Plasma Protein Therapeutics Association

July 29, 2015
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VIA E-MAIL
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Dear Dr. Epstein:

I am writing in follow up to our telephone conversation of June 22, 2015. The call was initiated by PPTA to alert you to a major flaw in FDA's codifying our inventory hold standard. During that conversation, you suggested that PPTA submit a proposal to right the wrong imposed by the addition of a 60-day quarantine in the regulations for collectors of Source Plasma.

MISINTERPRETATION OF PPTA'S VOLUNTARY STANDARD

The preamble to the Final Rule states, "Consistent with current industry standards, we have also finalized the inventory hold provision . . . to require establishments to hold Source Plasma . . . in quarantine for a minimum of 60 days."[1] This statement, in the context of requirements for the collectors of Source Plasma, is materially incorrect. Current industry practice is effected through the PPTA voluntary standards program, Quality Standards of Excellence, Assurance and Leadership (QSEAL).[2] **The QSEAL program is a standards program that is applied to fractionators of Source Plasma, not collectors.** It decrees that fractionators will ensure that units of Source Plasma are held in inventory for at least 60 days from the time of collection and not released for further manufacture until after the expiration of the 60-day hold period. The standard has been in place since the inception of the PPTA voluntary standards program. Manufacturing systems in place for U.S. and European fractionators are based on the provisions of that inventory hold standard. Changing the responsibility for the "hold" from the fractionator to the collector will represent a major disruption in the operations of both collectors and fractionators. The fact that the standard was misinterpreted in the proposed rule was included in PPTA's August 4, 2008, comment letter to the docket.[3] In our response to the proposed rule, PPTA advised, "PPTA notes that the proposed regulation, as written, is a requirement for the collector as a release test for the plasma

[1] *See* FR Notice, 80 Fed. Reg. 27973, 29844 (May 22, 2015)
[2] Quality Standards of Excellence, Assurance and Leadership (QSEAL). Plasma Protein Therapeutics Association website. http://www.pptaglobal.org/safety-quality/standards/qseal. Accessed July 20, 2015
[3] *See* Attachment 1 at 40-1

not as a manufacturing requirement prior to use of the plasma in manufacturing, as is the case for the PPTA voluntary standard."[4] In the preamble to the final rule, FDA did not address that concern at all. Instead, it chose to focus on where plasma could be stored and the definition of quarantine but not the primary concern that assigning responsibility to the collector as opposed to the fractionator would not be in conformance with the voluntary standard and would add appreciable burden.[5]

DECENTRALIZATION COMPLICATES QUALITY AND CONTROL SYSTEMS

For nearly two decades, PPTA's inventory hold standard has been managed and managed well by a limited number of fractionation facilities. FDA's final rule will decentralize that process to over 500 U.S. Source Plasma collection facilities. This disruption will require changes in: collection facilities and their employees with upgrades to facilities needed and additional hiring and training of staff; contracts between collection facilities and fractionators with possible addition of off-site storage facilities (if there is even adequate capacity for such storage in the U.S.); training and quality agreements between collection facilities and off-site storage facilities if those off-site storage facilities will attempt to perform the necessary lookback retrievals; regulatory filings with wait time for review and perhaps inspections; and your own regulatory approach including the addition of multiple filings for approving changes in manufacturing, conducting inspections to verify conditions and compliance, and routine monitoring. We cannot understand why you would upend a nearly two-decades old system with an excellent record of compliance to introduce alternative measures that are sure to increase burden on all parties and may result in a process that does not work as smoothly or as well as the current system.

SCIENTIFIC RATIONALE LACKING FOR INCLUSION IN REGULATIONS

In PPTA's 2008 response to the 2007 proposed rule, we explained that the inventory hold standard was introduced prior to the addition of NAT testing.[6] Prior to the addition of NAT testing, the units of plasma collected during the ramp-up phase before a seroconversion could contain appreciable virus and unless interdicted would increase the viral load of a manufacturing pool. Subsequent to NAT testing, this is no longer true. While PPTA has retained the inventory hold standard as an additional safeguard in the manufacturing of plasma protein products, we recognize that its value in terms of protecting the manufacturing pool is not the same as when it was introduced.

In the preamble to the final rule, FDA stated, "We solicited comments and supporting data in the proposed rule on whether other requirements would achieve the same results as these practices. We did not receive responsive comments and data."[7] We respectfully disagree. PPTA, in explaining that the standard was introduced prior to

[4] *See id*. at 40
[5] *See* 80 Fed. Reg. 29884
[6] *See* Attachment 1 at 40
[7] *See* 80 Fed. Reg. 29883

NAT testing, challenged FDA, "introduction of the 60-day inventory hold into regulations should require the Agency to prove that the 60-day inventory hold is necessary to assure the safety of plasma protein therapies."[8] FDA failed to address this comment when codifying 21 CFR 640.69(f) *Hold.* Instead, FDA continued to rely on the 1998 U.S. General Accounting Office (GAO) report.[9] This report includes data that were collected nearly 20 years ago, again before the institution of NAT testing, and for Source Plasma use data from a 4-month period in 1997 only.

The U.S. government's own scientists have affirmed the safety of plasma protein products. Dr. Edward Tabor, then an FDA scientist, published in 1999, an article that used the GAO data but presented it in the framework of modern fractionation processes. In this context, Dr. Tabor reported that products are safe from risk from hepatitis B, C and HIV-1.[10] Dr. Tabor's publication acknowledged that "there has been no transmission of these viruses since the end of 1987; the sole exception is IGIV, by which there has been no transmission since 1994."[11] Dr. Harvey J. Alter, renowned NIH scientist, in advocating for pathogen inactivation for blood components before the Advisory Committee for Blood Safety and Availability, stated, "Universal solvent-detergent treatment has rendered the formula that the formerly, most risky of blood transfusion products, plasma and plasma derivatives, will now be the safest."[12] He reiterated his views the next year at a Blood Products Advisory Committee meeting.[13] In spite of the long safety record of plasma protein products, there continue to be viral transmissions by blood components for transfusion.[14,15] The blood components that transmitted infections were all donated by FDA's comparator population used in arguments to insist on more stringent safety measures for "paid" Source Plasma.[16]

We must ask what problem FDA is attempting to solve in 2015 by instituting this regulation, which does nothing to increase the safety of plasma protein products, is inconsistent with current practices, may give an unfair and unwarranted competitive

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[8] *See* Attachment 1 at 40

[9] U.S. General Accounting Office, Report to Chairman, Subcommittee on Human Resources, Committee on Government Reform and Oversight, House of Representatives. *Blood Plasma Safety: Plasma Product Risks are Low if Good Manufacturing Practices are Followed*. 1998. http://www.gao.gov/assets/230/226266.pdf. Accessed July 21, 2015

[10] Tabor E. The epidemiology of virus transmission by plasma derivatives: clinical studies verifying the lack of transmission of hepatitis B and C viruses and HIV type 1. *Transfusion* 1999; 39: 1160-8

[11] *See id.* at 1166

[12] *See* A reductionist's view of pathogen reduction [transcript]. *33rd meeting of the U.S. Department of Health and Human Services' Advisory Committee on Blood Safety and Availability,* January 9, 2008

[13] *See 100th meeting of the U.S. Food and Drug Administration's Blood Products Advisory Committee* [transcript], April 28, 2011

[14] Dwyre DM, Fernando LP, Holland PV. Hepatitis B, hepatitis C and HIV transfusion-transmitted infections in the 21st century. *Vox Sang* 2011; 100: 92-8

[15] Centers for Disease Control and Prevention (CDC). HIV transmission through transfusion—Missouri and Colorado, 2008. MMWR Morb Mortal Wkly Rep. 2010; 59(41): 1335-9

[16] *See* 80 Fed. Reg. 29883

advantage to suppliers of "unpaid" plasma, and will lead to increased burden on our industry and resultant costs.

BURDEN AND COSTS ASSOCIATED WITH REGULATION

While FDA's presumed goal in promulgating regulations is to ensure or enhance safety and efficacy of its regulated products irrespective of costs, we would be remiss if we did not point out the inaccuracy that "this final rule is not a significant regulatory action. . . ."[17] Additionally, this rule will affect small entities disproportionately in sharp opposition to FDA's assertion, "Because the costs associated with this rule are expected to be minimal, the Agency certifies that this rule will not have a significant economic impact on a substantial number of small entities."[18] Some independent plasma collectors may not survive the burden of attempting to comply with this regulation.

This rule upends the industry with respect to its current practices in managing the PPTA voluntary standard for inventory hold. Substantial investments will need to be made to shift the responsibility of the 60-day hold to the collection facility. The majority of the source plasma collection centers in the USA are owned by fractionators, while there are over 50 centers that are owned by independent operators. The rule as it is written now will lead to the closure of a significant number of centers, reduce the availability of high quality source plasma and as such reduce the availability of plasma protein therapies. This is an unintended consequence of the rule and requires correction.

