



Advancing Transfusion and
Cellular Therapies Worldwide

01 August 2008

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

RE: Docket 2006N-0221, 08 November 2007, Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Proposed Rule

Via electronic submission:

<http://www.accessdata.fda.gov/scripts/oc/dockets/comments/commentdocket.cfm>

Dear FDA 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, and developing and delivering programs and services to optimize patient and donor care and safety.

We appreciate the opportunity to provide comments to *Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Proposed Rule* issued November 2007, as well as the additional 6 months in which to study the proposals and formulate our response. In recognition of the tremendous amount of information that is contained in the proposed rule, AABB pulled together a working group to review the proposed changes to the Code of Federal Regulations and to consider the various requests for comments and data that are in the Preamble. This working group is composed of AABB leadership drawn from various AABB committees and task forces such as the FDA Liaison Committee, the Transfusion Transmitted Diseases Committee, the Donor History Task Force, the Interorganizational Plasma Task Force and the Interorganizational Plateletpheresis Working Group. Various members of this working group are leaders in other organizations such as the American Red Cross, America's Blood Centers, College of American Pathologists, Department of Defense and Plasma Protein Therapeutics Association.

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The comments are arranged in the following format:

CFR Section / Preamble language – reprinted identifying information.

Recommendation / Response to Request for Comment / Request for Clarification – recommended modification with rationale or response to a request for comment on specific topics.

Background – information supporting the recommendation / comment / request for clarification.

21 CFR Section 606.160(e)(1) – *Establishments must maintain a record of all ineligible donors so that blood and blood components are not collected from such individuals while they are ineligible or deferred; and*

21 CFR Section 606.160(e)(2) – *Establishments must provide, to appropriate personnel at all locations operating under the same license or under common management, a collective list of ineligible donors with sufficient information to prevent the collection of blood and blood components from any donors currently identified at each location as not eligible to donate under Sec. 630.10(f) and (g)(1) through (g)(6) of this chapter, or deferred based on test results under Sec. 610.41 of this chapter.*

21 CFR Section 630.10(a) – *What factors determine the eligibility of a donor? You must not collect blood and blood components before you determine that the donor is eligible to donate. A donor is not eligible if the donor is not in good health or if you identify factors that may adversely affect:*

- (1) The health of the donor or*
- (2) The safety, purity, or potency of the blood or blood components collected from the donor.*

21 CFR Section 630.10(d)(1) – *How must you determine the eligibility of a donor? Before collection, you must determine the donor's eligibility by the following procedures:*

- (1) Assessing the donor's deferral status by checking the collective list of ineligible donors required under Sec. 606.160(e)(2) of this chapter;*

Preamble, Section C, Records (Proposed § 606.160(e)):

We are interested in receiving comments on:

- The information that should be included on a donor deferral registry used in common by all donor screening locations of a collecting establishment operating under a common organization (e.g., under the same license number);*
- The adequacy of the criteria listed in proposed Sec. 630.10(f) and (g)(1) through (g)(6) to prevent the collection of blood and blood components that may be harmful to the donor or that may result in an unsuitable product due to possible exposure of the donor to a transfusion-transmitted infection; and*
- The technical feasibility of complying with the proposed requirement.*

We are also seeking comments on the feasibility of sharing donor deferral lists between licensed establishments for deferrals required by the FDA. Such national deferral registries have existed for Source Plasma collections for many years.

...under proposed Sec. 606.160(e)(2), if a collecting establishment collected blood at four locations and three mobile sites, donors deferred from further donation at any of the seven sites would be listed on a donor deferral registry available at all seven sites. The requirement to

review the record of ineligible donors before collection and to make the record of ineligible donors available to collecting establishments operating under a common organization would improve blood safety by reducing the likelihood of accidental release of potentially infectious units.

We are considering whether to include, in the final rule, a provision requiring that donor deferral records be used and disclosed only for purposes consistent with subchapter F of 21 CFR Chapter I.

We request comment on this proposal, including the following specific issues:

- Whether the current practices and protections adequately protect the confidentiality of donor records;*
- Whether those current practices and protections will still be adequate if FDA requires that establishments make donor deferral records available at all collection sites operating under the same license or common management; and*
- Whether a regulation limiting the use and disclosure of such records would actually further the goal of protecting the confidentiality of the records.*

In addition, we request comment on the following:

- We believe that few, if any, blood collection establishments are HIPAA-covered entities under the HIPAA Privacy Rule. However, to evaluate the impact of this rule on any such HIPAA-covered entities, we are seeking public comment from any facilities that may be covered by the HIPAA Privacy Rule, regarding whether or how HIPAA requirements may impact their ability to comply with this proposed rule.*

Recommendation – Note: For purposes of these comments a “collective list of ineligible donors” is used interchangeably with “donor deferral registry” and will be indicated as DDR.

21 CFR Section 606.160(e)(1) – The proposed requirement that *all* deferrals, including deferrals for medical history or physical exam findings, must be entered into the establishment’s DDR is burdensome and should be modified. The requirement should be amended to state that deferrals that impact recipient safety need to be recorded, as well as those judged by the medical director to have a significant impact on donor safety. The inclusion of other deferral categories does nothing to enhance the safety of blood transfusion, and is overly burdensome.

21 CFR Section 606.160(e)(2) – The requirement to maintain a DDR at all locations operating under the same license or common management should be deleted. The proposals described in Part 606.160(e)(1) and (2) and 630.10(a) and (d)(1) as written cannot be carried out in all collection sites and would not allow for the collection of donors at a significant number of locations, due to the inability to maintain such a list.

21 CFR Section 630.10(a) and (d)(1) – DDR review should be defined as a requirement for donation suitability, not donor eligibility. Determination of eligibility should occur based on the health history questionnaire and physical exam that is performed prior to the collection. Review of the DDR is a part of record review and, as such, should be a part of determining that the donation is suitable for release. It is important that this be the case because it is impractical for all mobile blood collection sites to be able to conduct a DDR review as a part of determining donor eligibility prior to collecting a blood product.

Preamble C. Records – A national DDR (shared between different license holders) is neither medically necessary nor technically achievable.

Background – Scientific data showing limited, if any, value of DDRs – Given the logistical difficulties associated with DDR maintenance (see below), it is useful to review the contribution of DDRs to blood safety. Recently, data have accumulated showing the very limited or complete lack of value of the DDR in enhancing the safety of the blood supply. Cable et al (Transfusion 2008;48:34-43) reviewed the donation records of the American Red Cross from 1995 through 2002, encompassing 10.2 million first time donors. His group searched the records of donors who tested repeatedly reactive for HIV, HBV and HCV to determine if any had returned to donate. A total of 1107 first time donors who were repeatedly reactive returned for a subsequent donation. Of those, only seven (two HCV and five HBV) of the returning donors tested non-reactive. Of the 10.2 million donations, these seven were the only donations interdicted by the DDR. Investigation into the initial testing of these donors was consistent with false positive results. The authors thus concluded that checking over 10 million donations against the DDR had not prevented the release of any unsafe units. Zou et al (Transfusion 2006;46:1997-2003) investigated blood donors permanently deferred for their answers to questions regarding risk of viral hepatitis or of intravenous drug use. The deferred donors were found to have higher hepatitis marker rates than those who were not deferred, but no significant findings were identified for other markers, or for donors entered into the DDR on the basis of answers to other deferral questions. Furthermore, the hepatitis markers among the deferred donors would have been identified by routine donor screening tests. In another study, Zou et al (Transfusion 2005;45:1593-1600) showed that donors returning after a temporary deferral for potential exposure to infectious agents did not appear to pose a greater risk than non-deferred first-time or repeat donors.

Current practice and operational feasibility – The establishment's maintenance of a DDR has been a requirement of the FDA since the 1970's with the implementation of hepatitis B virus testing. Originally maintained as a manual list, the vast majority of the DDRs are now maintained in the Blood Establishment Computer System (BECS). Prior to the transition to computerized DDRs, donor names were checked against the DDR after collection. Once computerization occurred, many blood collection centers began checking potential donors against the DDR prior to collection and this process is routinely performed by many blood establishments today. However, they revert to a post donation check of the DDR when computers are not available, such as during computer outages or on some mobile collection operations where computer access may be limited or not available. During periods of computer downtime at some sites, a duplicate paper deferral list may be available for donor medical history screening. For some mobile collections, the latest deferral list is imported into the mobile computer terminals before departure for the blood drive or the mobile computer terminals are connected via wireless to the network server or a paper list is utilized. (Geographical isolation of some mobile locations imposes limitations on connectivity via wireless technology). For many organizations with multiple fixed locations and mobile operations – some of which operate nationwide – systems are stand-alone at each of the blood collection sites. Therefore, a particular blood collection site has access only to the DDR *for that* site. While many license holders have plans to upgrade to a system that is not stand-alone, this may not be attainable for several years.

While we agree that it may be preferable to review the DDR prior to drawing a donation, a requirement to do so would effectively shut down many mobile operations and would impact others when computer outages occur, having a significant negative impact on blood availability.

Privacy concerns – In addition to technical challenges in their use, DDRs pose significant risks of identity theft. The Federal Trade Commission recently released the results of a survey conducted in 2006 that showed that 8.3 million (3.7%) American adults were victims of identity theft in 2005. Recently, a Presidential Commission looking at the issue of Identify Theft issued a report entitled Combating Identify Theft, A Strategic Plan. One of the key recommendations of this report was to decrease the unnecessary use of Social Security Numbers (SSN) in the public domain. Because of these concerns, many blood centers no longer use the donor's SSN as the unique donor identification number in their DDR. Even without the SSN, several donor centers have faced the problems of lost or compromised computers and the need to notify donors of the potential breach of personal information. The loss or theft of paper backup deferral lists, particularly from mobile blood drives that are by their nature less secure than fixed donation sites, is an additional concern about the security of this information. Although HIPAA issues are not the primary concern of blood collectors as the majority of them are not covered entities, it should be noted that identity theft occurrences may facilitate unauthorized access to private medical information.

The concept of a national DDR – Further extension of multiple existing DDRs to a national DDR with other license holders is not achievable. In a recent editorial (Transfusion 2008;48:6-7), Paul Holland, MD, discussed the challenges of maintaining a DDR without a unique blood donor identification system, such as the SSN, in today's mobile population. He concludes that the ever-increasing amount of manpower expended in the upkeep of the DDR could be better used in other areas that would have an impact on blood safety and that the time has come to reexamine the need for a DDR. Without access to a nationwide unique identifier such as a SSN it is not possible to share DDRs widely due to duplication of names and birthdates. Many facilities already spend tremendous resources in an effort to prevent duplication of donor records *and* to keep separate the records that belong to donors with similar/same names and dates of birth; this problem would grow even larger in a national DDR system, while as noted above adding virtually no safety to the blood supply.

The system developed for plasma donors can not be adapted to meet the very different needs for collection of labile cellular products. A national DDR (nDDR) based on positive viral markers for HIV, HBV and HCV seems to work well for the plasma industry and its paid donors. The nDDR is dependent on use of the SSN. A plasma center must check every new donor that presents at their facility against the nDDR, and will recheck each donor on an annual basis at the time of the annual physical; this is a far less complicated process than maintenance of a national blood DDR with a required donor query prior to every donation. Additionally, plasma centers operate within the confines of a fixed location; they do not run mobile operations. For these reasons, this nation-wide plasma system is not applicable to the blood community.

In addition it is inappropriate for blood center personnel to be in a position of informing a presenting donor that he/she is deferred without having access to the necessary information to help the donor understand the reason for the deferral. Furthermore, with the requirement that *all* deferrals must be entered on the registry it is also quite possible that a donor will be deferred

by one establishment/license holder for a reason that another establishment would not consider to be a cause for deferral.

Proposed Rule Section VI. The Paperwork Reduction Act of 1995 (Proposed § 606.160(e))

We are proposing to revise current § 606.160(e). Paragraph (e) would require collecting establishments to maintain a list identifying ineligible donors (otherwise known as a deferral list or donor deferral registry) and to provide this list to appropriate personnel to prevent the collection of blood and blood components from such individuals.

Table 1. – Estimated Annual Recordkeeping Burden. 21 CFR section 606.160(e)...Hours per Record – 8

Response to Request for Comment – The estimated burden for recordkeeping related to the DDR (a collective listing of all deferrals provided to all collection sites operating under one license) of 8 hours per week is not realistic. The estimate may be adequate for an establishment that operates only at fixed locations with computer intra-connectivity or that is currently able to perform this activity by updating laptops, and they only have a few laptops to update, and if there are no complications with the update. In actuality, the estimated recording burden is inadequate for there are a multitude of circumstances that would increase the processing time for updating laptops; lack of direct connectivity, daily updating of laptops, and system downtime.

Additionally, establishments that provide a new hard copy DDR prior to each mobile blood drive would spend many hours (in excess of 8 hours per week) to accomplish this activity. In fact, according to the proposed CFR language a facility that updates the DDR and makes it available *only* on a weekly basis would not be in compliance with the regulation. Therefore, the calculation based on per week activity (annual frequency of 52) is totally inaccurate.

The footnote to Table 1 states “there are no capital costs or operating and maintenance costs associated with this collection of information.” This is an inaccurate statement/estimation. Please see background information on preceding pages.

