfusion-associated infectious risk in the United States today is bacterial contamination of platelet components. Bacterial contamination is estimated to occur in 1 in 1,000 to 1 in 3,000 platelet units. Although the incidence of severe episodes of transfusion-associated bacterial sepsis has not been clearly established, it is estimated to occur in connection with about one-sixth of contaminated platelet units transfused. Bacteria detection has been effective in identifying bacterially contaminated units and preventing their transfusion. The 22nd edition of "AABB Standards for Blood Banks and Transfusion Services" requires that an establishment have methods in place to limit and detect bacterial contamination in all platelet components.

Several issues present challenges for current methods being used to detect bacterial contamination in platelets. AABB has coordinated the development of an interorganizational task force to address the complexities of performing bacterial detection testing on whole blood-derived platelets as well as platelets collected by apheresis technology. FDA has already participated in work with the task force on several critical areas, and we anticipate continued collaboration in determining the appropriate research necessary to permit extension of the dating period for apheresis platelets and to permit extended storage of pooled whole blood-derived platelets.

FDA has indicated that it will require an extensive clinical study on the performance of bacterial detection devices as a condition for approving seven day dating for apheresis platelets. FDA should consider both the feasibility and the practicality of requiring a clinical study. There are several reasons why FDA should be open to considering that such a clinical study may not be necessary to increase storage to seven days:

- Previously, the dating period for platelets was seven days, at a time when it was not possible to perform bacterial testing.
- The major clinically significant bacteria are detectable at the time testing is currently performed (about 24 hours after collection.).
- Requiring such a study may set an unnecessary precedent for requirements to further extend platelet storage beyond seven days.

It also is important that FDA encourage the development of new bacterial detection methods and expedite review of new methodologies submitted for licensure as "point of release" testing.

Supplemental Testing of Blood Donors

Each donor of blood and blood components is tested for evidence of infection due to communicable disease agents, including human immunodeficiency virus, types 1 and 2 (HIV-1/2), and hepatitis C (HCV), using “screening tests that the FDA has approved for such use.” 21 CFR 610.40(e) requires that an establishment “must further test each donation, including autologous donations, found to be reactive by a screening test ... whenever a supplemental (additional, more specific) test has been approved for such use by FDA.” The supplemental test results are required to be used in determining the donor’s eligibility to continue to donate blood, as well as providing deferred donors with accurate information about their disease status.

Currently, the use of a supplemental Western Blot (WB) for reactive HIV screens and a supplemental recombinant immunoblot assay (RIBA) for reactive HCV screens are required. However, continued improvements in the sensitivity of HIV enzyme immunoassays (EIAs) without similar improvements in the sensitivity of the HIV-1 WB have resulted in the supplemental assay being less sensitive than the screening EIA. Superior, FDA-licensed nucleic acid test methodologies for the detection of viral antigen particles to HIV and HCV are being used by blood establishments. FDA, however, does not permit the results of these additional, more specific tests to be used as the supplemental test of record. In fact, FDA has not issued final guidance documents to blood establishments on the expected use of nucleic acid tests.

Because of the current FDA regulations and guidelines, many of the HIV WB results must be reported as Indeterminate, and these results must be reported to the blood donor. Indeterminate test results create confusion and anxiety for the donor. According to published data, the vast majority of such donors were both upset and confused when initially notified of their test results and remained upset and confused six to twelve months later. This is not surprising when donors have been told (based on indeterminate Western Blot results) that there is some possibility they are infected with HIV-1! This is not a trivial concern, as data projected nationally estimate that over 5,000 donors in the U.S. receive this message annually.

It is critical that final guidance is issued in the immediate future to provide instructions to blood establishments for the use of licensed NAT testing of blood donors, including management of blood components, donor notification and counseling, and re-entry algorithms.

These issues were presented to the Blood Products Advisory Committee (BPAC) on March 18, 2004. Following that discussion, the AABB Transfusion Transmitted Diseases Committee, functioning as an interorganizational group representing the blood banking community, organized discussions with FDA liaisons on this important issue. Blood bank researchers from the committee provided requested data to FDA that support development of alternative algorithms for supplemental testing to make use of the results generated by nucleic acid testing. The data presented establish the scientific validity of using reactive nucleic acid tests to establish the existence of HCV or HIV infection in

EIA repeat reactive donors. In such circumstances, HIV-1 WB and HCV RIBA add no useful information to the evaluation of the donor's status. HCV RIBA or HIV alternate EIA should serve as supplemental tests in circumstances in which minipool NAT is non-reactive.