Since the voluntary standard makes the hold part of the manufacturing process, the implementation of the final rule as written also requires changes in infrastructure and personnel in addition to contracts and the controls needed to effect the change in manufacturing and maintain compliance. While the preamble to the final rule provides that "an establishment may store the product at an appropriate off site facility during the 60-day Inventory Hold,"[19] there is no assessment as to the feasibility of transferring that responsibility from the fractionators to the collectors. Currently, collection centers are not equipped to store plasma for 60 days or more. Generally shipments are being done every week or bi-weekly. At present, we know that off site storage facilities are not located conveniently to facilitate such storage; even if such facilities could be secured, we are doubtful that they would have sufficient capacity. Especially for the smaller centers, it will be impossible to build off-site facilities and continue operating because of the extra financial burden.
In addition to the concerns described above with respect to quality and control systems, investments would be needed in information technology systems, including the donor management systems and logistics systems; standard operating procedures; transportation costs for shipping to and from the storage facility; insurance for off site

[17] *See id.* at 29887
[18] *See id.*
[19] *Id.* at 29884

storage; and staff (either company or contract) to manage the off-site inventory. Also, both the FDA and the European Medicines Agency require inspections of facilities that cull lookback units in addition to storing plasma. These regulatory requirements would increase the time to approval to use new facilities and costs. Unlike traditional pharmaceutical products, the majority of costs in the manufacturing of plasma-based protein therapies is represented by manufacturing costs and raw materials (57% v. 14%).[20] The increased costs resulting from decentralizing the inventory hold described above may have a significant impact on patient access.

FDA HAS OPTIONS

We respectfully ask that FDA remove 21 CFR 640.69(f) *Hold* from the final rule, Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use. Clearly, in 2015, the scientific rigor to introduce such a drastic and burdensome requirement to collectors of Source Plasma is not met. Should FDA want to acknowledge inventory hold in its regulatory activities, FDA has options that will not upend the industry and mis-apply the industry standard for inventory hold. Unique among regulators, FDA regulates both starting material (plasma) and the finished plasma protein products. FDA has the power and the authority to institute restrictions on use of plasma at the fractionator via its licensing authority. Using this option would at least mimic current industry practices and PPTA's inventory hold standard.

We hope that we will be able to resolve this mis-application of PPTA's industry standard for inventory hold from a responsibility of the fractionator to the collector of Source Plasma through administrative channels. I am available to discuss this issue further with you. While the effective date of the regulation is May 2016, it is imperative that we correct this wrong in a timely manner to prevent unwarranted burden to our industry.

Sincerely yours,

Jan M. Bult
President & CEO
Attachment

[20] Plasma Procurement and Safety. Marketing Research Bureau website. http://marketingresearchbureau.com/plasma-industry/current-uses-affecting-the-plasma-industry/. Accessed July 21, 2015

Plasma Protein Therapeutics Association

Attachment 1

Date: August 4, 2008 **VIA WEB & USPS**
Reference No.: FDAA08008

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

SUBJECT: Proposed Rule: Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use [Docket No.:2006N0221]

Dear Sir or Madam:

The Plasma Protein Therapeutics Association (PPTA) is pleased to provide these comments on the Food and Drug Administration's (FDA) Proposed Rule on "Requirements for Human Blood and Blood Components Intended for Transfusion or Further Manufacturing Use", [hereinafter referred to as Proposed Rule]. PPTA is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin which is used in emergency room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

PPTA comments are listed in order of the presentation of the Proposed Rule and in the following format:

Proposed CFR Section – language of proposed rule.

Preamble Requests, page number – any additional information sought by FDA and corresponding page number from Federal Register, Volume 72, No. 216 (November 8, 2007).

Recommendation – PPTA's recommendation or clarification of Proposed Rule with rationale or request for clarification.

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I. CFR 21 § 606.3 Definitions

Proposed 21 CFR § 606.3(a)

Blood Component means a product containing a part of human blood separated by physical or mechanical means.

Preamble Requests, p. 63421

No request for additional information

Recommendation

PPTA recommends that the definition for "blood component" include a cross reference to the CFR sections in which specific blood components are defined. The current proposed definition fails to impart the complexity of specific components and their intended uses. For instance, the current proposal for blood components encompasses, as examples, Platelets, Red Blood Cells, Fresh Frozen Plasma, Recovered Plasma, and Source Plasma. However, there is little similarity amongst these products, other than they are all derived from human blood. Source Plasma is a starting material for the fractionation of plasma-derived therapies. A distinction that Source Plasma is not like other blood components is necessary, as requirements for donor eligibility and testing for Source Plasma are different than other blood components used for direct transfusion. Definitions with regulatory impact and legal import need to clearly state what a component is and how it is used to ensure that there continues to be a complete understanding of the differences between blood components for transfusion, as opposed to those for further manufacturing.

II. 21 CFR § 606.160 Records

Proposed 21 CFR § 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 (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 § 630.10(f) and (g) (1) through (g) (6) of this chapter, or deferred based on test results under § 610.41 of this chapter.

Preamble Requests, p. 63420

FDA seeks comment 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 § 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; the technical feasibility of complying with the proposed requirement; and the feasibility of sharing donor deferral lists between licensed establishments for deferrals required by the FDA.

FDA also seeks comment on whether a provision requiring that donor deferral records be used and disclosed only for purposes consistent with subchapter F of 21 CFR Chapter I.

Recommendation

PPTA recommends the Agency maintain the current requirements under 21 CFR § 606.160(e). The Agency's proposals for uniform usage of a donor deferral registry (DDR) present a host of issues for many PPTA member companies. First, a significant proportion of the Source Plasma collection industry would find the Agency's proposed requirements unworkable, even given the usage of the current National Donor Deferral Registry (NDDR). Second, the lack of clear definition in terms of the operational capacity expected of the DDR program in the Proposed Rule present further problems.

Part of the confusion that would inhere in a system that attempted to fulfill the requirements of the proposed language would be a lack of clear distinction about ineligibility and deferral. Deferrals for a parameter such as low protein, which is something that can be corrected in a short period of time, would never be able to be administered as contemplated by the Proposed Rule. However, even if each and every juncture for deferral were to be identified via regulation and placement on a national deferral list, the operational aspects would be impossible to administer. Some deferrals have automatic "sunsets," such as time periods following an event, but other deferrals require some type of assessment, e.g., unacceptable temperature reading, in order to clear the deferral. These are all general examples of the need for a system that is centered on the individual collection centers, rather than establishing a centralized system that would hinder effectiveness of the systems already in place and functioning quite well.

PPTA believes it is important to take this opportunity to clarify the functions of the National Donor Deferral Registry (NDDR), operated by PPTA and its member companies, as there appears to be confusion regarding its operation and capacity. The NDDR is a web-based database containing information on all Source Plasma donors who have tested reactive for HCV, HBV or HIV at any International Quality Plasma

Program (IQPP) certified plasma donation center in the United States and Canada. Only donors who have received reactive test results are listed in this database, as it is a database for these permanent deferrals only.

The NDDR should be understood to be a system that is extraordinarily effective for what it is intended to do: holding information on donors that have been permanently deferred for one of the three reactive markers. Inclusion of temporary deferrals is not within the contemplation or capabilities of the NDDR, and deferrals for reasons other than reactive test results would dilute the purpose and effectiveness of the system and of the industry's standards. PPTA members, and others, have created efficient and safe operational systems around the NDDR's use, and any disruption of that intended use would have dramatic consequences far outside the intended scope of the database.

The Agency asked for comments with regard to confidentiality of information relevant to a DDR. Confidentiality of information is of extraordinary importance to the industry. Each company uses its own best methods for handling confidential information consistent with its operational policies and procedures in submitting relevant information to the NDDR.

The proposed FDA requirement would appear to make the entire content of the NDDR available, dramatically sacrificing security of information for no added value in terms of safety or quality. The NDDR itself is *never available in its entirety to its users.* When an NDDR check is performed, the potential donor is checked by the database; if a record is present, the establishment performing the check is informed that the record is indeed present. No other information is shared, and no one has access to the database without legal compulsion, such as a subpoena.

We would recommend that companies be allowed to continue to devise their own methods for ensuring confidentiality of information relevant to the submission of information to the NDDR, or in terms of the company's own internal systems already designed to comply with relevant Federal and state legal requirements. One is the above-stated reason of proprietary practices, policies and procedures. A second reason is that there are other Federal agencies, such as the Federal Trade Commission, currently tasked with promulgating rules and guidance documents protecting consumer information and establishing confidentiality requirements nationally, implementing Congressional statutes and policy. The third reason is that companies also require the flexibility to comply with different requirements installed by state governments, pursuant to the state police powers. Because of the national, and at least multi-state, scope of the majority of PPTA member companies, organizations must adapt to the local requirements as well. Additional requirements imposed by the FDA outside of its central domain of expertise could lead to significant legal and operational hurdles. In conclusion, each licensed establishment is best situated for determining the requirements for complying with national, state, and local laws and ordinances related to confidentiality of information.