21 CFR Section 610.40(e) – *You must further test each donation, including autologous donations, found to be reactive by a screening test performed under paragraphs (a) and (b) of this section using one or more FDA-approved supplemental (additional, more specific) test(s), or other appropriate, additional tests. You must perform such further testing as necessary and appropriate to determine the deferred donor's infection status for the purpose of donor notification required under Sec. 630.40 of this chapter, except:*

- (1) For autologous donations, you must further test under this paragraph, at a minimum, the first reactive donation in each 30-day period; or*
- (2) If you have a record for that donor of a positive result on a supplemental (additional, more specific) test approved for such use by FDA, you do not have to further test an autologous donation.*

Preamble, D.2 Testing further with one or more supplemental (additional, more specific) test(s) – *The intent of this section is to allow for the use of multiple screening tests to “confirm” infection or to provide additional information on the presence of the analyte when described in guidance, as appropriate. It is not FDA's intention to move away from confirmatory or*

supplemental testing where such an approved test exists, but rather to recognize that under certain circumstances alternative testing schemes may provide confirmatory or supplemental testing information.

Recommendation –We propose two options. First, the FDA should consider rewriting section 21 CFR Section 610.40(e) to allow supplemental-confirmatory testing following a repeatedly reactive screening result to be considered the practice of medicine. Second, if the FDA chooses to adopt the language in 21 CFR Section 610.40(e), it is imperative that FDA seriously consider alternate approaches to the approval of supplemental-confirmatory tests and testing claims for existing screening tests/rapid tests that would encourage test kit manufacturers to participate in the licensure process. This may be as simple as taking existing FDA licensed screening tests and allowing their use in dual test algorithms that have been shown to have a very high positive predictive value.

Background – While we agree with the concept of additional testing for donations found to be repeatedly reactive by a screening test prior to donor counseling, we believe that many of the current FDA licensed tests having a supplemental and/or confirmatory claim have outlived their usefulness for a variety reasons including limited availability, poor lot to lot consistency and, most importantly, very poor specificity and sensitivity that often are significantly worse than that of the accompanying screening test. Therefore, when supplemental-confirmatory results are obtained, those results are often inaccurate. The finding of a false-positive confirmatory test in an uninfected donor is alarming, and since incorrect, raises questions about the competence of the US blood donor screening system since these anxious donors then spend their time and money to be investigated and re-tested by their private physicians. These donors become extremely frustrated when they are told by their physician that they had negative test results. They return to the blood collecting facility, demanding reimbursement of the unnecessary expenses (often not covered by their health plans) and reinstatement as blood donors. Some centers will provide partial reimbursement, others will not. Few will attempt to reinstate the donors because of FDA regulations.

Due to the limited number of licensed supplemental-confirmatory tests currently available, and the absence of tests in development for the US blood donor screening market, we strongly believe that changes to the supplemental-confirmatory approach are needed. One approach is to state that further testing to accurately and appropriately establish the deferred donor's infection status is the practice of medicine and should conform to the standard of care, allowing the blood center physician to choose the most appropriate tests available, whether including specific FDA-validated claims for supplemental-confirmatory testing or not.

The stringent regulatory requirements for FDA approval of a supplementary-confirmatory claim discourage license submissions. It is appropriate to re-think the current licensing paradigm for supplemental-confirmatory tests and significantly reduce the burden to licensure. This can be easily facilitated by using tests that are already licensed for blood donor screening and through the years have been validated to show sensitivity and specificity superior to FDA licensed supplemental-confirmatory assays. Clinical studies validating a screening claim, which are currently very robust, could be followed by very limited additional studies to achieve a blood donor supplemental-confirmatory claim that in addition could be used for donor reentry. As such we agree with the use of a second licensed screening test in a dual test strategy and the use of licensed nucleic acid test or FDA-cleared rapid tests in algorithms where they serve as donor

supplemental tests. However, it should be noted that even with the use of HIV NAT as a supplemental test for donors who are HIV-1/HIV-2 repeat reactive, only 5% or fewer tests are RNA positive leaving 95% or more of HIV-1/HIV-2 repeat reactive donations that still require testing by the obsolete western blot (WB) licensed in 1991 or the immunofluorescence assay (IFA) licensed in 1992. We are still on version 1.0 for both of these tests. In a CDC study comparing various algorithms for HIV confirmation, they concluded that alternate algorithms using combinations of currently approved HIV tests function as well as, if not better than, the current algorithm with more flexibility, improved accuracy and lower cost. This study (Owen et al., 2008 J Clin Microbiol) compared 6 EIAs, 4 rapid tests and 3 NAT assays in various algorithms to the current FDA-required testing algorithm using samples from 621 HIV-1 and 34 HIV-2 infected individuals, 183 specimens from 15 HIV-1 seroconverters and 513 uninfected individuals. The results indicate that the alternate algorithm strategies not only compared favorably for diagnosing established infection but functioned better in diagnosing early infection and did so with fewer discordant or indeterminate results that require follow-up testing.

The FDA-required licensure process for a supplemental-confirmatory claim not only has prevented improvement of the supplemental-confirmatory tests used, but has prevented further technological advancements for the confirmation of other disease agents. In the case of HTLV infection, there have not been any supplemental-confirmatory tests available since donor screening began in 1989. From 2000-2004, the Red Cross had 30,429 HTLV-repeatedly reactive donors (Stramer et al. Transfusion 2006;46:703-707) with another 7,801 in 2007-2008 and likely a comparable number for 2005-2006. Through creative approaches consisting of a dual EIA algorithm (using assays without FDA licensed supplemental-confirmatory claims) and an unlicensed algorithm for further confirmation of concordant repeat reactive donations, only 29% of those reactive have required further testing by more complex confirmatory assays including the 5% that confirmed positive (Stramer et al. Transfusion 2006). However, none of the concordantly reactive donors or donors deferred due to or reactivity twice on the same assay can be reentered due to the absence of a licensed confirmatory test. Although the use of the current HTLV algorithm has helped notification, FDA requirements have precluded reentry of any false-positive donor since 1989.

The most alarming issue that we face with the use of the current FDA-licensed supplemental-confirmatory tests is specificity. Each year tens of thousands of donors are told that they are false positive or “indeterminate” after confirmatory testing, and that, while we are confident they are uninfected, they remain unsuitable blood donors unless they undergo complex reentry algorithms often times requiring an FDA variance request performed on a case-by-case basis to grant approval for reentry. The Red Cross alone has deferred 59,533 donors for HIV, HCV and HBV since 2003 of which 36,725 would be eligible for reentry but for which only 2332 (6%) have attempted to undergo the process (Stramer et al. AABB 2008 accepted abstract). In addition to the time and expenditure necessary from blood centers to reenter such donors, in many cases these donors, because of the mixed message they have received, have no confidence in the blood donor system. One solution to this issue would be alternate approaches such as dual test strategies that would not result in indefinite deferral of discordantly reactive donors, or if deferred, make their reentry process into the blood donor pool less complex.

21 CFR Section 630.1(a)(1) and (2) – *What is the purpose of subparts A, B, and C of this part? The purpose of these subparts, together with Sec. 610.40 and 610.41 of this chapter, is to provide certain minimum criteria for each donation of blood and blood components, for:*

- (1) Determining the eligibility of a donor of blood and blood components;*
- (2) Determining the suitability of the donation of blood and blood components; and*

Preamble, Section F. Definitions – *We are defining eligibility of a donor in proposed § 630.3(d) and suitability of the donation in proposed § 630.3(i) so as to distinguish between the acceptability of a donor for donation and the acceptability of the donation for transfusion or for further manufacturing use.*

Comment – We agree with the use of terms donor eligibility and product suitability. This is very helpful in clarifying many donor/donation requirements.

21 CFR Section 630.3(e) – *Intimate contact means an activity that could result in an exchange of body fluids, including blood or saliva, with another individual.*

21 CFR Section 630.10 (f) – *What factors make the donor ineligible because of an increased risk for, or evidence of, a relevant transfusion-transmitted infection? The donor is ineligible to donate when information provided by the donor or other reliable evidence indicates possible exposure to a relevant transfusion-transmitted infection. Information that a donor has participated in any of the following renders the donor ineligible if that risk of exposure is still applicable at the time of donation:*

- (5) Intimate contact with an individual who is at an increased risk for exposure to, or is known to be infected with, a relevant transfusion-transmitted infection that is spread by such type of intimate contact; and*

Recommendation – 21 CFR 630.3(e) – The section should be reworded:

(e) Intimate contact means an activity (sexual contact or living with) that could result in an exchange of blood with another individual.

Furthermore, a definition of “sexual contact” and “living with” (consistent with its use in the approved AABB Donor History Questionnaire (DHQ) materials) should be included in the guidance document that provides recommendations for complying with the rule.

21 CFR Section 630.10(f)(5) – The guidance document that provides recommendations for complying with the rule must clarify that malaria and vCJD, even though identified in the rule as relevant transfusion-transmitted infections (RTTIs), are not spread by intimate contact, and that donors are not subject to disqualification for intimate contact with these infections.

Background – AABB is concerned about the explicit inclusion of “exchange of saliva” in the definition of “intimate contact.” Proposed 21 CFR 630.10(f)(5) requires that a donor is ineligible to donate if he or she has engaged in “intimate contact with an individual who is at increased risk of exposure to, or is known to be infected with, a relevant transfusion transmitted infection that is spread by such type of intimate contact.” Of primary concern, this requirement is in stark conflict with standard public health messages that emphasize the *de minimis* risk of personal contact

(including kissing) with individuals infected with HIV and other parenterally transmitted infections. It is obvious that one common method of exchanging saliva is through kissing. Thus, since most people would interpret kissing as “intimate contact” according to the proposed FDA definition, donor deferral criteria would contradict the last two decades of public health messaging concerning the safety of personal contact with persons infected with HIV and HCV. This would undoubtedly create massive confusion in the blood donor population.

The proposed definition is without supporting scientific data. Available epidemiologic data do not support the transmission of any of the relevant transfusion transmitted infections by saliva, except in the unusual situation of saliva transfer by means of a human bite breaking the skin, which has transmitted HBV infection.

Exchange of saliva is not considered to be a route of infection for agents specifically identified in proposed 21 CFR 630.3(g)(i-viii). It is therefore unclear whether proposed 21 CFR 630.10(f)(5) would actually apply to saliva exchange or not. Furthermore, intimate contact (“sexual contact”, “lived with”) should not be applied to all RTTIs (e.g. CJD (which is further addressed below), vCJD, or malaria) as these diseases are not spread by sexual or close personal contact.

These same issues concerning the definition of intimate contact were discussed with FDA staff during development of the uniform DHQ. At that time, it was clear that explicitly deferring a donor due to the exchange of saliva with a person exposed to or infected with HIV, HCV, or HBV would contradict scientific data and would send an inaccurate public health message. The DHQ utilizes and defines “sexual contact” and “lived with” to cover these issues. New terminology should not be introduced as it would be confusing.

21 CFR Section 630.3(g) – Relevant transfusion-transmitted infection means:

- (1) Any of the following transfusion-transmitted infections:
 - (i) Human immunodeficiency virus, types 1 and 2 (HIV);
 - (ii) Hepatitis B virus (HBV);
 - (iii) Hepatitis C virus (HCV);
 - (iv) Human T-lymphotropic virus, types I and II (HTLV);
 - (v) *Treponema pallidum* (syphilis);
 - (vi) Creutzfeldt-Jakob disease (CJD);
 - (vii) Variant Creutzfeldt-Jakob disease (vCJD); and
 - (viii) *Plasmodium sp.* (malaria).
- (2) Other transfusion-transmitted infections not listed in paragraph (g)(1) of this section:
 - (i) For which appropriate screening measures are developed and/or an appropriate screening test for donor specimens is licensed, approved, or cleared for such use by FDA and is available; and
 - (ii) That:
 - (A) May have sufficient incidence and/or prevalence to affect the potential donor populationor
 - (B) May have been released accidentally or intentionally in a manner that could place donors at risk of infection.

Preamble: F. Definitions – *We are defining relevant transfusion-transmitted infection in proposed Sec. 630.3(g)(1) to identify the currently recognized disease agents that are associated with transmission from the donor to the recipient by transfusion, infusion, or injection of a blood component or blood derivative..*

.. In the proposed rule entitled "Requirements for Testing Human Blood Donors for Evidence of Infection Due to Communicable Disease Agents" (64 FR 45340, August 19, 1999), we solicited comments, with supporting data, from the public in regard to the value of donor testing for syphilis as a marker of increased risk behavior, as a surrogate test for other infectious diseases, and in preventing the transmission of syphilis through blood transfusion. After reviewing the comments and submitted scientific data, we determined that the comments did not provide sufficient supporting data to justify eliminating the requirements for screening and testing the donor for syphilis. We continue to consider this issue, including any further studies that address the issues of transfusion-related syphilis infection or testing for syphilis as a surrogate marker for other communicable diseases; and we again request comments and data concerning whether establishments could discontinue syphilis testing without adversely affecting the safety of the blood supply. If we receive adequate data, we will eliminate or modify this testing requirement in the final rule.

Recommendation – CJD is not a relevant transfusion-transmitted disease and should be removed from the definition.

Serological tests for syphilis do not add to the safety of blood products transfused in the United States. The requirement to perform such testing should be deleted.