AABB understands that the Public Health Service (PHS) has now established an interagency working group to review the existing data and to consider the current supplemental testing algorithms. AABB anticipates that the FDA will make full use of the extraordinary amount of data collected from the blood banking community in their discussions within this PHS working group, and that the blood banking community will be included in these discussions.

Lack of a supplemental testing claim from manufacturers of the licensed NAT tests apparently creates an inherent regulatory obstacle to progress in this area. AABB understands that the current regulation requires that a supplemental test be approved by the FDA for such use. We request that FDA not require additional clinical trials, but permit test manufacturers to submit data collected during the five years in which donor testing has occurred. Further, FDA should expedite review of such data submissions.

Licensure and Approval Processes

(a) Product licensing

During initial implementation and development of the Biologics License Application, there was a good communication/consultation process with FDA. This process should be re-established.

Automated blood collection devices, licensed by the FDA, are commonplace in blood establishments and are used to collect red blood cells (single or double units), platelets, and plasma, either individually or in some combination. Even though blood establishments are licensed to manufacture these products, the establishment must re-submit an amendment to the licensed product when using a new or different automated collecting device. The requirements that must be met are not always easy to find, and the amendment submissions appear to be inconsistently reviewed by FDA. AABB has established an interorganizational task force to prepare guidelines intended to assist blood establishments in meeting the requirements for submission of license amendments. To ensure that all FDA requirements would be incorporated into this guideline, we requested a copy of the "DBA, OBRR, CBER, FDA Regulatory Checklist for Platelets Pheresis Submissions" from the Freedom of Information (FOI) Office on March 16, 2004, and indicated that CBER had forwarded the checklist to FOI on March 15, with a note that AABB would be asking for the checklist. However, AABB has yet to receive this information.

Although FDA has permitted submission of a comparability protocol, it has not fully explained this mechanism to the blood banking community. It is unclear to what extent comparability protocols can be utilized to expedite licensure. It is critical that FDA utilize

a mechanism that does not require submission of platelet products from each collection site. AABB has requested that quality control records be submitted in lieu of submitting actual product. This policy would permit platelets to be retained for patient treatment, which is particularly important in the face of recurring blood shortages. .

The FDA memorandum currently in use for the collection of platelets by an automated method was issued in October 1988. These FDA requirements are clearly outdated. The BPAC considered several issues related to issuance of an updated guidance document at its March 2004 meeting. AABB encourages FDA to consult with the blood banking community about appropriate requirements, and to quickly issue new guidance for the automated collection of platelet products.

(b) Computer licensing

Computer software used by blood establishments in the collection, processing, and distribution of blood products, as well as in the management of donor, patient, and product records, requires a 510(k) review process. 510(k) requirements and the extensive delays inherent in that process constitute the single largest barrier to technological development to improve the accuracy and efficiency of computer systems. As a result, many blood establishments continue to use old systems that do not take advantage of the newest tools that have been developed. FDA should consider a risk/benefit approach where new technologies can be used, provided the risk is measured and exposure monitored. In its discussions of appropriate guidance for 21 CFR Part 11, FDA is taking a new and innovative look at the issue of Electronic Records and Electronic Signatures. This approach actively involves consulting the stakeholders, and should be the model for addressing blood bank computer systems.

These comments have delineated some of the issues that AABB believes could be addressed by applying principles in the Critical Path Initiative to those concerns. AABB stands ready to work with FDA on these and other initiatives that will enhance the safety and availability of the nation's blood supply.

Questions concerning these comments may be directed to M. Allene Carr-Greer, Deputy Director, Regulatory Affairs, AABB (acarrgreer@aabb.org).

Sincerely,

A handwritten signature in black ink that reads "Kathleen Sazama, MD, JD". The signature is written in a cursive style with a large initial "K" and a distinct "S".

Kathleen J. Sazama, MD, JD
President