III. 21 CFR § 610.40 Test Requirements

Proposed 21 CFR § 610.40 Test Requirements

(*a) Human blood and blood components. Except as specified in paragraphs (c) and (d) of this section, and except for syphilis, which must be tested under § 610.40(i), for each donation of blood and blood components intended for use in preparing a product, including donations intended as a component of, or used to prepare a medical device, you, an establishment that collects blood and blood components, must test:(1) For evidence of infection due to the following relevant transfusion transmitted infections described in § 630.3(g)(1)(i) through (g)(1)(iv) of this chapter: (i) Human immunodeficiency virus, types 1 and 2; (ii) Hepatitis B virus; (iii) Hepatitis C virus; and (iv) Human T-lymphotropic virus, types I and II; (2) In addition, for evidence of infection due to relevant transfusion transmitted infections described in § 630.3(g) (1) (vi) through (g) (1) (viii) and 630.3(g) (2) of this chapter, provided that testing for the disease agent or disease is available and necessary to reduce the risk of transmission of the relevant transfusion transmitted infection by the blood or blood component. (e) Further testing. 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 § 630.40 of this chapter, except:*

Preamble Requests, p. 63421

No request for additional information

Recommendation

PPTA does not have substantive comments to this proposed section. However, please note that proposed § 610.40 (a) was revised to reflect a different list of relevant transfusion transmitted diseases and the revised list is not reflected in § 610.40 (c) as stated, resulting in having section (c) include references to sections of section (a) that no longer exist.

IV. 21 CFR § 630.3 Definitions

Proposed CFR 21 § 630 (b) Blood Component

Blood component means a product containing a part of blood separated by physical or mechanical means.

Preamble Requests, p. 63421

No request for additional information

Recommendation
PPTA refers to comments made in Section I above on proposed § 606.3(a).

Proposed CFR 21 § 630 (c) Donor

Donor means a person who: (1) Donates blood or blood components for transfusion or for further manufacturing use or (2) Presents as a potential candidate for such donation.

Preamble Requests, p. 63421

No request for additional information

Recommendation

PPTA proposes the following definition: *"Donor means a person who: (1) donates blood or blood components for transfusion or for further manufacturing; or (2) a potential candidate who has begun the interactive assessment of eligibility by center personnel."*

The proposed FDA definition of donor is far-reaching and encompasses individuals who may self-defer before the active process of assessing donor eligibility is initiated. Clarification on when does a person "present" themselves is necessary. Under this current proposed definition, anyone who walks through the door of a plasma center would be a donor, when in fact, center personnel may have not begun to determine their eligibility. For example, a person "presents" themselves at a plasma center by walking through the door. As they are sitting in the waiting room, reading over the education material posted on the walls or brochures available, they realize they are not eligible to donate and leave. This individual presented themselves as a potential donor but left before center staff collected any demographic information. Furthermore, specialty centers that collect from a specific donor population would be more likely to have issues on maintaining records for donors who "present" themselves. Their selection process involves a more rigorous preliminary check to see if the individual meets the necessary criteria of that specific specialty center. It would be unduly burdensome for these centers to maintain the proposed mandatory record requirements for individuals that "present" themselves because the specialty centers determine specialty qualifying information before assessing the general eligibility of the potential candidate.

Proposed CFR 21 § 630.3(e) Intimate Contact

Intimate contact means an activity that could result in an exchange of body fluids, including blood or saliva, with another individual.

Preamble Requests, p. 63421

No request for additional information

Recommendation

PPTA recommends the Agency not use the term intimate contact. The proposed definition of intimate contact includes exchange of saliva. This FDA proposed definition item is without supporting scientific data. Available epidemiologic data do not support the transmission of hepatitis and HIV by saliva, except in the unusual situation of saliva transfer by means of a human bite breaking the skin, which has transmitted HBV infection.

Furthermore, this proposed definition contradicts past and current public health messaging. It is obvious that one common method of exchanging saliva is through kissing. Thus, since most people would interpret kissing as being 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 and plasma donor population.

These same issues concerning the definition of intimate contact were discussed with FDA staff during the design of the Uniform Donor History Questionnaire (UDHQ). 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.

“Intimate contact” is a term used neither in the AABB DHQ nor the PPTA version under review at FDA. New terminology which undermines long-standing but still valid public health principles should not be introduced without compelling new evidence which would dictate the importance of a different regulatory treatment. We recommend that this proposed definition of intimate contact be abandoned and that wording to prevent transfusion from persons that may have been exposed to transfusion transmitted infections be stated like the current (AABB) and proposed (PPTA) Uniform Donor History Questionnaire, which use the terms “sexual contact” and “lived with.” For the risk of transmission of hepatitis, PPTA suggests using the term “lived with”, with the definition *to live at same residence with shared kitchen and bathroom*. *“Lived with” would not include college dormitories unless the individuals were roommates.* This is consistent with modern public health practice and policy.

Proposed 21 CFR § 630.3 (f) Physician Substitute

(f) Physician substitute means a trained and qualified person(s) who is: (1) A graduate of an education program for health care workers that includes clinical training; (2) Currently licensed or certified as a health care worker in the jurisdiction where the

collecting establishment is located; (3) Currently certified in cardiopulmonary resuscitation; and (4) Trained and authorized to perform specified functions under the direction of the responsible physician.

Preamble Requests, p. 63422

No request for additional information

Recommendation

PPTA agrees with the proposed definition of *Physician substitute;* however, the term "physician substitute" could be misleading for the general public. It may imply that these individuals can perform all duties of a licensed physician at the Source Plasma establishments.

Proposed 21 CFR § 630.3(g) (1) (v) Treponema pallidum (syphilis) and (g)(1)(vi) CJD

(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 population or (B) May have been released accidentally or intentionally in a manner that could place donors at risk of infection.

Preamble Requests, p. 63422

FDA requested information on 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. FDA would like information on 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 data concerning whether establishments could discontinue syphilis testing without adversely affecting the safety of the blood supply. FDA states if adequate data is received, FDA will eliminate or modify this testing requirement in the final rule.

Recommendation

PPTA member companies recommend that *Treponema pallidum* (syphilis) be removed from the list of agents in proposed 21 CFR 630.3(g) (1) (v) and the requirement for syphilis testing of Source Plasma donors be abandoned. The *Treponema palladium* pathogen is destroyed by freezing plasma, and, furthermore, the process of fractionation and purification into finished product destroys bacterial, viral, and parasitic organisms. In fact, syphilis testing as performed is a donor screening test not a release test for final product. Therefore, performing the syphilis test on donors adds no additional margin of safety to the final product. Discontinuing the test will not adversely impact the safety of the final product.

One of the common reasons cited for retention of the syphilis test is its alleged value as a surrogate, either for another pathogen (such as HIV) or as a marker for a high-risk lifestyle. Highly specific and sensitive HIV and hepatitis C and B tests have obviated the need for syphilis as a surrogate for those pathogens. Similarly, if syphilis is considered to be a lifestyle surrogate, there are no compelling data nor any scientific justification that would indicate that syphilis testing is a more appropriate measure of lifestyle than the direct testing for HIV or hepatitis, which are tests performed routinely and with greater regularity than the syphilis testing administered by the Source Plasma collection industry.

PPTA compiled preliminary data on the prevalence of syphilis in Source Plasma donors. PPTA emphasizes that the *Treponema palladium* does not survive the fractionation process and poses no threat to the safety of the final therapies. The data collected thus far is small, making statistical conclusions difficult.[1] In applicant donors, some of the syphilis positive donors were positive for another viral marker, while no qualified donors tested positive for the other viral markers. The data, even though limited, support the published literature conclusions (1995 NIH consensus conference and Transfusion 1997 article by Herrera et. al) that syphilis testing is not a useful surrogate test. Based on final product safety and the value of syphilis testing as a surrogate, PPTA can find no basis for continued syphilis testing of source plasma donors. The occasional positive found and reported to public health authorities does not justify the cost and the impact to operations of donor centers.

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[1] PPTA qualifies this data by stating it is preliminary and represents only a portion of the industry. PPTA continues to compile and review syphilis data and plans on submitting more information at a later date. Some initial data show the rate of nonconfirmed syphilis positive tests since 2002 has been approximately 3/1000 applicant donors. Among qualified donors, the nonconfirmed positive rate has varied from 5 in 10,000 donors to 1.5 per 1000 donors. From 2001-2003, about 7% of the syphilis positive applicant donors were positive for another viral marker; that dropped to 2-4% between 2005 and 2007. None of the qualified donors had seroconverted for another virus at the time they tested positive for syphilis.