Background – CJD – There is no report of human transfusion transmission of classic CJD. (Zou S, Fang CT, Schonberger LB. Transfusion transmission of human prion diseases. *Trans Med Revs* 2008;22:58-69). The American Red Cross lookback study on recipients of blood from donors who subsequently were diagnosed with CJD reveals no evidence this has occurred. 429 recipients of blood from 34 such donors have been followed for a total of 2023 person-years without any cases of CJD. 145 recipients survived for five or more years after transfusion. This observation is statistically significant ($P = 0.0156$) when compared to the frequency of clinical vCJD in recipients of blood from donors who subsequently developed vCJD. Inclusion of CJD in the list of RTTIs is inappropriate. Nevertheless, we are not recommending any change in current donor eligibility or product suitability criteria relating to classic CJD.

Syphilis – In a published study (Prevalence of circulating *Treponema pallidum* DNA and RNA in blood donors with confirmed-positive syphilis tests. *Transfusion* 2002;42:94-99) Orton and colleagues used nucleic acid amplification to test for the presence of *T. pallidum* DNA (91) and/or RNA (97) in a total of 169 platelet products from donors with confirmed positive serological tests for syphilis. No sample was found positive. Platelets represent the worst case scenario, since storage of RBCs and whole blood at refrigerator temperatures is lethal to *T. pallidum*. (Turner TB, Diseker TH. Duration of infectivity of *Treponema pallidum* in citrated blood stored under conditions in blood banks. *Bull Johns Hopkins Hosp* 1941;68:269-79 and Kilmer JA. A note on the survival of *Treponema pallidum* in preserved citrated human blood and plasma. *Am J Syph Gonorrhea Vener Dis* 1942;26:156-8).

With respect to the surrogate value of syphilis testing, Herrera et al (Serologic test for syphilis as a surrogate marker for human immunodeficiency virus infection among United States blood

donors. Transfusion 1997;37:836-840) concluded that amongst almost 5 million blood units analyzed, syphilis testing would have removed only 0.2 HIV window-period donations in 1994, when the window period was much longer than it is now. More recently, ARC estimated the surrogate role of syphilis testing for other significant RTTIs using data from collections between 2002 and 2006. There were significantly higher frequencies of HIV, HCV, HBsAg and HTLV positive donations among those with positive syphilis tests for the 2005-2006 period. However, the actual sensitivity of the syphilis test for identifying such samples was between 1.6% and 5.9%. Given that HIV, HCV and HBV testing relies upon redundant serologic and NAT procedures, the syphilis test provides no additional security in detecting such prevalent infections. Accordingly, ARC has also evaluated the relationship between a new confirmed positive syphilis test and test results for HIV, HCV, HBsAg and HTLV among repeat donors by looking at data from 2002 – 2006. There were 390 new syphilis infections among just over 5 million donations. However, of the 171 HIV infections, only 2 were found in the syphilis-positive group, for a sensitivity of 1.2% and a PPV of 0.5%. There were no HCV, HBsAg or HTLV seroconversions among the syphilis positive group. Accounting for the current length of the window period, it is estimated that the syphilis test might identify approximately 0.04 HIV window period donations annually in the Red Cross donor population. Thus, the current surrogate value of the syphilis test appears to be negligible.

Likewise the 1995 NIH Consensus Development Conference Report on Infectious Disease Testing for Blood Transfusions concluded that serologic tests for syphilis have very little value as surrogate markers for HIV/HBV/HCV/HTLV.

21 CFR Section 630.3(j) – *Trained personnel means authorized individuals, including physician substitutes, who are adequately instructed and qualified to perform specified functions under the direction of the responsible physician.*

Recommendation – The section should be reworded:

(j) Trained personnel means authorized individuals, including physician substitutes, who are adequately instructed and qualified to perform functions under the direction of the responsible physician as specified in the establishment’s standard operating procedures.

The establishment’s procedures should define what constitutes “adequately instructed” and “qualified to perform”.

21 CFR Section 630.3(k) – *Transfusion-transmitted infection means a disease or disease agent:*

(1) *That could be fatal or life-threatening, could result in permanent impairment of a body function or permanent damage to body structure, or could necessitate medical or surgical intervention to preclude permanent impairment of body function or permanent damage to a body structure; and*

(2) *For which there may be a risk of transmission by the blood and blood components collected, or by a blood derivative product manufactured from the collected blood or blood*

components, because the disease agent or disease is potentially transmissible by that blood, blood component, or blood derivative product.

Preamble, F. Definitions – *The definition of a transfusion-transmitted infection differs from a relevant transfusion-transmitted infection in that the existence of sufficient incidence and/or prevalence to affect the potential donor population is not a part of the definition. Available screening and testing methods may also be limited. One example of such a transfusion-transmitted infection is leishmania.*

Recommendation – The definition of transfusion-transmitted infection (TTI) and all references to it should be deleted.

Background – AABB recognizes the need to develop a guidance document as agents emerge, but sees no positive value in defining TTI in the proposed rule. As written, the definition lacks precision and provides no useful information for industry. Furthermore, reference to this definition in proposed 21CFR 630.10(g) will create an insoluble dilemma for the blood community in determining the conditions in which to establish deferral criteria for travel or residence. AABB has developed an incomplete listing of no fewer than 69 agents that meet, or potentially meet, the proposed definition of TTI. To comply with the proposed requirements, for each of these agents, would not be possible, practical, or effective. Furthermore, having a formal definition of TTI in a regulation would likely lead to unexpected pressures and requirements to regulate for each and every infection found to be transmissible by transfusion, even if such transmission were exceedingly rare or remotely plausible. It is the opinion of AABB that the current system of Guidances has proven safe and effective in the management of emergent threats to blood safety such as WNV, SARS and vCJD. No other rulemaking appears to be necessary. Even in the absence of FDA guidance industry has taken the lead and published recommendations when necessary. For example, AABB Association Bulletin 06-04 *Recommendations for Blood Collection Facilities in Response to Epidemic Mumps in the Midwest* was published in April 2006. Finally, AABB recognizes that *Leishmania* spp. appear to fit the proposed definition of TTI, however, it illustrates some of the problems outlined above. For example, it is not necessary to defer donors who have lived, or traveled in Mediterranean countries where *Leishmania* occurs.

21 CFR Section 630.5(a)-(d) – (a) *Who must determine the eligibility of a donor? The responsible physician authorized by you, as described in Sec. 630.3(l), must determine the eligibility of a donor of blood or blood components in accordance with this part.*
(b) *Must the responsible physician be present at the collecting establishment at all times? Except as provided in paragraphs (c) and (d) of this section and Sec. 630.15(b)(1) and (b)(4), you must assure that the responsible physician is in attendance when any of the following activities are performed at the collecting establishment:*
(1) *Determining the eligibility of a donor;*
(2) *Collecting blood or blood components;*
(3) *Collecting Source Plasma in an approved collection program from donors who are otherwise determined to be unsuitable;*
(4) *Returning red blood cells to the donor during plasmapheresis; or*
(5) *Immunizing a donor in an approved hyperimmunization program.*

(c) What specified functions of the responsible physician in the collection of Source Plasma may be performed by a physician substitute? You may authorize a physician substitute to perform any specified function listed in paragraph (b) of this section in the collection of Source Plasma except for red blood cell immunizations performed under paragraph (b)(5) of this section.”

(d) What specified functions of the responsible physician in the collection of blood and blood components may be performed by a physician substitute or trained personnel? In the absence of the responsible physician, you may authorize a physician substitute or trained personnel to determine donor eligibility and collect blood and blood components.

Recommendation – The guidance document should clarify that trained personnel, instructed and qualified by the collection establishment, may determine eligibility and collect blood and blood components, including plasma components collected by a procedure involving the return of red blood cells to the donor.

Background – The proposed requirement is unclear about the personnel required for the collection of plasma components involving the return of red blood cells in programs that do not collect Source Plasma. Section 630.5 (b)(4) “returning red blood cells to the donor during plasmapheresis” would require the presence of a physician substitute in the collection of Source Plasma. Red cells are now routinely returned to donors during plasma collection by automated equipment, both as a separate plasma donation and as part of procedures collecting red cells and/or apheresis platelets. With modern automated equipment that is continuously attached to the donor, return of red cells does not pose a special risk, and there is no need for a responsible physician or physician substitute to be present during collection from Source Plasma or Whole Blood donors.

21 CFR Section 630.5(e) – *Must emergency medical services be available? Yes, you must establish, maintain, and follow standard operating procedures for providing within 15 minutes emergency medical services for donors when medically necessary.*

Preamble, Section G. Medical Supervision – *The collecting establishment would be required in proposed § 630.5(e) to have SOPs for providing emergency medical services to a donor within 15 minutes when necessary. Although we currently require the presence of appropriately trained medical personnel, our current regulations do not directly address the availability of emergency medical services, which a donor may require. We are interested in receiving comments on what would be considered as appropriate for available emergency medical services.*

Recommendation – In an effort to provide clarity to the proposed regulation, we recommend that the section be reworded to include public emergency medical services.

(e) Must emergency medical services be available? Yes, you must establish, maintain, and follow standard operating procedures for providing within 15 minutes emergency medical services, which may include public emergency medical services, for donors when medically necessary.

Background – The establishment of standard procedures for providing emergency medical services within 15 minutes, if necessary for donors seems appropriate. It is a widely accepted fact that the most qualified medical professionals to respond to an emergency are trained,

practicing emergency physicians or emergency medical technicians using the proper equipment, who have the ability to transport an unstable patient to an appropriate health care setting. Furthermore, there are several publications in the peer reviewed literature showing that emergency medical personnel frequently respond to calls within a time frame that meets the requirements of this section. (Lerner et al, The J. of Emergency Medicine 2003;25:171-174; Pons et al. ibid 2002;23:43-48).

21 CFR Section 630.10(b) – *What educational material must you provide to the donor before determining eligibility? Before determining eligibility, you must provide the donor with educational material containing useful and current information concerning the relevant transfusion-transmitted infections defined in Sec. 630.3(g). The educational material must include an explanation of the signs and symptoms of and the readily identifiable risk factors closely associated with exposure to the relevant transfusion-transmitted infections. You must present educational material in an appropriate form, e.g., in oral, written or multimedia, and in a manner designed to be understood by the donor. The educational material must state that the donor may not donate blood and blood components when such signs and symptoms or risk factors are present.*

Preamble, Section H. General Donor Eligibility Requirements, 1. Educational Materials – *The proposed rule would also require that educational material include behavioral risks and signs and symptoms for hepatitis and other relevant transfusion transmitted infections determined to present a risk to the blood supply. We are soliciting comments on this provision, particularly on how comprehensive the educational material should be and the format or style in which it is presented.*

Recommendation – We do not agree with the proposed requirement that signs and symptoms of relevant transfusion-transmitted infections (RTTIs) be included in the education materials. The section should be reworded:

(b) What educational material must you provide to the donor before determining eligibility? Before determining eligibility, you must provide the donor with educational material containing useful and current information concerning the relevant transfusion-transmitted infections defined in Sec. 630.3(g). You must present educational material in an appropriate form, e.g., in oral, written or multimedia, and in a manner designed to be understood by the donor.

Background – The signs, symptoms and risk factors for HIV infection already appear in the AABB DHQ Educational Materials and all other FDA approved donor history materials. Many of the risk factors adequately cover risks for other RTTIs including hepatitis B and C. We do not consider it appropriate to add additional items to this section. In fact, we question the value of including a signs and symptoms section in the current DHQ materials. Most of the signs and symptoms are decidedly non-specific and can be found in numerous other medical conditions. For example, a woman having night sweats could simply be menopausal. Further one would expect the other items would be picked up by the routine donor questions, beginning with, “Are you feeling well and healthy today?” This question would capture swollen lymph nodes, sores in mouth, cough, shortness of breath or diarrhea that won’t go away. Coughs and shortness of breath would also be identified by the question regarding problems the donor has with his lungs. Fevers would be identified when a donor has their temperature taken during the mini-physical. In

addition, issues such as mouth sores, blue or purple spots on mouth or skin, etc are indicative of well established AIDS. It is highly unlikely that persons who are already ill with HIV infection would be coming to donate blood.

The AABB Donor History Task Force recommended the removal of this list of signs and symptoms at the time the uniform DHQ was developed due to the non-specific nature of the list. FDA did not agree with this at the time, but it is surely time to reconsider. It is well known that the denser the reading material presented to donors, the less comprehension occurs. This was supported by the task force consultants – National Center for Health Statistics (NCHS) – on comprehension of written materials at that time. In a discussion with NCHS and recent re-evaluation of the Educational Materials, it was determined this information is repetitive in getting at the question for donors to consider which is, “Am I sick?” It was felt the density of the materials strained donor attention. Further it was noted that in the absence of very specific and unique signs/symptoms it is better to keep the Educational Materials as simple as possible to enable the donor to focus on the more specific questions.

21 CFR Section 630.10(c) – *When must you determine the eligibility of a donor? You must determine donor eligibility on the day of donation, and before collection. When a donor is donating blood components that cannot be stored for more than 24 hours, you may determine the donor's eligibility and collect a sample for testing required under Sec. 610.40 and Sec. 640.5 of this chapter, 1 day before the donation. You must have standard operating procedures in place for identifying such components.*

Preamble, Section H, General Donor Eligibility Requirements 2. Assessment of the Donor's Eligibility to Donate Current – *Proposed § 630.10(c) would require that the collecting establishment perform an assessment of the donor's eligibility on the day of donation, and before collection. An exception would be allowed for the collection of blood components that cannot be stored for more than 24 hours, such as granulocytes for transfusion. For such components, the collecting establishment may perform a donor assessment and the testing required under § 610.40(a) and (b) 1 day before the collection of such products. Establishments would be required to have SOPs in place to identify such components.*

Recommendation – Eligibility determination on day of collection – While we agree that it is desirable to complete the donor eligibility determination prior to collection we oppose an interpretation of this requirement (assessment of a donor's eligibility on the day of donation, and before collection) that would deny a retrospective eligibility determination (e.g., in the case of missing or incompletely explained questionnaire responses due to GMP error). We recommend that FDA clarify, in a guidance document that contains recommendations for complying with the regulations, interpretive criteria that will prevent the needless destruction of life-saving blood components.

Short shelf-life products – We agree that collecting a sample for testing at the same time a short shelf-life product is collected may not be feasible; however, it is also probable that a sample collected within the previous 24 hours may not be able to be tested prior to release of the product. We recommend that facilities be permitted to collect a sample for donor testing three (3) days prior to product collection. Alternatively, we believe that a donor who has donated within

the previous 30 days in accordance with proposed rule 640.21(d) and current rule 610.40(c)(1) would be acceptable.

Background – Eligibility determination on day of collection – The current and proposed regulatory language has been interpreted by FDA such that components collected from a donor whose eligibility was not adequately determined on the day of collection have been deemed unsuitable for use. While it is unfortunate that an error occurred in the original donor eligibility determination, the suitability of the donation should not be linked to the eligibility of the donor unless the missing data cannot be reasonably assessed during the dating period of the component. De-linkage would permit the product to be deemed suitable for transfusion, thus preserving the availability of an adequate blood supply. Examples of missing data that can accurately be determined during the dating period of the component are those elements that would not change. These include, but are not limited to, travel history, history of disease, history of transfusion, “living with” someone with hepatitis, and history of CJD. Other data are related to the donor’s health and have no bearing on the suitability of the product and are irrelevant after the collection. These include, but are not limited to, donor’s weight, blood pressure, pulse, and general health status.

Short shelf-life products – A more reasonable approach to collecting a sample the same day or one day prior to collection of a short shelf-life product would be to allow apheresis donors who have donated within the previous 30 days, and were cleared on all testing, to serve as a granulocyte donor based on the results of the prior donation. The granulocyte donation would be tested as well, but the product would be released prior to the availability of those results. Should any of the results be reactive, the hospital would be notified immediately. Generally, granulocyte recipients are gravely ill and the administration of the granulocytes is a last treatment option to help them clear a bacterial/fungal infection.

21 CFR Section 630.10(d)(2) – *How must you determine the eligibility of a donor? Before collection, you must determine the donor's eligibility by the following procedures:*

(2) Assuring that the interval since the donor's last donation is appropriate, taking into account the donor's participation, if any, in other blood or blood component collection programs;

Recommendation – This section should be reworded:

(2) Assuring that the interval since the donor's last donation is appropriate;

Background – While earlier versions of the DHQ asked a similar question, it was not a requirement by the FDA or AABB. The AABB Donor History Task Force subsequently removed the question addressing donation at other sites, with FDA approval, and placed emphasis on asking very specific questions to identify donors who have given blood, platelets, plasma or double red cells by apheresis at specific time intervals. The current approach to questioning by specific types of donations should capture all donations regardless of the facility where the donor last donated.

21 CFR Section 630.10(e) – *How do you assess the donor's medical history? Before collection, you must take a medical history designed to determine if the donor is in good health and if health care practitioners have ever advised the donor not to donate; to identify risk factors closely associated with exposure to, or clinical evidence of, infection due to a relevant transfusion-transmitted infection; and to determine if there are other conditions that may adversely affect the donor or the safety, purity, or potency of the blood or blood components or any product produced from the blood or blood components.*

Recommendation – We recommend that the statement, “and healthcare practitioner ever advised the donor not to donate” be deleted from the final rule.

Background – Although a question asking whether the donor was advised against donation by a health care practitioner was on an earlier version of the DHQ, neither the FDA nor AABB required collection facilities to ask a specific question regarding this issue. The question was eliminated with the approval of FDA, in a subsequent version of the DHQ. The rationale for the elimination of this query was based on the fact that this is a nonspecific query and becomes a reiterative issue when donors are asked this question at each donation. For instance, if a donor was told by a physician in 1993 not to donate until a simple bacterial infection cleared, in theory, the answer to this query would always be “YES.” Although the reason for deferral is long past, the donor will have to answer “YES” to this question at each and every visit, a situation that is a waste of time for both donor and health historian, and which adds nothing to the safety of the blood supply. Furthermore, most primary care physicians (and even specialists) are not familiar with the specific eligibility requirements for donors and as such are rarely in a position to make such a determination. Instead, the donor is directly queried regarding very specific risk factors such as heart disease, lung disease, cancer, antibiotics, history of hepatitis and other specific infectious diseases. The phrase “if health care practitioners have ever advised the donor not to donate” does not add to the safety of the blood products but will complicate the donation process.

21 CFR Section 630.10(f) – *What factors make the donor ineligible because of an increased risk for, or evidence of, a relevant transfusion-transmitted infection? The donor is ineligible to donate when information provided by the donor or other reliable evidence indicates possible exposure to a relevant transfusion-transmitted infection. Information that a donor has participated in any of the following renders the donor ineligible if that risk of exposure is still applicable at the time of donation:*

(1) *Social behaviors...*

(2) *Medical treatments and procedures associated with exposure to relevant transfusion-transmitted infections;*

(3) *Signs and symptoms of relevant transfusion-transmitted infections;*

(4) *Institutionalization in a correctional institution;*

(5) *Intimate contact with an individual who is at an increased risk for exposure to, or is known to be infected with, a relevant transfusion-transmitted infection that is spread by such type of intimate contact; and*

(6) *Nonsterile percutaneous...*

Preamble, H. 2. Assessment of the Donor’s Eligibility to Donate – Institutionalization

(630.10(f)(4) *A collecting establishment would determine whether a donor is currently an inmate of a correctional institution or has been incarcerated within the last 12 months, and if so, whether the risk of exposure related to that incarceration is still applicable at the time of donation. Current guidance recommends that a donor not be eligible to donate if incarcerated in a correctional institution for more than 3 consecutive days during the past 12 months.*

Recommendation – We recommend that 21 CFR Sections 630.10(f)(2) and (3) be deleted from the final rule.

Comment – We agree with the principle of deferral from blood donation based on incarceration (21 CFR Section 630.10(f)(4)) and with the principle of addressing the time period in a guidance document rather than codifying it in the CFR. In addition, we agree that institutionalization is adequately addressed in current guidance recommendations and the currently used donor history screening questionnaires.

Please see our response elsewhere in this document to 21 CFR Section 630.3(e) – definition of intimate contact.

Background – 21 CFR Section 630.10(f)(2) – We believe that existing screening questions on donor forms adequately cover issues of medical treatments and procedures. These would include dura mater transplant, blood transfusion, organ, tissue or bone marrow transplant and use of clotting factor concentrates. We are concerned that the wording of the proposal is too broad and might be applied inappropriately to situations that are not as yet agreed upon by the agency, industry and the public. The Guidance process is a more appropriate venue for recommendations for specific medical treatments and procedures that may affect donor and/or patient safety.

21 CFR Section 630.10(f)(3) – The response to 630.10(b) – see elsewhere in this document – applies to this section as well with respect to the requirement for ‘signs and symptoms of relevant transfusion-transmitted infections’.

21 CFR Section 630.10(f)(5) – See comments to 630.3(e) elsewhere in this document that are relevant to intimate contact.

21 CFR Section 630.10(g) – *What other factors make the donor ineligible to donate because of risk to the health of the donor, or to the safety, purity, or potency of the blood or blood component? You must assess the donor for each of the following factors to determine whether donating could adversely affect the health of the donor, or whether the safety, purity, or potency of the blood or blood component could be affected, and if so, you must determine the donor to be ineligible:*

- (1) *Medical or dental treatment, or symptoms of a recent or current illness;*
- (2) *Medication;*
- (3) *Major surgical procedure;*
- (4) *Travel to, or residence in, an area endemic for a transfusion-transmitted infection;*
- (5) *Xenotransplantation product recipient or intimate contact of a xenotransplantation product recipient;*

- (6) *Exposure or possible exposure to a released disease agent or disease relating to a transfusion-transmitted infection, if you know or suspect that such a release has occurred;*
- (7) *Pregnancy ...; and*
- (8) *Unreliable answers to medical history questions due to the apparent influence of drugs or alcohol, or due to another reason affecting the reliability of the donor's answers.*

Preamble, Section H. 2. Assessment of the Donor’s Eligibility to Donate – *Major surgical procedure (Proposed § 630.10(g)(3)). We would require establishments to defer donors who have experienced major surgery within the past 12 months. This deferral is to protect the donor whose health may be compromised by the donation and to address the possibility that the donor may have unknowingly received blood or blood components during surgery.*

Preamble, H. 2. Assessment of the Donor’s Eligibility to Donate – *Travel to endemic areas for transfusion-transmitted infections – It is known that several transfusion-transmitted infections exist for which the risk is closely associated with a geographic area, e.g., leishmania. Typically, such infections would not be “relevant transfusion-transmitted infections” requiring broader screening and testing because they do not have sufficient incidence or prevalence in the potential donor population. This provision is designed to identify donors who may be at risk for additional transfusion-transmitted infections. Because donors harboring such infections may be asymptomatic, or the signs and symptoms may be mild enough to go undetected at the time of donation, we would require the collecting establishment to assess whether the donor has visited or is a former resident of endemic areas known to harbor the disease agent or disease, whether the risk of exposure is still applicable at the time of donation, and, if so, determine the donor ineligible to donate.*

Recommendation – 21 CFR Section 630.10(g)(1) – We recommend that the phrase “or dental” be deleted.

21 CFR Section 630.10(g)(2) – should be reworded for clarity:

- (2) Medication, as indicated by FDA guidance;

We recommend that 21 CFR Sections 630.10(g)(3), (4), (5), (6), and (8) be deleted from the final rule.

Background – Dental procedures– The question regarding dental treatment was removed from the AABB DHQ, with FDA approval, based on published information demonstrating that bacteremia from dental procedures was very transient (15 minutes or less) and that even if the donor was scheduled to donate immediately after a dental procedure, by the time a donor traveled to the blood collection facility, the donor would no longer be bacteremic (PM Ness, HA Perkins. Transient bacteremia after dental procedures and other minor manipulations, Transfusion 1980;20(1):82–85).

Medication – The CFR should be clear that the medications currently covered by FDA guidance are the only ones that *must* be evaluated. Other medications may be screened for at the discretion of each institution’s medical director.

Major surgical procedure – A requirement for a 12 month deferral (as explained in the Preamble) after “major surgery” is not medically warranted because the existing questions on the DHQ

adequately protect donor and recipient safety. Donors must feel healthy and well on the day of donation, must pass the focused physical examination and must have an acceptable hemoglobin concentration. If a donor meets these requirements, and all other eligibility requirements, within an interval shorter than 12 months after surgery, he or she is qualified to donate blood.

In addition, donors are asked specifically about blood transfusion in the last 12 months. If a donor is not certain whether or not they were transfused, most donor centers would defer the donor for 12 months from the date of surgery or until they are able to provide the information about transfusion. It is not reasonable to make assumptions about whether a donor was transfused or not, based on the type of surgery when this information is available to the donor from their medical record.

Operationally, “major surgery” would have to be defined in the blood center’s standard operating procedures, and likely would not be defined in the same way by different blood centers. Since surgery is not an independent risk factor for transfusion-transmitted infections, there is no need to add a less specific question to the DHQ about surgery, when the more specific question about blood transfusion and other possible blood exposure are already asked.

Travel to areas endemic for a TTI – Please see our response elsewhere in this document to 630.3(k) where we recommend that “the definition of transfusion-transmitted infection (TTI) and all references to it should be deleted.” In the event that a particular TTI poses a threat to blood safety in the US, FDA can rapidly establish donor deferral policies through the guidance mechanism. This proposal defines a donor as ineligible if he or she has traveled to or has resided in an area endemic for a TTI. However, the proposed definition of TTI is too imprecise to be codified in regulations. With regard to donor deferral, there are many examples of transfusion-transmitted infections that have not risen to a high enough level of concern to warrant a travel or residency deferral: current examples are Dengue, Chikungunya, and Leishmania (with the exception of the unusual circumstances in Iraq). The appropriate policy for each such agent can be established through public forums (such as the Blood Products Advisory Committee) where all stakeholders can advance their points of view which can then be taken under advisement by FDA, followed by guidance when warranted. If broad language requiring travel deferrals for TTIs is codified in the CFR, there is a risk that the opportunity for informed decision-making on an agent-by-agent basis will be reduced. Also, a blanket application of the rule to all TTIs might result in deferral for a very large percentage of travel and, in this increasingly mobile society, might jeopardize blood availability without providing any material safety benefits. Issuance of guidance on a case-by-case basis is effective, as documented by the travel deferrals implemented during the SARS epidemic.

Xenotransplantation – While we agree that individuals who have undergone xenotransplantation should not be eligible as blood donors, we strongly object to the addition of questions to identify the vanishingly small number of such recipients. It is extremely unlikely that a xenotransplant recipient would become a blood donor due to the strong recommendation for deferral of xenotransplant recipients made in the “Guidance for Industry: Source Animal, Product, Preclinical and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans” issued in April 2003. Section J of this document contains a recommendation that recipients of xenotransplants be counseled not to donate blood or tissues during the informed consent process.