More detailed data from one large PPTA member company show the confirmed positive rate has been 1-2/10,000 applicant donors between 2005 and 2007. For qualified donors it was 5 in 100,000 in 2006 and 1.2/10,000 in 2007. In 2006 20% of the applicant syphilis positive donors were confirmed positive for another virus, while in 2007 13% were confirmed positive for another virus. None of the qualified donors seroconverted to virus positivity at the time they were found to be syphilis positive.

CJD should also be removed from the list of agents (proposed 630.(g)(1)(vi)). There is no report of transfusion transmission of classical CJD. Lookback studies and surveillance have not resulted in any cases of classical CJD that might be attributable to transfusion or infusion of plasma-derived therapies. While PPTA does not propose that current donor eligibility or product suitability criteria relating to CJD be changed, it is inappropriate to identify classical CJD as being transfusion transmitted.

Proposed 21 CFR § 630.3(h) Responsible physician

(h) Responsible Physician means an individual who is:(1) Licensed to practice medicine in the jurisdiction where the collecting establishment is located; (2) Adequately trained and qualified to direct and control personnel and relevant procedures concerning the determination of donor eligibility; collection of blood and blood components; the immunization of a donor; and the return of red blood cells or other blood components to the donor during collection of blood component(s) by apheresis; and (3) Designated by the collecting establishment to direct and control personnel, and to approve relevant procedures specifying decision-making criteria for determining donor eligibility, the collection of blood or blood components, the immunization of a donor, and the return of red blood cells or other blood components to a donor during collection of blood component(s) by apheresis.

Preamble Requests, p. 63422

No request for additional information

Recommendation

PPTA recommends clarification of the duties of the Responsible Physician and acknowledgement of the roles and responsibilities of physicians acting at the corporate level and those at the center. We suggest the following terms be used with corresponding definition to assist in clearly defining the duties performed by the responsible physician.

Corporate Responsible Physician or Corporate Responsible Medical Director: An individual who is licensed to practice medicine; qualified by education, training, and experience to oversee all medical aspects associated with the source plasma and immunization programs; has the responsibility and authority for all medical policies, processes and procedures that relate to the care and safety of the donors and the safety of the Source Plasma or other blood products collected for immunization purposes; and approves relevant procedures specifying decision-making criteria for determining donor eligibility for the participation in the plasmapheresis and immunization programs as well as the management of any potential donor reactions associated with these programs.

Center Physician or Center Medical Director: An individual who is licensed to practice medicine in the jurisdiction where the collecting establishment is located; trained and qualified to perform the duties of the physician and assure the performance of the "Physician Substitute" duties as established by the corporate or firm's medical standards approved by the responsible physician.

Proposed CFR 21 § 630.3 (k) Transfusion-transmitted infection

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 Requests, p. 63422

FDA states that the Agency intends to issue guidance following the good guidance practices in 21 CFR § 10.115 to advise when FDA believes that a new disease agent or disease meets the criteria for a RTTI and what recommended steps to screen or test donors of all or certain blood components for that particular risk of transmission.

Recommendation

PPTA recommends the terms relevant transfusion-transmitted infection and transfusion-transmitted infection not be used. We object to the usage of these terms for a number of reasons. First, the language is needlessly confusing through the use of duplicative terms and the insertion of a single modifier ("relevant"). Furthermore, the term "relevant" would seem to imply that there are "irrelevant" transfusion-transmitted diseases; for the purposes of public health, we would object to the reasoning that would lead to this understandable confusion in language. There may indeed be pathogens that have no impact on the safety of blood, blood components, or derivatives, but the term "relevant" is potentially confusing and misleading.

Second, we would recommend that the Agency adopt an approach that is based on the intended, final use of the product. This is the approach already proposed by FDA in section 630.15(b) (7), excluding Source Plasma donors from malaria-endemic deferral. The ability to test for a pathogen should not be indicative of the perceived importance of the disease, but rather the ability to maintain high quality and safe products, no matter what the threat or pathogen. Indeed, the terminology itself ("transfusion-transmitted") ignores this most crucial distinction: Source Plasma is *not* transfused…it is a starting material used for further manufacture. The entire relevance of the term itself is therefore at issue.

The same reasoning would apply to crafting an approach to address an emerging infectious disease. Rather than tagging the pathogen with an appellation found suitable under the language of the Proposed Rule in 630.3(g) (2), the best inquiry to determine would be the intended use of the product. A product that undergoes robust processing and manufacturing processes must be handled differently than one which does not; we would therefore ask that the approach identified in proposed 630.15(b)(7) be adopted here, and with the concerns involving syphilis mentioned above in these comments.

It is, therefore, unclear to us that the regulation and the preamble language delineating the intended relevance of Good Guidance Practices adds any value to safety or quality of blood, blood components, or derivatives regulated by the Agency. Any production of Guidance Documents based solely on the availability of screening methods and test kits, at the expense of the critical recognition of the use of the products themselves, is fundamentally flawed. Ultimately, the industry supports a science-based approach formed on the basis of intended use of the products. There would be no interference with the promulgation of Guidance Documents or GGPs, and would be instead based on a more robust, logical, and science-based foundation.

V. 21 CFR § 630.5 Medical Supervision

Proposed 21 CFR § 630.5(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.

Preamble

No request for additional information

Recommendation

PPTA agrees with this proposed section. However, PPTA refers to comments stated previously on proposed 21 CFR § 630.3(h) in section IV and recommends the adoption of language that differentiates the center physician from the corporate responsible physician.

Proposed 21 CFR § 630.5(b) and (c)

(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.

Preamble

No request for additional information

Recommendation

PPTA agrees with the statements provided in proposed § 630.5 (b)(1), (b)(2), (b)(3) and (b)(5). However, please refer to PPTA's recommended definitions for Center Physician and Responsible Physician in section IV above. Proposed § 630.5 (b)(4) indicates that the physician substitute must be present each time the red blood cells are returned to the donor during plasmapheresis. However, FDA cleared apheresis devices routinely and automatically returns the red blood cells to the donor. These devices are operated by trained personnel who must follow the device operator's manual and applicable SOPs. The presence of the physician substitute is not required during the daily operation of these devices unless they are summoned to the donor floor to manage donor reactions as needed. Therefore, although PPTA is not aware of any plasma organization that may still use manual process for plasmapheresis, we recommend that the FDA clarify this statement by indicating that this requirement is only directed to plasma collection facilities performing manual plasmapheresis.

Proposed 630.5(c) would permit a collecting establishment to authorize a physician substitute to perform the same functions of a responsible physician in the collection of Source Plasma, except the responsible physician would be required to be present for red blood cell immunizations.

PPTA assumes that FDA is requiring the presence of the responsible physician for the red blood cell (RBC) immunization to assist the RBC recipient if a life-threatening situation arises during the immunization process. This is most likely based on the fact that potential life-threatening reactions most commonly occur within 10 to 15 minutes of the start of the transfusion with as little as 10 mL transfused.

PPTA understands the potential risks associated with the RBC immunization. However, having a physician present during the immunization process does not protect against

the single greatest risk to RBC recipients, which is human error when identifying the blood product or misidentification of the RBC recipient. Therefore, in protecting against this risk, it is imperative that plasma establishments have processes and procedures in place to assure that the correct RBC product is infused to the intended recipient. This is currently achieved by the center staff by following Good Manufacturing Practices (GMP) as required. In addition, other processes that help decrease potential risks to the RBC recipients in this program is the fact that the volume of RBCs infused during each immunization is small (typically 1 to 5 mL of RBCs during booster immunizations with a maximum of 10 mL during the initial immunization) and the use of group O RBCs (universal blood) that decreases the risk of having immediate hemolytic reactions due to ABO incompatibility.

In addition, to investigate the current rate of RBC recipient reactions, PPTA surveyed the membership regarding the number of RBC immunizations administered from 2005 to 2007 as well as the number of reactions observed at the center and after the RBC recipient left the premises. A total of 12,198 RBC immunizations were administered during that period with a total of 1,243 (10.19 %) reactions observed. However, for the purpose of the above comment regarding the required presence of the center physician during immunization, only 16 (0.13 %) RBC recipients developed a reaction before leaving the premises (with the center physician present during immunization and at least 15 minutes post-immunization as required). These 16 reactions are summarized below:

1) 9 mild vasovagal reactions most likely associated with the plasmapheresis procedure performed immediately prior to the RBC immunization. Donors were released from the center with no further complications.
2) 2 mild reactions associated with muscle ache and chills that lasted for 2-3 hours with no other complications
3) 2 mild febrile reactions
4) 1 tachycardia not attributed to the RBC immunization (previous history of high pulse rate pre-donation).
5) 1 severe reaction associated with lower back pain/chills and cyanosis noted at mouth. EMS activated and donor transported to ER. Reaction lasted for about 2 hours and donor was released from the hospital with no further complications.
6) 1 arm ache.