In addition, the DHQ already asks donors about transplants in the last 12 months; donors who have undergone xenotransplantation are likely to provide this history even if their transplant occurred over 12 months ago. Consequently, most blood centers will defer donors who report a history of xenotransplantation through already established procedures.

There is no need for the addition of unwarranted and incomprehensible questions to an already extensive and exhaustive DHQ. Xenotransplantation products are subject to regulation by the FDA (e.g., under section 351 of the Public Health Service Act and the Federal Food, Drug, and Cosmetic Act). In accordance with the statutory provisions governing premarket development, xenotransplantation products are subject to FDA review and approval. Investigators of such products need to obtain FDA review of proposed xenotransplantation clinical trials before proceeding. Consequently, FDA is in the ideal position to make sure that investigators of xenotransplantation products advise recipients not to donate blood because of the potential risk of infection with both recognized and unrecognized infectious agents. This certainly will be a more effective strategy than searching for the rare individual at theoretical risk among the millions of individuals who volunteer to donate blood. We believe these queries will not only be ineffective, but may also divert the donor's attention from questions that address real risks to blood recipients (i.e., donors in the window of seroconversion for hepatitis and HIV).

Additionally, we are concerned that deferral of intimate contacts of xenotransplantation recipients casts too broad a net and could defer perfectly safe blood donors. It is important to note that a major factor in the transmission of zoonotic pathogens to xenotransplant recipients is that the immunosuppression required to prevent rejection will render them uniquely susceptible to infection. In contrast, immunosuppression is not an issue in contacts who would be qualified as eligible blood donors.

There is currently a moratorium on xenotransplantation that effectively renders the issue moot for now, and further erodes the efficacy of a requirement for donor history questions. If and when the moratorium is lifted, guidance based on the state-of-the-art can be used without enshrining a requirement in CFR now.

Exposure to a released TTI – The potential for accidental or intentional release of a biological, chemical or nuclear agent capable of causing or potentially causing disease that could affect the safety, purity or potency of a blood product is speculative. Since it is unknown when or if such an event will occur, it is not possible to assess their potential effect on a routine basis. When these events have occurred in the past, for example the anthrax attacks of 2001 and SARS, the industry worked in conjunction with the FDA, CDC and other public health entities to determine the potential impact on donors and products. Industry and regulators have proven their ability to respond to such incidents rapidly and effectively on a case-by-case basis. We believe it is best to deal with such situations through guidance as they occur rather than codify them in the CFR. This proposal does not enhance the safety of blood products and should be deleted from the final rule.

Unreliable answers – While, we agree with the deferral of donors who appear to be under the influence of drugs or alcohol, or due to any other reason affecting the reliability of the donor's answers, we believe this should be managed by each institution's standard operating procedures. The AABB DHQ does include attention questions that would likely identify donors who are not able to provide reliable answers for various reasons. This proposal does not enhance the safety of blood products and should be deleted from the final rule.

21 CFR Section 630.10(h) – *How do you perform a physical assessment of the donor? You must determine that the donor is in good health based on the following, at a minimum:*

(1) *Temperature ...*

(2) *Blood pressure. The donor's systolic blood pressure must not measure above 180 millimeters of mercury or below 90 millimeters of mercury, and the diastolic blood pressure must not measure above 100 millimeters of mercury or below 50 millimeters of mercury. A donor with measurements outside these limits may be permitted to donate only when the responsible physician has examined the donor and determined that the health of the donor would not be adversely affected by donating.*

(3) *Hemoglobin or hematocrit determination for allogeneic donation.*

(i) *You must determine the donor's hemoglobin level or hematocrit value by using a sample of blood obtained by fingerstick, venipuncture, or by a method that provides equivalent results. Blood obtained from the earlobe is not acceptable; and*

(ii) *An allogeneic donor must have a hemoglobin level no less than 12.5 grams per deciliter of blood, or a hematocrit value no less than 38 percent. An autologous donor must have a hemoglobin level no less than 11.0 grams per deciliter of blood, or a hematocrit value no less than 33 percent.*

(4) *Pulse. The donor's pulse rate must be regular and between 50 and 100 beats per minute. A donor with an irregular pulse rate or measurements outside these limits may be permitted to donate only when the responsible physician has examined the donor and determines that the health of the donor would not be adversely affected.*

(5) *Weight. The donor must weigh a minimum of 50 kilograms (110 pounds) and must not have had an unexplained loss of greater than 10 percent of body weight within the past 6 months; and*

(6) *Skin examination*

Preamble, Section H. 2. Assessment of the Donor's Eligibility to Donate, b. The donor's medical history *Blood pressure (Proposed § 630.10(h)(2)) — For the purpose of this rulemaking, we would require under proposed paragraph (h)(2) that the collecting establishment determine not to be eligible a donor whose blood pressure measures above 180 mm of mercury or below 90 mm of mercury for the systolic value, and above 100 mm of mercury or below 50 mm of mercury for the diastolic value. These limits are currently an industry standard in use by many blood establishments. We are soliciting comments with supporting scientific data on the need for such limits on systolic and diastolic values, adverse events associated with donation that have been attributed to blood pressure. In particular, we are seeking comments with supporting scientific data on the necessity, or lack of necessity, of specific upper or lower blood pressure limits in blood donation, and any adverse events attributed to blood pressure and associated with donation. We are also seeking comments on the accuracy and interpretation of blood pressure measurements taken in the setting of blood and plasma donation.*

Hemoglobin or hematocrit determination (Proposed § 630.10(h)(3)).—“We are specifically soliciting comments and supporting data on the following:

- *Changing the minimum acceptable hemoglobin level to 12.0 grams per deciliter of blood or a hematocrit value of 36 percent as acceptable minimal values for female allogeneic donors;*
- *The possibility of adverse effects caused by the collection of blood and blood components from Allogeneic donors with such minimum hemoglobin level of 12.5 grams per deciliter of*

blood or a hematocrit value of 38 percent for males, and hemoglobin level of 12.0 grams per deciliter of blood or a hematocrit value of 36 percent for females, which are considered below normal by medical criteria; or if such decisions should be left to the discretion of the medical director of the collecting establishment on a case-by-case basis;

- *Establishing a more stringent interdonation interval; and*
- *The use of copper sulfate solution based methods as an appropriate method to determine acceptable hemoglobin levels.*

Recommendation – 21 CFR Section 630.10(h)(2) and (4) – We recommend that the requirements for upper and lower limits for blood pressure and pulse requirements be deleted from the proposed rule.

There is no evidence to support their inclusion and paucity of evidence is not a justification for mandating common practice that is not based on evidence. We feel that it is inappropriate for the FDA to enshrine criteria that are based on nothing but tradition. If upper and lower limits of blood pressure and pulse must be established, we urge that it be set by the establishment's medical director.

21 CFR Section 630.10(h)(5) – AABB recommends that the criterion for deferring a donor for an unexplained weight loss of greater than 10 percent of body weight within the past 6 months be deleted from the proposed rule.

Request for Comment on acceptable hemoglobin levels – The issue of changing the acceptable hemoglobin/hematocrit levels for males or females is controversial and requires further investigation. It is anticipated that some relevant data will become available from the REDS II study and should inform any subsequent guidance. The study aims to evaluate the effects of blood donation on iron and hemoglobin levels among donors. It also will help identify the optimal measures for predicting iron and hemoglobin depletions that lead to blood donor deferrals. Until the results of the REDS II study are published, we believe that it would be premature to specify changes to hemoglobin or hematocrit requirements in the final rule.

Background – Blood Pressure – Current FDA regulations state that blood pressure should be normal but do not specify the actual values. While the proposed values are ones commonly used by some blood collection facilities, the practice is not universal. Some facilities use similar but different criteria. In the UK blood pressure is not even measured at the time of whole blood donation. There is simply no data to indicate that the measurement of blood pressure, yet alone specific criteria, is useful in terms of donor safety. A single measure of blood pressure, especially in the setting of an anticipated blood donation, would never be used clinically to determine a donor's true blood pressure. Inaccurate determinations occur under stress, mismatch of the subject's weight and the cuff size used, ingestion of caffeine or decongestants, recent exercise, smoking, food intake, etc.

The suggested values for the upper limit of blood pressure, 180/100, whether commonly used or not, is entirely arbitrary. There is no evidence that otherwise healthy donors with elevated systolic blood pressures would be harmed by blood donation. There is little data on the effect of lower blood pressures. Some reports in the older literature suggest that the incidence of vasovagal reactions may be higher in donors with lower blood pressure levels. Ogata et al (Transfusion 1980;20:679) state that donors with lower diastolic blood pressure were more prone

to reaction. Kasprisin et al (Transfusion 1992;32:23) reported that donors with systolic pressure of 80-100 had a higher incidence of vasovagal reactions than did donors with systolic pressures of 120-140. However, other studies (Zervou et al, Transfusion Medicine 2005;15:389) found no relationship between either blood pressure or pulse and the incidence of vasovagal reactions. Even if it were true that donors with lower blood pressures had a slightly higher vasovagal reaction rate, it does not necessarily follow that they should be deferred from donation. There are many categories of donors well known to have somewhat higher reaction rates than others (e.g. first time donors, females, lower weight donors, younger donors) yet we do not hesitate to accept them for donation.

Pulse – Currently there are no FDA regulations concerning measurement of pulse in blood donors. Although AABB Standards do currently state that the pulse should be between 50 and 100 beats per minute, there are no data to indicate that this is appropriate. It is common for healthy people to have pulse rates below 50 beats per minute. It is also not universal practice to measure the pulse. Pulse is not determined in the UK. Health Canada has authorized Hema-Quebec to abandon the use of pulse in donor qualification based on data provided by Dr. Gilles Delage (personal communication Dr. Delage). In Dr. Delage’s study, 106 autologous donors were accepted for donation in spite of a pulse that did not meet the standard acceptance criteria, no adverse effects were seen. The rate of moderate and severe adverse reactions was no different in a series of over 300,000 donors drawn when pulse measurement was not part of the qualifying criteria (1995-1996) than it was in a series of over 600,000 donors drawn with such criteria in place. Finally, these investigators followed 2005 donors who were deferred for failing pulse criteria for 2-3 years and compared them to 2005 donors who donated on the same day but passed the pulse criteria. There was no significant difference in the incidence of cardiac events. Thus there is no evidence that the measurement of pulse, let along specific criteria, is useful in terms of donor safety.

The suggested requirement that the pulse be “regular” is even more problematic. It is common for normal donors to have sinus arrhythmia (a perfectly normal rhythm) or occasional extrasystoles, and deferring such donors would be entirely inappropriate. Even with more complicated rhythms, there is no evidence that drawing a unit of blood would result in harm to a donor who is otherwise healthy. We feel that the criteria for acceptability of donors with an irregular pulse (if the pulse is even measured) should be determined by the policies of the collection facility, under the guidance of the facility’s medical director

Unexplained weight loss – The medical/scientific rationale for the unexplained weight loss recommendation is not stated nor is it obvious. Weight in some individuals can fluctuate dramatically. Weight loss is not a very specific sign of a medical illness that could pose a safety threat to either the donor or the recipient. Medical conditions that might require donor deferrals are better identified though the use of other questions on the donor questionnaire.

There are also a number of practical problems with the proposed criterion for unexplained weight loss. Firstly, the proposed rule assumes that a donor will have accurately recorded their weight on multiple occasions in recent months. Secondly, it is unlikely that the individual donor will be able to easily compute whether their weight loss was less than or greater than 10%. For example, proper application of this proposed rule would require that a 150 pound donor who lost 15 pounds be deferred whereas a 160 pound donor with the same weight loss would be accepted. Given the variation in education level among donors, it is unrealistic to expect each donor to

reliably make this determination themselves. In practice, the donor screener would need to 1) ask about the absolute amount of weight loss; 2) ascertain the donor's previous baseline weight at various times during the previous six months and then 3) perform a calculation to determine the percentage weight loss. Even after this determination, a further assessment would need to be made about whether this weight loss was explained or unexplained; this is clearly a subjective evaluation. A situation could arise where the weight loss was explainable according to the donor's thinking, but was interpreted as unexplainable by the donor screener.

21 CFR Section 630.10(i) – *What additional requirements must you complete before determining the eligibility of the donor? Immediately before donation, you must obtain the following:*

(1) Proof of identity and mailing address. You must obtain proof of identity of the donor and an address where the donor may be contacted for 8 weeks after donation; and

(2) Donor's written statement of understanding. You must provide a written statement of understanding to be read and signed by the donor. You must establish procedures in accordance with Sec. 606.100 of this chapter to provide assistance to those unable to read the written statement of understanding. You must design those procedures to assure that the donor understands fully the material in the donor's written statement of understanding, and provide for a signature or acceptable substitute for a signature to indicate that understanding. The written statement of understanding must not include any exculpatory language through which the donor is made to waive or appear to waive any of the donor's legal rights. The statement must clearly state the following:

(i) The donor has reviewed the provided educational material required by Sec. 630.10(b) regarding relevant transfusion-transmitted infections, including the fact that relevant transfusion-transmitted infections present potential risks to the safety, purity, or potency of the blood supply;

(ii) The donor agrees not to donate if the donation could result in a potential risk to the safety, purity, or potency of the blood supply as described in the educational material;

(iii) A sample of the donor's blood will be tested for specified relevant transfusion-transmitted infections required in Sec. 610.40(a) of this chapter and for syphilis.

(iv) If any of the tests required in Sec. 610.40(a) of this chapter are reactive, the sample of blood will be tested further, as required in Sec. 610.40(e) of this chapter;

(v) If the donation is determined to be not suitable under Sec. 630.30(a) or if the donor is deferred from donation under Sec. 610.41 of this chapter, the donor's record must identify the donor as ineligible to donate and the donor must be notified under Sec. 630.40 of the basis for the deferral and the period of deferral;

(vi) The hazards and risks of the donation procedure or of hyperimmunization, if applicable; and (vii) the donor has the opportunity to ask questions and withdraw consent at any time.

Recommendation – We strongly recommend that the requirement to obtain an address where the donor may be contacted for 8 weeks after donation be deleted.

AABB agrees that donors should be adequately informed about the blood donation process and that there should be documentation that the donor has been so informed. However, we do not believe that this documentation requires the donor's written signature. We recommend that the

guidance document that will be issued to provide recommendations for compliance with the rule clarify that electronic records are an acceptable method for documenting a donor's statement of understanding.

Background – Mailing address – According to the US Census Bureau, more than 40 million of 282 million people move annually in the US, for a total of 14.19 percent each year. From a blood availability perspective, if 3-5 percent of these individuals were blood donors (per national donation estimates), a cohort of at least 123,000-204,000 donors would be expected to move each year, some of whom will move in the 8 weeks following a blood donation.

US Census Bureau data also show that most moves are by individuals within the 18-34 year age group. This would comprise students, young families, and many military personnel. From a donor recruitment and retention perspective, this is the most critical age group to retain and grow because of the aging of the donor population. Even a temporary decrease in donations by this group – because they cannot produce their expected new address on the day of donation – will not only reduce overall annual blood donations, but will also make it more difficult to maintain and increase the blood donor base as current donors, who are generally middle age, become ineligible to donate.

The impact of this requirement on spring blood drive activity on college campuses is especially troublesome due to mass movement of college students to other addresses for the summer. This can have a critical impact on blood availability during the summer months

It is assumed that the reason for this regulation is a concern about the ability to notify donors who have reactive infectious disease tests. According to the US Postal Service, which collects data for the National Change of Address file, most individuals who move do leave a forwarding address, and donors can be contacted through this mechanism. Also, although standard mail delivery has historically been the predominant means of contacting people, we believe that this is increasingly being replaced by newer communication technologies such as email and cell phones, and these can be used for notification purposes when necessary.

Donor's written statement of understanding – Although blood establishments have traditionally obtained donor signatures as part of the donation process, in the past there has never been a requirement to do so for whole blood or plateletpheresis donors. Many blood collection facilities are moving to computerized donor registration and screening processes. The reasons for doing this are twofold. First, to eliminate errors due to donor and staff failure to complete elements of the donor record (the computer system will not allow the process to advance until all requirements are completed); second, to move to a paperless system. Requiring a written signature defeats the purpose on both counts and will impede implementation of optimal error reduction strategies by blood establishments. Some of the computerized systems have already received FDA approval to proceed without either actual or electronic donor signatures.

The consent that donors traditionally have signed is an affirmation that the donor has read the informational materials, has answered the questions truthfully, understands that infectious disease testing will be done, and agrees to donate. In our modern era, these sorts of affirmations are commonly handled electronically and no written signature is involved. The same approach should suffice for blood donation.

As noted above, there has not previously been a regulatory requirement for a written signature for whole blood collection or for plateletpheresis donation. Although it is required under the current 21 CFR 640.61 for plasmapheresis donors, the regulation applies only to manual apheresis procedures that are not now routinely used for plasma collection. The informed consent referred to in part 640.61 is more than the affirmation of understanding at issue in the present discussion; it represents consent to undergo a risky procedure.

It is important to note that the requirement for a written signature was deleted from the AABB Standards a number of years ago in recognition that it was not necessary and that a paperless system would be desirable. We firmly believe that it is important to progress to paperless systems. Adding a requirement for a written signature to this process would not allow this to occur, it would provide no additional benefit, unnecessarily complicate the process, and insert an additional opportunity for error. We encourage the FDA to champion this forward thinking approach by clarifying that the donor's understanding can be documented in a number of ways, including the electronic methods described above.

21 CFR Section 630.15(a) – *What additional donor eligibility requirements are specific to Whole Blood?*

(1) Donation frequency. Whole Blood must not be collected from a donor more than once in 8 weeks if the donor participates in a single unit collection program; or more than once in 16 weeks if the donor participates in a double unit collection program, unless the donor is examined and certified to be in good health by a responsible physician at the time of donation and one of the following three conditions exist:

- (i) An individual presents a physician's prescription for therapeutic phlebotomy for medical reasons; or*
- (ii) The donation is for autologous use; or*
- (iii) The donation is a dedicated donation based on the intended recipient's documented medical need.*

(2) Therapeutic phlebotomy. When a donor who is determined to be eligible under Sec. 630.10(d) undergoes a therapeutic phlebotomy to promote the health of the donor, the container label must conspicuously state the disease of the donor that necessitated phlebotomy. However, no disease labeling is required under this section for a donation collected from a donor who meets all eligibility criteria and undergoes a therapeutic phlebotomy as ordered by a physician treating the donor for Hereditary Hemochromatosis, provided that you perform without charge therapeutic phlebotomies for all individuals with Hereditary Hemochromatosis.

Request for Clarification – This section discusses the continuation of the requirement that establishments collect a single unit of whole blood no more than once in 8 weeks or 16 weeks if two units of red blood cells are collected by an automated method. FDA is also proposing that a donor may donate sooner if the collecting establishment's physician examines the donor and certifies the donor to be in good health. We request clarification in the regulation that hemochromatosis is an exception to the 8 week or 16 week requirement. In addition, we request clarification in the regulations that hemochromatosis patients can be collected more frequently without a variance.

21 CFR Section 630.15(b) – *What additional donor eligibility requirements are specific to Plasma collected by plasmapheresis?*

(1) Physical examination and informed consent.

(i) In addition to the physical assessment required in Sec. 630.10(d), the responsible physician must examine the donor for medical conditions that would place the donor at risk during plasmapheresis. If the donor is determined to be at risk, you must defer the donor from donating. In a program of repeat plasmapheresis, i.e., collections occur more than once every 28 days, the donor must be examined on the day of the first donation or no more than 1 week before the first donation and at subsequent intervals of no more than 1 year.

(ii) When conducting the physical examination, the responsible physician must explain the hazards of the procedure to the donor. The explanation must include the risks of a hemolytic transfusion reaction if the donor is given the cells of another donor, and the hazards involved if the donor is hyperimmunized. The explanation must be made in such a manner that the donor may give informed consent and has a clear opportunity to refuse the procedure as required under Sec. 630.10(i)(2).

(2) Weight. You must weigh a donor at each donation.

(3) Total protein level. Before each plasmapheresis procedure, a donor must have a total plasma protein level of no less than 6.0 grams per deciliter and no more than 9.0 grams per deciliter of plasma sample or the comparable level for a serum sample.

(4) Examination before immunization...

(5) Deferral due to red blood cell loss. You must defer a donor from donating plasma for a period of 8 weeks after any of the following events...

(6) Exceptions to deferral due to red blood cell loss...

(7) Malaria. Freedom from risk of malaria is not required for a donor of Source Plasma.

Request for Clarification – 21 CFR Section 630.15(b)(1) – For plasmapheresis donors, the distinction between the statement of understanding (21 CFR 630.10(i)(2)) and the informed consent stated in this section should be clarified.

Recommendation – Some of the donor eligibility requirements for plasmapheresis provide no additional safety to the donor or recipient and should be removed from the final rule.

21 CFR Section 630.15(b)(2) – The requirement that the donor’s weight be determined at each plasmapheresis donation is necessary for the plasma volume nomograms; however weight should not be used as an indicator of general health.

21 CFR Section 630.15(b)(3) – The requirement for total protein should be reworded:

(3) Each firm shall have a plan acceptable to FDA to measure serum proteins and immunoglobulins by methods and frequency that assure that the donor’s health will not be seriously impacted by reduction in essential serum proteins. In the absence of a firm’s submission of specific proposal to FDA the use of serum or plasma protein measured at each donation and every four months along with a serum or plasma electrophoresis will be required. For the donor to donate, the total plasma or serum protein shall have a value of no less than 6.0 grams per deciliter. The acceptable upper limit may be established by the firm based on

applicable statistical analysis of test results on their donors. Values outside of these limits would require deferral until the donor's protein level is at an acceptable range.

Comment – 21 CFR Section 630.15(b)(7) – We agree with excluding Source Plasma donors from malaria-endemic deferral. We would also suggest that this approach be adopted for other parasitic diseases, which, due to the nature of Source Plasma donation and the manufacturing process, have no impact on product quality or safety.

Background – Informed consent – The proposed rule eliminates 21 CFR 640.61 Informed Consent, and proposed section 630.10 (i)(2) requires that donors sign a statement of understanding that includes a statement that the donor has been informed of and understands the collection procedure and the educational material. This would appear to replace the informed consent, however, proposed section 630.15 (b)(1)(ii) requires that the responsible physician explain the hazards of the procedure to the donor, and that the explanation must be made in such a manner that the donor may give *informed consent*. For plasmapheresis donors, the distinction between the statement of understanding and the informed consent should be clarified.

Donor weight – As addressed in our response to 21 CFR Section 630.10(h)(5) weight should not be used as an indicator of good health. Donors are asked at each donation if they are in good health and other questions to elicit specific information about the donor's health that might disqualify the donor from donating. Tracking donor weight for eligibility does not add valuable information beyond the donor history questions and medical screening. While weight is essential for the plasmapheresis volume nomograms, in contrast, whole blood donations should not be required to have the donor's weight recorded.

Total Protein – FDA proposes to continue to require a measurement of total protein and have a value of no less than 6.0 g/dL or no more than 9.0 g/dL. The basis for the upper limit is not clear. The basis for the lower limit is presumably to assure adequate protein levels in the blood prior to donation and that these levels are not seriously lowered by plasmapheresis. We agree with the concept that there should be laboratory measurements to assure that the donor is not adversely affected by serial donation and has adequate levels of certain essential proteins such as albumin and immunoglobulins. However, it is not clear that the 6.0 and 9.0 values are necessarily the correct ones by all measurement systems. In Europe, for example, IgG levels are measured.

Malaria and other comparable pathogens – The exclusion of Source Plasma donors from malaria-endemic deferral permits by logical extension, that this science-based approach could also be made applicable to syphilis and other similar pathogens which hold no relevance to the final products made from Source Plasma. Because malaria and a host of other pathogens do not impact plasma products or are removed by the processing, we suggest that a consistent approach be applied with the following guiding principles: an awareness of the distinctions between materials collected for direct transfusion and those of further manufacture, and the intended final use of the products. Anything that could be removed by filtration should not be a deferrable criterion.

21 CFR Section 630.20 – *You may collect blood and blood components from a donor who is*

determined to be not eligible to donate under Sec. 630.10(d) and 630.15, or deferred under Sec. 610.41 of this chapter only if:

- (a) *The responsible physician examines the donor and certifies in writing that the donor's health permits the collection procedure;*
- (b) *The collection is performed under the supervision of the responsible physician who is aware of the donor's health status; and*
- (c) *At least one of the following is met:*
 - (1) *The donation is for autologous use as prescribed by the donor's physician, and is not for allogeneic transfusion or for further manufacturing use;*
 - (2) *The donor is participating in a plasmapheresis program that collects plasma for further manufacturing use into products for which there are no alternative sources, and the collection program has received prior approval from the Director, Center for Biologics Evaluation and Research; or*
 - (3) *The donation is restricted for use solely by a specific recipient based on documented medical need and the responsible physician determines that the donation presents no undue medical risk to the recipient.*

Recommendation – We recommend that the language throughout this section refer to “responsible physician or physician substitute.”

In addition, the proposed requirement that a physician examines the donor and certifies in writing that the donor’s health permits the collection procedure, and supervises the collection procedure, should be deleted.

Background –The requirement that a physician examines the donor and certifies in writing that the donor is healthy enough to donate is not only unnecessary, but would severely disrupt the ability to provide patient care, especially for plasma therapy where there is not an alternative source or in the case of a donation restricted for use (directed donation) solely by a specific recipient based on documented medical need. With regard to directed donations the most common scenario in which this occurs is a platelet donor who has been selected on the basis of HLA type to donate for a specific patient. At presentation the donor’s hematocrit is 37%. It is perfectly reasonable under this circumstance for the physician to approve the platelet collection, and it serves no useful purpose to require that the physician to examine the patient. We thus feel that the proposed requirements are too restrictive when it comes to medical determinations by the collection facility physicians.

Autologous donors who do not meet allogeneic criteria are quite common; it is simply not practical for a blood center physician to examine all of these donors, some of whom are drawn at sites some distance from the central facility, or to be aware of the specifics of the reason for their allogeneic ineligibility. An autologous donor/patient’s health has already been assessed by their personal physician.

These issues are properly and adequately handled by the facility’s policies and procedures which spell out the specific circumstances under which the facility’s physicians should become involved.