In all 16 cases, the assistance provided to the RBC recipient is consistent with the typical care provided by the physician substitute when donor reactions occur in association with the plasmapheresis procedure. The presence of the center physician made no difference in regards to the care provided to the RBC recipients.

Moreover, other programs such as Home Transfusion have been successfully used in the United States without requiring the presence of a physician in spite of the fact that

these blood products may be transfused to very ill patients and may require transfusion of at least a full unit of RBCs or other blood components. However, in order to perform these activities, they must follow strict transfusion guidelines to assure that the administration of blood or blood components is safe to the patients.

Based on the above information, PPTA recommends that FDA remove the requirement of having a physician present during the RBC immunization as long as applicable guidelines followed by the Home Transfusion program are met:

1. There are proper procedures in place for the identification of blood samples and RBC recipients. This will ensure proper matching is confirmed immediately prior to the administration of RBCs. This is part of the GMP currently followed by the Source Plasma organizations.

2. There is a mechanism to obtain immediate physician consultation (e.g., Center Physician or Corporate Responsible physician). Please refer to comments on proposed 21 CFR § 630.3(h) in section IV above.

3. There is a system to immediately activate the local emergency medical service (EMS).

Proposed 21 CFR § 630.5(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.

Preamble

No request for additional information

Recommendation

PPTA agrees with this proposed section. However, PPTA refers to comments stated previously on proposed 21 CFR § 630.3(h) in section IV and recommends the adoption of language that differentiates the center physician from the corporate responsible physician.

Proposed 21 CFR § 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

FDA requests comment on what would be considered appropriate for available emergency medical services.

Recommendation

PPTA recommends the language on time of 15 minutes be removed. PPTA agrees with the FDA statement that Source Plasma centers must establish and follow their own standard operating procedures for providing emergency medical services. Each plasma center must have processes and procedures indicating when and how to contact the local EMS. However, local EMS response time is community dependent and Source Plasma Centers cannot control how quickly they respond or guarantee a 15 minute response time.

Proposed 21 CFR § 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.

Preamble

No request for additional information

Recommendation

PPTA recommends the term "adequately" be removed from the definition of trained personnel. This qualifier adds ambiguity into how someone would determine "adequacy." PPTA would also like to refer to comments stated previously on proposed 21 CFR § 630.3(h) in section IV and recommends the adoption of language that differentiates the center physician from the corporate responsible physician.

VI. 21 CFR § 630.10 General donor eligibility requirements

Proposed 21 CFR § 630.10(b) Educational Material

(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 Requests, p. 63423

FDA solicited information on the requirements of this provision and stated the current recommendations for educational material are described in the memorandum entitled "Revised Recommendation for the Prevention of Human Immunodeficiency Virus (HIV) Transmission by Blood and Blood Products," issued April 23, 1992. Additionally, FDA stated that it intends to issue additional guidance on educational material in the future. The proposed rule would expand requirements to include educational material on behavioral risks and signs and symptoms for hepatitis and other relevant transfusion-transmitted infections determined to present a risk to the blood supply. FDA specifically solicits information on how comprehensive the educational material should be and the format or style in which it is presented.

Recommendation

PPTA recommends the proposed rule acknowledge the existence of, and perhaps even encourage the use of, the approved Uniform Donor History Questionnaires (UDHQs), perhaps in a manner similar to that used in 21 CFR § 606.100 (d) for SOPs, or through the appropriate guidance documents. PPTA supports overall efforts to provide donors with consistent and up to date educational materials regarding transfusion transmitted infections and recognizes that it is an important aspect of the pre donation screening process, as was demonstrated by the body of work on the blood donor history questionnaire (DHQ) that occurred as a result of the AABB/FDA sponsored workshop "Streamlining the Blood Donor History Questionnaire" held in October 2000.

As described in FDA's October 2006 guidance document *Guidance for Industry Implementation of Acceptable Full-Length Donor History Questionnaire and Accompanying Materials for Use in Screening Donors of Blood and Blood Components,* following this workshop AABB convened a multi-organizational task force to address several issues related to the donor questionnaire process. The goals of the task force included reducing the complexity of the questionnaire and the educational materials to assure that donors will better comprehend the information and provide more accurate responses. The task force consisted of representatives from the blood and plasma industry and professional trade organizations to ensure, to the greatest extent possible, that all blood establishments would be represented, as well as support and use the donor history questionnaire and accompanying materials prepared by the task force. The task force also included an ethicist, statistician, experts in survey design and cognitive methods, and liaisons from the Centers for Disease Control and Prevention and FDA.

The task force revised and redesigned the pre-existing AABB UDHQ and developed a new process for interviewing donors. The new process includes use of the following

methods and materials to obtain information about a donor. The materials are intended to be used in their entirety.

- Full-Length Donor History Questionnaire - contains all initial donor screening questions.

- Donor History Questionnaire User Brochure - includes a glossary, flow charts and references; describes how questions should be administered; and contains follow-up questions to further evaluate a potential donor's response to capture questions. "Capture" questions ask a general question about a donor's history or behavior and are followed up by more specific questions if needed.

- Medication Deferral List - companion document to the questionnaire that contains a list of medications that may serve as a basis for donor deferral.

- Blood Donor Educational Materials - educates the donor about the donation process and risks and conditions that are the basis for deferrals.

The task force developed and evaluated new questions to determine if donors could comprehend them and provide correct information. Previously published focus group studies showed that questions should be simple and focus on one behavior rather than ask about several different behaviors, and that some terms required clarification in order to enhance donor comprehension.

Cognitive interview studies, conducted as part of the task force efforts, provided information on recall, suggested that questions should be reasonably specific, and indicated that individuals tended to answer the questions conservatively, even if they did not always interpret the questions uniformly. The results of the tests showed that there is a need to educate donors about why certain behaviors put them at risk to transmit diseases to recipients. Blood donor interviewers in several blood collection establishments also evaluated the final questioning process. The blood collection establishments stated that the new process for asking questions and for providing information to the donors was an effective, easy-to-use tool.

The new donor questionnaire process was discussed during several Blood Product Advisory Committee (BPAC) meetings. Informational presentations were given during the BPAC meeting held on June 14, 2001. These presentations described the task force activities, the new questionnaire process developed by the task force, and the focus group study design. The progress of the task force's activities and the results of the cognitive studies were presented during the BPAC meeting held on June 13, 2002. The BPAC unanimously supported the task force's efforts at each meeting.

The work performed by the UDHQ task forces (the AABB Whole Blood task force as well as the PPTA sponsored task force that produced a UDHQ for donors of Source Plasma) have shown that educational material must be carefully integrated into the

process for determining donor eligibility. The proposed rule requires that the educational material address signs, symptoms, and risk factors associated with exposure transfusion transmitted infections. Simply taking this requirement at face value would require a rather comprehensive document or presentation that could be difficult for a potential donor to comprehend. The difficulty in donors' even reading educational material, let alone, reading and understanding extensive and complicated educational material was noted in the FDA-funded research by the American Institute for Research that resulted in the direct questioning for HIV-associated risks. Any educational material should be used to supplement other materials, especially the health history questions, since these represent the primary interaction between staff and donor and thus present the opportunity to control the donor's exposure to the educational material and allow for an assessment of the donor's comprehension of the educational material. While this approach is not precluded by the Proposed Rule, the regulations should reflect that the presentation of the educational material is one of the sub processes of determining donor eligibility, and that the educational material could be designed to be used as an adjunct to the donor suitability questions as part of the process of determining donor eligibility. Lastly, the flexibility to use various methods to present the educational material to the donor is appreciated.

PPTA encourages development of an improved approach to organizing and issuing guidance documents. The preamble to the proposed rule states that "One objective of this rulemaking is to make more visible the connections between the regulations and current recommendations. In many cases in this preamble, we will describe the general intended meaning of the proposed regulations and will also discuss those recommendations, contained in current guidance, which fall under a proposed regulation. Although it is neither possible nor desirable to codify all the specific details contained in recommendations, we believe the proposed rule will more explicitly describe donor eligibility standards and will clarify the relationship between the regulations and the applicable recommendations."

PPTA applauds this effort, and encourages FDA to develop guidance documents that will be comprehensive, yet easy to understand and to use. By ease of understanding and use, the primary measurement of success will be a presentation of information in the guidance document recommendations.

PPTA presented recommendations to FDA for guidance documents at the December 2003 PPTA/FDA Liaison Meeting. The recommendations included organizing guidance documents into one comprehensive document with at least three sections:

- A section containing the background material. FDA does an excellent job of summarizing the medical issues for emerging threats to the blood supply, and should continue to provide this information.

- A section that describes donor eligibility issues. This section would include all current recommendations for screening donors to determine eligibility and could

reference or even include the approved UDHQs. This section would provide a comprehensive list of all recommended questions that should be included in determining donor eligibility. Under the current system of guidance documents determining the current version of all recommended donor screening questions is an onerous, needlessly difficult task.

- A section that describes product suitability, i.e., primarily testing, issues. This section could include, for each required test, the testing algorithm, donor deferral requirements, any donor reentry algorithms, product retrieval and disposition algorithm (including special labeling requirements), lookback and recipient tracing and notification requirements, BPDR requirements, and comprehensive labeling statements.

Under the proposed structure for guidance documents, FDA would issue new recommendations for determining donor eligibility or product suitability as revisions to the comprehensive guidance document. The benefits of this approach would include:

- Industry would have one place to look for the current information. As already mentioned, under the current system of guidance documents determining the current version of all recommended donor screening questions is cumbersome.

- This format would allow for a continuous and comprehensive review of existing recommendations as knowledge evolves and new recommendations are issued. Examples would include the incorporation of new geographic exclusion requirements into existing (UDHQ) questions rather than adding another new question, as has been recommended in the past for vCJD and SARS. Another example would be the potential for early recognition that the requirement to evaluate donors for a greater than 10 pound weight loss in less than two months (as a marker of HIV infection) could be eliminated as EIA and NAT tests for HIV were implemented.

- Increased compliance and safety.

Subsequent discussion between FDA and PPTA indicated a degree of interest in this approach. It is important for FDA to develop draft guidance documents when considering new policy that is not implicitly delineated in regulations. It is critical that new policy be published by FDA for public and industry comment. While PPTA appreciates FDA's willingness to discuss "current thinking" in other settings, it is only through the Good Guidance Practices process of developing guidance documents that industry and others have the opportunity to provide comments on the Agency's "current thinking". In addition, it is inappropriate for FDA to implement new policies or "current considerations" in the review of license applications/supplements prior to the guidance document or regulation becoming final. PPTA encourages FDA to finalize guidance documents once vetted through the public process to allow industry to fully understand and implement changes appropriately.

Proposed 21 CFR § 630.10(c) When must you determine the eligibility of a donor?

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 § 610.40 and § 640.5 of this chapter, 1 day before the donation. You must have standard operating procedures in place for identifying such components.

Preamble Requests, p. 63423

No request for additional information

Recommendation

PPTA does not oppose the requirement that donor eligibility be determined on the day of collection and before collection except in the case of short-dated (less than 24 hours) components. We do oppose the interpretation of this requirement to include denying a retrospective eligibility determination (e.g., in the case of missing or incompletely explained questionnaire responses due to GMP error) after the 24-hour window from the time of collection. The current regulatory language has been interpreted by FDA to deny allowing components collected from a donor whose eligibility was not adequately determined within 24 hours of collection to be deemed suitable for use. In Source Plasma donation programs, the donor may return at two-day intervals (although not more than twice in a seven day period), thereby allowing ample opportunity to re-interview the donor. While it is unfortunate that an error occurred in the original eligibility determination, the suitability of the donation, which was collected, should not be linked unless the missing data cannot be reasonably assessed during the dating period of the component. 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 and pulse. We request that if the regulation is retained as proposed, FDA discuss the interpretive criteria in the preamble to the Final Rule to prevent the needless destruction of life-saving blood components.

Proposed 21 CFR § 630.10(d) (1) How must you determine the eligibility of a donor?

(d) 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 § 606.160(e)(2) of this chapter; (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; (3) Assessing the donor's medical history; and (4) Performing a physical assessment of the donor.

Preamble Requests, p. 63424

No additional information requested

Recommendation

It would be cumbersome and unmanageable to check a donor's deferral status by checking the collective list of ineligible donors required under proposed 21 CFR § 606.160(e) (2). PPTA reiterates comments in section III above on proposed 21 CFR § 606.160 (e) (1) & (2) Records.

Proposed 21 CFR § 630.10 (e) How do you assess the donor's medical history?

(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 <u>if health care practitioners have ever advised the donor not to donate</u>; 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.

Preamble Requests, p. 63424

No additional information requested

Recommendation

PPTA recommends that the requirement to ask if a health care practitioner has ever advised you not to donate be eliminated from the Final Rule. Although a question asking whether the donor was advised against donation by a health practitioner was on an earlier version of the donor history questionnaire (DHQ), neither FDA nor AABB required collection facilities to ask a specific question regarding this issue. This question was eliminated with the approval by 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. This rationale should apply to facilities using the approved DHQ or another approved questionnaire. 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. Therefore, PPTA recommends that the statement, "and healthcare practitioner ever advised the donor not to donate" be deleted from the Final Rule.

Proposed 21 CFR § 630.10(f) What factors make the donor ineligible because of an increased risk for, or evidence of, a relevant transfusion-transmitted infection?

(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 associated with relevant transfusion-transmitted infections; (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 inoculation.

Preamble Requests, p. 63425

FDA made no request for additional information. However, PPTA appreciates FDA publicly sharing its policy on accepting donors who have received a tattoo or piercing using a procedure with a sterile needle from a state licensed or credentialed establishment.

Recommendation

PPTA supports the FDA proposal to hold workshops and public meetings on social behaviors associated with increased risk of transfusion transmittable infections. We encourage the Agency to consolidate and finalize guidance documents and produce

one document on donor eligibility. As the Agency considers these issues, PPTA would like to take this opportunity to propose the following:

1. Change the deferral period from 12 months to 4 months for those social behaviors and medical treatments that result in risk for transmission. The 12 month restriction is based on the long window period of serologic testing when first introduced for HIV. With the use of Nucleic Acid Amplification testing, the 12 month deferral is no longer rational. This would harmonize with Council of Europe Guidelines. This would include all the sexual contacts with high risk groups , receipt of blood transfusion, receipt of tissue, percutaneous contact with blood, tattoo or piercing, treatment for sexually transmitted disease such as gonorrhea (syphilis would remain at 12 months post successful treatment), incarceration and hepatitis risk.

2. Change the deferral for "institutionalization". This should also be changed to a four month deferral. The assumption is that risk behavior within such institutions might result in transmission of a disease transmissible by blood or plasma. With NAT, four-month period is adequate to reflect the risk of the behavior with modern testing techniques and protocol. The three consecutive days requirement should be retained. It represents a reasonable estimate of the length of time needed for risk event to be likely and prevents deferral of individuals held overnight on a lesser charge such as a traffic problem. We also propose that this recommendation of more than 3 consecutive days during the past 12 months stated in the preamble be included in the Final Rule.

3. Not use the term "intimate contact". Current questions about risk use the term "sexual contact" which is better understood by donors as it is currently used in the AABB DHQ and is defined in the proposed PPTA UDHQ. For the risk of transmission of hepatitis, use the term "lived with" to mean lived at same residence with shared kitchen and bathroom. This would exclude college dormitories unless the individuals were roommates. This is consistent with public health practice.

4. Eliminate the current requirement under 21 CFR 640.63(c)(11) that defers any donor who has a history of hepatitis after the 11th birthday and replace it with a 4-month deferral. The current regulatory position is contradictory. For example, Source Plasma donors who are hepatitis B core positive are allowed to donate if they have no recollection of hepatitis, although they were most certainly infected. Similarly a donor who tests positive for HAV is still accepted for donation if he has answered that he has no history even though he was most certainly infected. Individuals who have had hepatitis A will constitute the largest portion of the group with a history of hepatitis, but do not constitute a risk. Those with hepatitis B or C who are carriers would be detected by current testing. The four-month deferral would assure not accepting any donor in the window period.

Proposed 21 CFR § 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?***

(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 at the time of, or 6 weeks before, donation; 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 Requests, p. 63425

No request for additional information

Recommendation

PPTA reiterates comments made previously on the need to consolidate and finalize guidance documents on donor eligibility and product suitability. In addition, as FDA considers issues surrounding the proposed rule and corresponding guidance documents, we propose the following changes:

1. In (1), we recommend that the phrase "or dental" be deleted. FDA has not required a question on dental treatments in the AABB DHQ and it is not in the proposed PPTA UDHQ. The rationale for not including the question is that bacteremia from dental procedures is transient. Additionally, bacteremia from dental procedures is not applicable due to the fact that plasma derivatives undergo pathogen reduction processes during manufacturing. The multiple steps in the fractionation process are robust and capable of inactivating and/or removing bacteria at concentrations that may be present in the plasma, resulting in no impact on the safety of the final plasma protein therapy.

2. In (4), we recommend that the current travel restrictions be reviewed to determine if they provide any added margin of safety. Some, such as vCJD geographic areas and time periods, are confusing to donor and screener alike. Given the complete absence of vCJD in any American who has traveled to

Europe or been in the US military in Europe, these restrictions would appear to no longer be warranted.