21 CFR Section 630.25 – *You are not required to perform a physical examination of the donor for medical conditions under Sec. 630.15(b)(1), to perform a test for total protein under Sec. 630.15(b)(3), to determine the immunoglobulin composition of the serum or plasma under Sec. 640.65(b)(1)(i) of this chapter, or to review the laboratory data as required in Sec. 640.65(b)(2)(i) of this chapter, if:*

- (a) The donor has not donated Whole Blood in the preceding 8 weeks, Plasma by plasmapheresis in the preceding 4 weeks, or participated in a double Red Blood Cells unit collection program within the preceding 16 weeks;*
- (b) The donor has not donated more than 12.0 liters of plasma (14.4 liters of plasma for donors weighing more than 175 lbs.) in the past year;*
- (c) The donor is determined by the responsible physician to be in good health under Sec. 630.10(d); and*
- (d) The donor is not participating in an immunization program for the production of high-titer plasma.*

Request for Clarification – The intervals allowed between an infrequent plasma donation and whole blood, plasmapheresis and double red cells are defined. We request clarification on the interval allowed between an infrequent plasma donation and a platelet donation by apheresis.

21 CFR Section 630.30(a)(5) – *When is a donation suitable? A donation is suitable when:*
(5) For platelet components, you have taken adequate steps to assure that the donation is tested for bacterial contamination and found negative; and

Recommendation – The proposal to obtain a negative test result prior to determining a platelet donation to be suitable should be deleted. An appropriate requirement is for a “negative to date” test result at the time of distribution of the platelet, while the incubation continues.

Background – The language is ambiguous in that a culture-based bacterial test is not negative until completion of its incubation, a duration that is arbitrary and currently extends to the outdate of the product. This extended incubation allows an attempt at withdrawal of distributed, non-transfused platelets when a positive culture occurs late in storage. If applied as the proposed language suggests, it would be impossible to distribute a platelet before outdate. In current practice, cultured platelets are released as ‘negative to date’ while incubation is continued. The duration of incubation of a culture-based test before release will always be somewhat arbitrary, balancing adequate time to detect clinically significant bacterial contamination with the need to make platelets available for transfusion. This language should be deleted and the CFR should remain silent on this issue.

The language proposed in 630.30(a)(5) would include platelets derived from whole blood donations, that are not currently addressed in professional standards, and are not generally subjected to bacterial testing until surrogate methods are applied near or at release in the transfusion service. Systems exist that allow pooling of whole blood derived platelets before storage and testing with culture-based methods early in storage, as are used for apheresis platelets. These systems have not been enthusiastically embraced by collection facilities as they are operationally poorly suited to most collection facility component laboratories. The proposed language would operationally prohibit the use of platelets derived from whole blood and pooled

immediately prior to transfusion. These account for around 25% of platelet doses transfused in the US. It is inappropriate for FDA to require the implementation of these systems via the CFR without extensive public discussion of the issue.

Preamble Section D, 3. Testing for bacterial contamination for platelets and other transfusable blood components – *In some instances, specific bacteria identified as contaminants in a blood component could indicate an underlying bacteremia or serious illness in the donor. Therefore, we are also soliciting comments on: (1) Whether to require, in the context of testing of platelet components prior to release, the identification of the species of the bacterial contaminant and (2) whether to require donor deferral and notification when identification of the contaminant indicates possible endogenous bacteremia, and not contamination during collection and processing. Additionally, we are also considering whether to extend, to other blood components for transfusion, the requirement for testing for bacterial contamination, and donor deferral and notification based on the results.*

Response to request for comment – We consider both of these issues to fall within the purview of the collection facility's medical director as the practice of medicine. The standard of care already includes speciation of isolated bacteria and donor notification when felt to be medically appropriate, and regulation is not required in this area.

Background – No definition of endogenous bacteremia is provided, and we are aware of no bright line dividing an endogenous bacteremia from contamination, since the organisms involved overlap significantly. While the presence of a pathogen, e.g. listeria, is a clear cut indication for referral for evaluation of a donor, and the association of *Streptococcus bovis* with intrinsic colon pathology is well recognized and has resulted in early diagnosis of colonic lesions in platelet donors, these are the exceptions. On the other hand, both coagulase negative staphylococci and *Staphylococcus aureus* are well recognized as causes of native valve endocarditis in otherwise well individuals and could be considered endogenous, when it is accepted in the setting of platelet cultures that they are almost always contaminants from the skin. Are oral streptococci that commonly cause transient bacteremia and community-acquired endocarditis endogenous? A requirement for deferral, notification and referral for such an ill-defined spectrum of organisms can result in unneeded medical evaluation and stigmatization of donors for what we are certain is minimal return. These decisions should not be prescribed in CFR, but left to medical directors who can exercise reasonable clinical judgment.

Additionally, the agency is considering whether to extend, to other blood components for transfusion, the requirement for testing for bacterial contamination, and donor deferral and notification based on the results. It is not appropriate to extend requirements for bacterial detection to other components.

In the BaCON study (Kuehnert et al. *Transfusion* 2001;41:1493), the ratio of sepsis associated with RBC transfusion to that from apheresis platelets was approximately 1:50 (.2/million RBC vs. 10/million apheresis platelets). This is most probably due to the inhibitory effects of storage of RBCs at 4°C, rather than room temperature for platelets, on growth of the contaminating bacterial inoculum. In the 2005 National Blood Collection and Utilization Survey there were 1,527,000 apheresis platelet collections and 15,288,000 RBC collections (including RBC apheresis, autologous and directed). If one assumes the same culture approach, generally an aerobic and anaerobic bottle, extension of culturing to whole blood would require at least 10

times the investment in culture materials, incubators, computer interfaces, personnel, etc. as required for platelets to detect .02 times the risk.

It is not appropriate to extend requirements for bacterial detection to other components.

Current CFR language 640.3(c) – *Additional qualifications of donor; viral hepatitis. No individual shall be used as a source of Whole Blood if he has--*

(1) A history of viral hepatitis after the 11th birthday;

(2) A history of close contact within 12 months of donation with an individual having viral hepatitis;

(3) A history of having received within 12 months of donation, human blood or any derivative of human blood which the Food and Drug Administration has advised the blood establishment is a possible source of viral hepatitis.

Recommendation – We recommend removal of the current requirement for indefinite deferral of presenting donors with a history of viral hepatitis after the 11th birthday.

Background – A number of countries (for example, England and Australia) now require only a one-year deferral period for a history of viral hepatitis. There does not appear to be a good rationale for maintaining an indefinite deferral, given the properties of the relevant viruses, use of multiple screening tests for HBV and HCV and the absence of any chronic form of infection with HAV or HEV (with the exception of patients undergoing transplantation who may develop chronic HEV disease, but would not be eligible donors). Further, there no longer appears to be any evidence for residual transfusion-associated hepatitis with an infectious etiology. Finally, the putative “hepatitis viruses” GBV/C or HGV and TTV/SEN-V have not been found to be associated with clinical hepatitis.

21 CFR 640.21(a)(2) – *Under Sec. 630.10(i)(2)(vi) of this chapter, the statement of understanding must include a statement that the long-term effects of frequent apheresis are unknown.*

Recommendation – Delete section 640.21 (a)(2) to be consistent with the “Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods” dated December 2007 and to be consistent with practice for all other donated components.

Background – In its response to “Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods” (Docket No. 2005D-0330, 03 October 2005) AABB noted that no long term adverse effects have been reported to frequent apheresis, and that they do not believe it is necessary to include this statement with information provided to the donor. However, if a statement must be included, it is more accurate to indicate that there are no data to indicate any harmful effects. Discussions in the literature that address the possibility of long term adverse effects raise this as a speculative concern rather than a firm conclusion. The subsequently released “Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods” dated December 2007, makes no mention of a requirement to include

the above statement. Furthermore, the statement is not required for donors of plasma or red cells by apheresis or for whole blood donation, all of which share similar small unknown risks.

21 CFR 640.21(b) – *A donor must not serve as a source of platelets for transfusion if the donor has recently ingested drugs that adversely affect platelet function.*

Recommendation – The language should be rewritten:

(b) A donor must not serve as the sole source of platelets for transfusion if the donor has recently ingested drugs that adversely affect platelet function.

Background – A donor of apheresis platelets who has ingested drugs that inhibit platelet function should be deferred as described in “Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods” dated December 2007. However, donors of whole-blood-derived (wbd) platelets do not need to be deferred. A wbd platelet component from a donor who has ingested platelet inhibitory drugs would not be given as a single unit dose.

21 CFR Section 640.21(c) – *A plateletpheresis donor may donate at intervals shorter than 8 weeks provided:*

- (1) *The establishment performs a platelet count before starting the initial plateletpheresis procedure and before each subsequent procedure;*
- (2) *The platelet count required in paragraph (c)(1) of this section is greater than 150,000/microL;*
- (3) *The donor's post-donation platelet count is no less than 100,000 platelets/microL; and*
- (4) *The donor donates the following...*

Recommendation – We recommend that the language be reworded:

- (c) A plateletpheresis donor may donate at intervals shorter than 8 weeks provided:
- (1) The establishment performs a platelet count before starting the initial plateletpheresis procedure;
 - (2) The platelet count required in paragraph (c)(1) of this section is greater than 150,000/microL;
 - (3) The establishment has procedures in place that assure that donors will have a platelet count equivalent to or above 150,000/microL before collection and no less than 100,000/microL after the collection; and
 - (4) The donor donates the following...

Background – AABB believes the regulation should be less prescriptive in defining requirements for when platelet counts are taken but still require establishments to adequately monitor donors to be sure that they are within appropriate levels before and after donation. We agree that the platelet counts of donors before and after collection are important to donor health. In fact, the stated platelet counts of greater than 150,000/ μ L pre-donation and not less than 100,000/ μ L post donation are appropriate. However, various blood centers, and various collection devices used, approach the assurance of these targets differently. “Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods” dated December 2007 recognizes that platelet counts are not always known. However, it does

recommend that action be taken when the collecting establishment becomes aware of decreases in platelet count below 100,000/ μ L. Assurance that pre-donation platelet counts above 150,000/ μ L is also recommended.

As we discussed previously in our comments to the Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods, it is not usually a platelet count immediately before the collection that is completed, but a pre-collection sample that is drawn. “A pre-donation platelet count is only one of the ways recommended by the manufacturer and approved by FDA to set the target yield parameters. Other options include:

- Average of the last three venous platelet counts;
- Utilize the platelet count obtained from a pre-collection venous blood sample from the donor’s previous donations;
- Utilize average donor pre-platelet count for local donor populations; and
- Use the default count for the collection equipment being used.”

In addition, many establishments validate and regularly re-qualify devices to assure that target levels are within correct boundaries.

21 CFR Section 640.21(c)(4) – *A plateletpheresis donor may donate at intervals shorter than 8 weeks provided:*

(iii) For a double or triple component collection procedure, no more than one procedure within a 7 calendar day period.

Recommendation – Delete 640.21 (c) (4)(iii) in order to reduce the regulatory burden on blood collectors created by a restriction that is not evidence based.

Background – There is no evidence to support a regulatory requirement for a 7 day donation interval following collection of a double or triple product. As outlined in our response to the “Draft Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods” (Docket No. 2005D-0330, 03 October 2005), AABB is not aware of any evidence to support a position that donor safety is compromised under current donation policy that restricts donations to 24 times each year, requires a pre-donation count of >150,000 and an interval of 2 days between platelet donations. Adherence to these policies and to the device manufacturer’s instructions to ensure that there is not excessive plasma loss will provide adequate safeguards for donor safety and will preclude donation at an excessive frequency.

From an operational standpoint it will be exceedingly difficult, if not impossible, to track complicated donor eligibility algorithms using currently approved blood establishment computer software according to whether a double or triple product was collected. The “Guidance for Industry and FDA Review Staff on Collection of Platelets by Automated Methods” dated December 2007, includes language which creates a non-binding recommendation that “the interval between collection of a double or triple Platelets, Pheresis and any subsequent collection of Platelets, Pheresis should be at least 7 days.” Given the lack of scientific basis for this recommendation, it would be unwise to incorporate a 7 day restriction into the CFR. The Guidance process would allow blood collectors to more readily gain approval of a different protocol by validating the safety of more frequent donations.

Direct Final Rule/Proposed Rule: Revisions to the Requirements Applicable to Blood, Blood Components and Source Plasma, Docket 2007N-0264, August 2007. Definition of Plasma (21 CFR Section 640.30(a)(2)) amended.

(2) *The fluid portion of human blood intended for intravenous use which is prepared by apheresis methods as specified in the directions for use for the blood collecting, processing, and storage system including closed and open systems.*

Recommendation – In comments to the August 2007 docket the AABB Interorganizational Plasma Task Force proposed that the definition should be further amended to include further manufacturing use:

(2) The fluid portion of human blood intended for intravenous use *or further manufacturing use* which is prepared by apheresis methods as specified in the directions for use for the blood collecting, processing, and storage system including closed and open systems.

Background – We believe this modification of the definition for plasma facilitates interoperability for blood centers to assign plasma collected by apheresis to use for either transfusion or further manufacturing as needed. The modified definition is compatible with the AABB Interorganizational Plasma Task Force recommendation that FDA recognize a new product, Component Plasma. Comments to 21 CFR Section 640.34 (see below) provides a more in-depth discussion of this issue

21 CFR Section 640.34 Component Processing

Recommendation – Include requirements for Component Plasma previously submitted to the Office of Blood Research and Review, April 2007, and to docket 2007N-0264 “Direct Final Rule/Proposed Rule: Revisions to the Requirements Applicable to Blood, Blood Components and Source Plasma”, October 2007, and attached to this document.