3. Regarding (5), while we agree that people who have had xenotransplants should not donate blood, plasma or tissues, we disagree with the addition of donor history questions to identify the extremely small number of such recipients. Xenotransplantation is highly regulated and limited. We are concerned that deferral of contacts of xenotransplantation recipients casts too broad a net and could defer safe donors. There are also definitional issues that confuse and may restrict donations.

   Furthermore, Xenotransplantation has been defined as any procedure that involves the transplantation, implantation, or infusion into a human recipient of either a) live cells, tissues, or organs from nonhuman animal source, or b) human body fluids, cells, tissues or organs that have had ex vivo contact with live nonhuman cells, tissues or organs. Xenotransplantation product(s)[2]. Include live cells, tissues or organs used in xenotransplantation (defined above). The above definition does not indicate what a nonhuman animal is. It would be helpful to know if the FDA is only referring to mammals (warm-blooded animals that nurse their young with milk) or all vertebrates, which include mammals, fish, amphibians, reptiles, and birds. For example, some donors report that they have received shark-derived products. Sharks are classified as fish. In addition, the above definition includes terms such as "live cells, tissues, or organs". Based on this definition, it appears, that licensed biological products, drugs, or medical devices sourced from nonliving cells, tissues or organs are not considered xenotransplantation products. Some examples of non-living cell graft products are: Porcine heart valves, porcine intestine, cow bone implants, pig skin graft, etc. FDA needs to be clear that xenotransplants do not include medical devices made from animal material such as porcine valves.

   Moreover, plasma derivatives undergo multiple steps in the fractionation process capable of inactivating/removing different pathogens including viruses, parasites and bacteria at concentrations that may be present in the plasma. Therefore, any theoretical risk of disease transmission is minimized. Based on the above information, PPTA recommends FDA change the donor deferral status for individuals who have undergone treatment with licensed biological products, drugs, or medical devices sourced from nonliving cells or tissues.

Proposed 21 CFR 630. 10 (h) How do you perform a physical assessment of the donor?

(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. The

[2] *Guidance for Industry: Source Animal, Product, Preclinical, and Clinical Issues Concerning the Use of Xenotransplantation Products in Humans, issued in April 2003.*

donor's oral body temperature must not exceed37.5 °C (99.5 °F), or the equivalent if measured at another body site; (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. (i) The donor's phlebotomy site must be free of infection, inflammation, lesions, and pitted skin; and (ii) The donor's arms and forearms must be free of punctures and scars indicative of injected drugs of abuse.

Preamble, p. 63427

1) *Temperature* - No request for additional information

2) *Blood Pressure* - FDA is soliciting comments with supporting scientific data on the need for such limits on systolic and diastolic value, on the limits proposed, and on adverse events associated with donation that have been attributed to blood pressure. In particular, FDA is seeking information with supporting scientific data on the necessity, of specific upper or lower blood pressure limits in blood donation. Additionally, FDA is also soliciting comments on whether an abnormal blood pressure may be an indication that the donor has an undetected illness, such as cardiovascular or renal disease, may not be in good physical health and, therefore, may be harmed by the act of donating. Lastly, FDA is seeking comments on the accuracy and interpretation of blood pressure measurements taken in the setting of blood and plasma donation.

3) *Hemoglobin* – FDA is 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.

4) *Pulse* - No request for additional information

5) *Weight* - FDA requests comments and supporting scientific data regarding both the volume of blood that can be safely collected from a donor in relation to the donor's body mass, and the criteria to define a standard unit of blood. The agency also is seeking comments on the feasibility and impact of determining that a donor has experienced a significant recent and unexplained loss of weight, and, if so, whether an unexplained loss of 10 percent of the donor's weight is an appropriate marker of possible underlying illness, and whether loss of weight in the 6 month time period prior to donation is an appropriate time frame to indicate that such weight loss is an appropriate marker for such potential illness.

6) *Skin Examination* - No additional information request

Recommendation

1) *Temperature* - PPTA believes the temperature requirements are appropriate.

2) *Blood Pressure* - PPTA recommends the Agency allow flexibility in evaluating donors regarding blood pressure measurements. Current FDA regulations state that the blood pressure should be normal but do not specify values. FDA proposes that the systolic blood pressure be between 90 and 180 mm Hg and diastolic blood pressure between 50 and 100 m Hg. While the proposed values are commonly used, there are no data to support the criteria. Blood pressures are variable depending on a number of factors. While hypertension is a major national health concern, donation by hypertensive individuals generally does not cause any harm. Similarly a low blood pressure that is normal for an individual could be acceptable. We are aware of some literature that state there might be increased donor reactions in individuals with low blood pressure. However, this would be simply another such factor as lower weight or gender that is found more frequently among donors who experience reactions. In addition, the categorization of hypertension by national health expert panel's changes over

time, and firms should be able to respond accordingly and not be locked into a particular set of numbers by regulation. However, a baseline blood pressure for all donors on each donation is needed in the event of a reaction.

In the absence of the data requested by the Agency, we propose that the regulation should be: "The blood pressure must be determined prior to donation." We suggest that additional parameters related to the blood pressure reading be addressed in guidance.

FDA is seeking comments on the accuracy and interpretation of blood pressure measurements. It is known that many factors can influence blood pressure along with pulse such as stress, exercise, and caffeine intake. In addition, inter-observer differences are found with measurements that rely on sphygmomanometers and stethoscopes. Therefore, a general preference for automated devices is found not only among donor centers but also among clinics, hospitals, and for use at home. Techniques for assessing and validating these techniques have been put forth by the European Society of Hypertension (Blood Pressure Monitoring 2002, 7:3-17). These devices are commercially available and approved for sale. We recommend that FDA acknowledge the acceptance of automated devices in either the preamble to the final rule or in guidance.

FDA also notes that an isolated measurement of blood pressure may not reliably assess acceptability for donation. Therefore, we recommend that FDA provide the following, or similar, guidance: "Firms should have a procedure for re-measuring the vital signs if there is reason to believe stress or other factors have affected the initial measurement."

3) *Hemoglobin* - PPTA supports the lower minimum hemoglobin level for female donors in view of the literature indicating females could have such lower values without any abnormality. PPTA is in the process of reviewing current methods for monitoring hemoglobin/hematocrit levels to assure the health and safety of donors and evaluating procedures and technologies that have been adopted in other regions. We have explored the use of non-invasive devices and the protocols utilized in Europe that allow acceptance of the donor and initiation of the plasmapheresis procedure before the hemoglobin value is obtained. We have also explored alternative monitoring methods that would not include having a measurement at each donation since unlike whole blood donation, the donation of source plasma by plasmapheresis does not impact the iron stores or the level of hemoglobin or hematocrit of the donor. While we have not completed our process and do not have a specific plan to propose at this time, we request that FDA consider a flexible regulation to allow for the development of an acceptable alternative to the current procedures. Accordingly we recommend the following addition to the proposed regulation: (iii) except that for donors of Source Plasma,

the Director, Center for Biologics Evaluation and Research, may approve an alternative procedure for monitoring a donor's hemoglobin level.

4) *Pulse* - PPTA recommends the Agency not include a pulse requirement. Currently, there are no FDA regulations concerning the measurement of the donor pulse. While it is common procedure to measure the pulse and use an acceptable range of 50 to 100 for acceptance, there are no data to support this practice. Other developed countries such as the UK do not measure donor pulse. Determining the regularity of the pulse beat is subjective.

5) *Weight* - PPTA does not object to the minimum weight of 110 pounds from a practical standpoint. The existing nomogram for volume collection is based on a minimum weight of 110 pounds. PPTA objects to using the weight of the donor, collected for determining the volume of plasma to be collected from the donor, as a parameter of continuing 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 weight loss, specifically a 10 percent loss over a 6 month time period, does not add valuable information beyond the donor history questions and medical screening. FDA cites no medical or scientific rationale for proposing this requirement. In fact in the preamble, FDA asks for comments on the feasibility and impact of the requirement and if an ". . . unexplained loss of 10 percent of the donor's weight is an appropriate marker of possible underlying illness, and whether loss of weight in the 6 month time period prior to donation is an appropriate time frame to indicate that such weight loss is an appropriate marker for such potential illness."