Background – The AABB Interorganizational Plasma Task force has had several communications with the Office of Blood Research and Review regarding proposed licensure requirements for a product called Component Plasma. Excerpts are provided here as background.

April 2007 “...the issue of the use of infrequent plasmapheresis and concurrent plasma as an option for further manufacturing is a critical consideration today as blood centers seek to maximize the use of life-saving blood donations, whether the components are for transfusion or for the manufacture of plasma-derived therapies. The issue of maximizing blood donations is of utmost importance as blood centers seek to identify ways to minimize the likelihood of TRALI...The Task Force has also considered the different options available as the organizing point for the product and believe that donor criteria is an appropriate organizing point...Use of the totality of donor qualifications, frequency of collection, collection volumes and other donor oversight provisions appear the most reasonable approach to differentiating Component Plasma from Source Plasma.”

June 2007 “...Recent discussions at the HHS Advisory Committee on Blood Safety and Availability reiterated the importance of increasing the supply of plasma available for therapeutic use. Concurrent collection of recovered plasma (that, in fact, is the same quality as FFP) to be used for fractionation could have a positive impact on this issue. Fractionators report they currently see difficulty on the part of recovered plasma suppliers to meet obligations for recovered plasma due to the shift to automated platforms.

We believe that there must be a pathway available that will allow concurrent FFP to be converted to recovered plasma (plasma for fractionation) when it is not needed for transfusion inventories. Blood establishments view this as an ethical issue and again ask for assistance from FDA in establishing this pathway. It is vitally important that the pathway recognize the donor suitability requirements and donation frequencies used in blood centers and allow interchangeability at the blood center level between plasma for transfusion and plasma for fractionation based on need. We view that this can best be accomplished by modifying the definition of Plasma in Title 21, Code of Federal Regulations (21 CFR), Subpart D, to include plasma for fractionation as well as plasma for transfusion.

With increased dependence on automated collection platforms to meet the ever-present demand for blood products, blood centers need the same flexibility in managing plasma inventories for transfusion and for manufacturing that they have with manual collections. These processes should not be limited based on intent at time of collection. Serious consideration should be given to plasma availability for both transfusion recipients and for recipients of therapeutics proteins to avoid shortages of such life-saving products.

The task force respectfully requests that FDA initiate the process for updating existing regulations to reflect the current technology of blood collection. In the interim, we ask for assistance in obtaining a product name and corresponding code for Source Plasma collected in an *infrequent* program, and consideration of an exception to 21 CFR 640.30 under 21 CFR 640.120 to include the option of collecting plasma to be used for fractionation. These issues have very high priority to our community. Timing is critical as blood establishments are currently taking measures to mitigate TRALI in transfusion recipients and continue their move toward blood collection utilizing automated methods.”

Data submitted with the June 2007 letter – “As noted in the 2005 AABB Nationwide Blood Collection and Utilization Survey Report (2004 data), approximately 824,000 units of red cells were produced using automated methods. Since the volume of red cells collected did not significantly change, each red cell manufactured by automation displaced one whole blood collection. Demand for FFP and cryo-poor plasma for transfusion remained relatively stable during this period and was satisfied by approximately 29% of whole blood collected. The remaining plasma was available for further manufacturing. Recent data (2006) from a subset of US blood collectors (BCA member centers representing 30% of the supply) show red cell automation rates at 18%, representing an absolute amount equal to that seen for the entire blood collection system in 2004. It is thought that the entire market is capable of reaching red cell automation levels of 20% in the near future. When this occurs, 3 million units of whole blood will be replaced, leading to a loss of approximately 825,000 liters (3 million x 275mL) that would be available for further manufacturing.

Further data in the AABB report document the increased reliance on apheresis platelets collected by automation to meet current demand. But, from the more than 1 million plateletpheresis procedures performed in 2004, only about 25% collected a concurrent plasma because this product can only be used for transfusion and not further manufacturing. It is estimated that nearly 70% of these procedures could, in theory, produce an additional unit of concurrent plasma, resulting in over 250,000 liters of plasma for further manufacturing.”

21 CFR Section 640.65(b)(1)(i) – *Except as provided under Sec. 630.25 of this chapter, a sample of blood must be drawn from each donor on the day of the initial physical examination or plasmapheresis, whichever comes first, and at least every 4 months thereafter. A serological test for syphilis, a total plasma or serum protein determination, and electrophoresis or quantitative immuno-diffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum, must be performed on the sample.*

Recommendation – We believe that the regulations should allow flexibility in protein monitoring. See comments elsewhere in this document regarding proposed 21 CFR Section 630.15(b)(3).

21 CFR Section 640.72(a)(3) – *The original or a clear copy of the donor's written statement of understanding for participation in the plasmapheresis program or for immunization.*

Recommendation – Guidance material should provide recommendations for use of electronic records to satisfy this requirement. Such a recommendation will be in agreement with proposed 21 CFR Section 630.10(i)(2) that allows for a “signature or acceptable substitute for a signature to indicate that understanding”.

21 CFR Section 640.72(a)(4) – *Documentation by the responsible physician that the donor is in good health under 630.10 and 630.15 of this chapter on the day of examination; such documentation must address the eligibility of the donor as a plasmapheresis donor and, when applicable, an immunized donor.*

Recommendation – Guidance material should clarify that trained personnel, including the physician substitute, are appropriate to make this determination. See comments elsewhere in this document to 21 CFR Section 630.5(a)-(d).

21 CFR Section 640.73(a) – *If a donor has a fatal reaction which, in any way, may be associated with plasmapheresis, you must notify the Director of the Center for Biologics Evaluation and Research by telephone as soon as possible.*

Recommendation – We recommend that the language reflect what is currently in 21 CFR Section 606.170(b). Proposed 21 CFR Section 640.73(a) should be reworded:

(a) – If a complication of donation is confirmed to be fatal, you must notify the Director of the Center for Biologics Evaluation and Research by telephone as soon as possible.

Background – The proposed regulatory language is too broad and would greatly increase the reports that must be submitted. To require a report of a fatality that “in any way” can be associated with plasmapheresis is extremely burdensome and provides no benefit beyond the current requirements of 640.73(a) to report complications of donation that are confirmed to be fatal.

21 CFR Section 640.73(b) – *If a donor enrolled in an immunization program for the collection of Source Plasma under this subpart has an adverse experience related to your administration of the immunizing agent, you must report the event to FDA:*

(1) *By telephone, facsimile, express mail, or electronic mail as soon as possible, if the adverse experience is a serious or life threatening adverse experience, as described in Sec. 600.80(a) of this chapter; or*

(2) *In an annual report, if the adverse experience is neither serious nor life threatening. Such a report is due to FDA on the anniversary of FDA's approval of your immunization program.*

(c) *You must follow up the initial report required under paragraphs (a) and (b)(1) of this section by submitting a written report of the investigation to the Director, Office of Compliance and Biologics Quality, Center for Biologics Evaluation and Research, within 7 days of your first learning of the donor's reaction. (See § 600.2 of this chapter.)*

Preamble, Q. Reporting of Donor Reactions (Proposed Sec. 640.73) – *Because manufacturers of blood and blood components are currently exempt from the safety reporting requirements under Sec. 600.80, we do not receive adequate information to monitor and assess safety-related information (other than fatalities) concerning donors enrolled in immunization programs and the collection of Source Plasma by plasmapheresis. Such information is essential for evaluating our scientific and regulatory policies and for monitoring industry practices and their implications on donor and blood safety.*

Recommendation – We recommend that this requirement not be included in the Final Rule on the basis that no valuable data will be forthcoming under the proposed reporting of adverse events for immunizing agents such as red cells or vaccines. Vaccine events are already reported to the Vaccine Adverse Event Reporting System (VAERS) and as necessary to the manufacturer as required in 21 CFR § 600.80. Currently, red cells are exempt from the requirement. In view of the low risk of adverse events and the ability of FDA investigators to access these reports on inspections, we believe that exemption should be continued.

Background – We believe that industry data will become available that will support current observations that reactions are infrequent and generally mild.

21 CFR Section 640.120(b) – *In a public health emergency, the Director may issue an exception or alternative to any requirement in subchapters C and F of chapter I of title 21 of the Code of Federal Regulations regarding blood, blood components, or blood products, if a variance under this section is necessary to assure that blood, blood components, or blood products will be*

available in a specified location to respond to an unanticipated immediate need for blood, blood components, or blood products.

Recommendation – We believe that this proposed section should include areas in which the FDA is willing to grant a variance. We recommend the section be modified as follows:

(b) Several examples of variances that would be considered are:

(1) Decreased interdonation interval provided the donor meets other criteria as specified in section 630.10

(2) Allogeneic donation hemoglobin/hematocrit level of ≥ 11 g/dL / 33% provided the donor meets other criteria as specified in section 630.10.

Background – We acknowledge that the FDA has responded in the recent past with guidance to the blood community during public health emergencies. However, if specific variances to current regulations were known in advance, establishments could plan appropriately. This would enable a blood establishment to further prepare by modifying BECS configurations and testing, modifications to standard operating procedures, and the necessary training, all within an acceptable cGMP environment.

AABB strongly supports initiatives that improve the safety of patients and donors and stands ready to interact with FDA as necessary. AABB requests that FDA carefully consider product availability and safety issues when evaluating the requirements put forth in this final rule.

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

Sincerely,



Karen Shoos Lipton, JD
Chief Executive Officer

Attachment (see below)

Proposed Requirements for Component Plasma

April 2007

I. Product Name

The new name shall be Component Plasma.

II. Donor Qualification

The requirements for donor qualification shall be the same as those used for allogeneic Whole Blood. For Component Plasma collected concurrently with the automated collection of cellular products for transfusion or by apheresis, FDA Memorandum of March 10, 1995, "Revision of FDA Memorandum of August 24, 1982: Requirements for Infrequent Plasmapheresis Donors" applies.

III. Method of Preparation

Component Plasma shall be prepared in one of three ways: 1) by separating plasma from Whole Blood, 2) from infrequent plasmapheresis concurrent with the automated collection of cellular products for transfusion, or from infrequent plasmapheresis, and 3) by converting plasma for transfusion to Component Plasma.

Component Plasma prepared by separation from Whole Blood may be separated at any time during the dating period for Whole Blood. (However, it must be labeled as to the time of preparation. See Section V., Labeling)

Plasma for transfusion may be converted to Component Plasma at any time during its dating period, or up to one year after its outdate as a transfusable component, provided it meets all requirements for Component Plasma.

IV. Expiration Date

The expiration date of Component Plasma shall be three (3) years from the date of collection.

V. Testing for Infectious Disease

Component Plasma shall be subject to the same requirements for infectious disease testing as allogeneic Whole Blood with two exceptions: 1) a negative test result for anti-HBc is not required, and 2) anti-HTLV I/II is not required to be performed.

VI. Labeling

Labels for Component Plasma must contain the following information:

Product Name

The proper name of the product: “Component Plasma”

Statement of Freezing Time*

“Frozen Within ___ Hours After Phlebotomy”

Caution Statement

“Caution: For Manufacturing Use Only into Injectable Products”

Product Code

From Uniform Labeling Guidelines or ISBT 128

Amount

The total volume or weight of plasma

For Whole Blood derived Component Plasma

The name and volume of source material, e.g., “From 500 mL CPD Whole Blood.”

For Component Plasma collected by plasmapheresis

The total type and volume of anticoagulant used.

Storage Temperature

Store at –18 C or colder.

Facility Identification

Name, address, and license number of collection facility, and name, address, and license number of institution where separated (if different than collection facility).

Testing Statement

The statement “A sample from each donation has been tested by FDA-licensed test and found negative for antibodies to human immunodeficiency virus (anti-HIV-1/2), hepatitis C virus (anti-HCV), and nonreactive for hepatitis B surface

* This proposal does not specify freezing temperature and freezing within a specific time frame. Because of the multiple types of products prepared from **Component Plasma**, there is no one temperature or freezing time which is appropriate. Rather, it is important to specify the temperature and time on the label so that the fractionator can determine that the **Component Plasma** is suitable for the intended use.

antigen (HBsAg). Licensed nucleic acid tests (NAT) for HCV RNA and HIV-1 RNA have been performed and found to be nonreactive. A serologic test for syphilis has been performed and found to be nonreactive.”

If HTLV I/II testing has been performed the statement “found negative for antibodies to human T-cell lymphotropic virus (anti-HTLV-I/II)” should be included in the testing statement.

Collection Date

Month, date, and year.

VII. Component Retrieval

The requirements for component retrieval (based on subsequent test results or other donor information) shall be the same as those currently required by FDA for Source Plasma or recovered plasma.

VIII. Records

Records shall be retained for 10 years from the date of collection. Records related to traceability of donor, plasma units, and recipients shall be retained for 30 years.

Additional comments

This proposal assumes that Short Supply Agreements will no longer be necessary once licensure of Component Plasma is available.

Currently, the collection date is noted on the label of recovered plasma. We propose continuing this practice, but once an expiration date is established for Component Plasma, it would be acceptable to require expiration date and / or collection date based on the manufacturer’s requirements.