Prior to testing for HIV, FDA recommended that weight loss be tracked in the donor. This recommendation was rescinded when testing was available. Even so, the criteria remained in FDA's "Guide for Inspection of Source Plasma Establishments." When the discrepancy was brought to FDA's attention, FDA advised (in a letter dated April 18, 2005, see attachment 1) that ". . . unexplained weight loss is still considered a general indicator of a disease process." At that time, FDA did not provide substantive evidence that tracking weight for an "unexplained weight loss" offered value beyond the recognized donor eligibility criteria. Furthermore, in the cited letter, FDA advised PPTA that the donor's weight-loss data could be reviewed by medical personnel at the time of the annual physical. PPTA member companies developed policies and procedures on how to best capture and review the data during the annual physical. The proposed rule complicates the existing procedures by adding the obfuscating language of "10 percent of body weight within the past 6 months." As stated above, PPTA knows of no situation in which unexplained weight loss was the sole determinative factor in deferring a donor for health reasons other than when the person drops below a 110 lbs. The proposed rule would add the burden of calculating a 10 percent weight loss over an undefined 6 month period in a donation structure that allows 2 donations per week with no rationale as to why it

is necessary and what benefit it might provide. In the absence of good science and value to the process or a donor's health and well-being, PPTA recommends that the proposed requirement be amended to delete the following: "and must not have had an unexplained loss of greater than 10 percent of body weight within the past 6 months."

6) *Skin Examination* – PPTA recommends the term "pitted skin" be removed. The proposed rule requires the collecting establishment to examine the skin at proposed venipuncture sites for evidence of infection, inflammation, lesions or pitted skin and for punctures and scars indicative of injected drugs of abuse.
PPTA is raising concern about pitted skin being a cause for deferral. We understand that there have been reported instances of contaminated platelet transfusions thought due to bacteria in areas of pitted skin not disinfected by the agent used to prepare the site. However, frequent plasmapheresis donors would be expected to have pitted areas of their skin due to the frequency of the needle punctures for their donations as frequent as twice per week. Thus, close examination for pitted skin could lead to deferral of committed donors. In addition, a clinical problem related to bacterial infection of source plasma has not been noted and would not be anticipated in the source plasma collected. If the FDA retains this wording to prevent infection of platelet and red cell components that are not frozen, we suggest adding wording: "It is understood that pitting of the skin would not be a basis for deferral of long term source plasma donors, but would be used to guide choice of venipuncture site to avoid areas that are pitted to the extent possible."

Proposed 21 CFR § 630.10 (i) What additional requirements must you complete before determining the eligibility of the donor?

(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 § 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 § 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 § 610.40(a) of this chapter and for syphilis. (iv) If any of the tests required in § 610.40(a) of this chapter are reactive, the sample of blood will be tested further, as required in § 610.40(e) of this chapter; (v) If the donation is determined to be not suitable under § 630.30(a) or if the donor is deferred from donation under § 610.41 of this chapter, the donor's record must identify the donor as ineligible to donate and the donor must be notified under § 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.

Preamble Requests, p. 63428

No request for additional information

Recommendation

PPTA recommends the term "immediately" before donation be deleted from the final rule. The phrase "immediately" before donation implies that at each donation an individual must sign a new written statement of understanding. For donors participating in a serial program like donating at a Source Plasma Center, this continual renewal of a written statement of understanding would be excessive. Currently, when an individual initiates the process of becoming a plasma donor a statement of written informed consent is provided to the individual. Center staff reviews the statement with the individual to ensure they understand all aspects of their donation. This informed consent is maintained in the donor record file and renewed at the annual physical or if the individual does not continue to donate within a six month period. The statement of written informed consent contains the necessary information delineated in the current regulation of 21 CFR § 640.61 and "Guidance for Industry: Informed Consent Recommendations for Source Plasma Donors participating in Plasmapheresis and Immunization programs".

PPTA seeks clarification that the requirements under proposed 21 CFR § 630.10 (i) "written statement of understanding" replace the informed consent regulation § 640.61 that was deleted in the proposed rule. PPTA does not dispute the nomenclature change of informed consent to written statement of understanding but requests the Agency consistently use the term throughout the regulation. For instance, 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. PPTA's interpretation of the proposed regulation 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, which replaces the informed consent requirements. PPTA requests the Agency clarify these terms to eliminate further confusion.

VII. 21 CFR § 630.15 Donor Eligibility Requirement Specific to Whole Blood and to Plasma collected by plasmapheresis

Proposed 21 CFR § 630.15 (b) What additional donor eligibility requirements are specific to Plasma collected by plasmapheresis?

(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 § 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 § 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. (i) In addition to the determination of donor eligibility required in § 630.10(d), the responsible physician must perform the physical examination no more than 1 week before the first immunization injection for the production of high-titer plasma. It is not necessary to repeat the physical examination requirement in paragraph (b)(1) of this section, if the immunized donor's plasma is collected within 3 weeks of the first immunization injection; and (ii) A donor determined to be eligible under § 630.10(d) and currently participating in a plasmapheresis program, does not need to be reexamined before immunization for the production of high-titer antibody plasma.

(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:
(i) The donor experienced a red blood cell loss of equal to or greater than 200 milliliters of red blood cells during a single automated plasmapheresis procedure; or (ii) The

donor experienced an unexpected red blood cell loss of any volume in an automated apheresis procedure on two occasions within the last 8-week period; or
(iii) The donor experienced a red blood cell loss equivalent to or greater than 200 milliliters of red blood cells as a result of failure to return red blood cells during a manual plasmapheresis procedure; or (iv) The donor donated a unit of Whole Blood.

(6) Exceptions to deferral due to red blood cell loss. You are not required to defer a donor from participation in a plasmapheresis program due to red blood cell loss if the following occurs:(i) The donor is examined at the time of the current donation and certified by the responsible physician to be in good health under § 630.10(h) and the donor's health permits the plasmapheresis; and (ii) The donor possesses an antibody that is transitory, of a highly unusual or infrequent specificity, or of an unusually high titer, and (iii) The special characteristics of the antibody and the need for plasmapheresis of the donor under § 630.20(c)(2) are documented at your establishment.

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

Preamble Requests, p. 63429

1) Examination by a responsible physician – No request for additional information

2) Weight- FDA is soliciting comments with supporting data on the usefulness of measuring weight loss at the time of donation by apheresis as an indicator to identify health problems in the donor.

3) Total Protein – No request for additional information

4) Deferral due to red blood cell loss – No request for additional information

Recommendation

1) *Physical Examination and Informed Consent* - PPTA recommends the Agency clarify the terms being used to describe 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. This confusion is another example of a consequence of including all blood components, including those for transfusion as well as those for further manufacture, into the definition of "blood components" and then applying this

broad definition to donor eligibility and product suitability issues. FDA should consider the approach taken in other sections of the proposed rule and consider maintaining separate donor eligibility criteria for blood components based on the intended use of the product, i.e., for transfusion or for further manufacture.

2) *Weight* - We agree that a donor's weight should be determined at each collection and refer back to comments made in section VI above on proposed § 630.10(h)(5). Measuring a donor's weight is required for the plasmapheresis nomograms. It is difficult to use this as an indicator of donor health with no accepted parameters. Therefore, we do not believe it can serve that purpose. Instead at the time of the annual physical examination, the donor's weight on that occasion can be compared to the weight one year ago, and the examiner can explore any basis for a significant difference. We recommend that the regulation simply state: "Source plasma donors must be weighed before each donation"

3) *Total Protein* – PPTA is in the process of reviewing current methods for monitoring protein levels in donors to assure their health and safety against more modern technologies and technologies that have been adopted in other regions. While we have not completed our process and do not have a specific plan to propose at this time, we request that FDA consider a flexible regulation to allow for the development of an acceptable alternative to the current procedures. In the proposed rule, 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 what the ideal program is. Nor is it 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. PPTA recommends the following language be adopted: "Total protein level. Before each plasmapheresis procedure, a donor must have a total plasma protein level (or comparable level for a serum sample) of no less than 6.0 grams per deciliter, unless an alternative procedure for monitoring a donor's protein levels has been approved by the Director, Center for Biologics Evaluation and Research."

4) *Malaria* – PPTA agrees with the Agency's approach captured in the Proposed Rule's 21 CFR § 630.15(b)(7), 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. Indeed, by logical extension, 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. The FDA approach in proposed 630.15(b)(7) is emblematic of the paradigm that we suggest be used with regard to other transfusion transmitted infections and syphilis. The language in the Proposed Rule indicates that the Agency should rightly consider the intended use of the product and the robust processing, manufacturing, and purification steps that are used to manufacture modern, high-quality plasma protein therapies. Because malaria and a host of other pathogens do not impact our industry's therapies or 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 criteria.

21 CFR § 640.30(a)(2)

(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.

PPTA would also like to take this opportunity to discuss an applicable regulation that was not included in the proposed rule. PPTA reiterates comments made previously on **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.

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.

PPTA is a member of the AABB Interorganizational Plasma Task force and supports the recommendations made to FDA previously.

Proposed 21 CFR § 640.34 Component Processing

Recommendation

PPTA would also like to take this opportunity to discuss an applicable regulation that was not included in the proposed rule. PTA requests that FDA 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. PPTA is a member of the AABB Interorganizational Plasma Task force and fully supports comments and rationale provided previously and again by AABB to this Proposed Rule. PPTA views it more appropriate to provide a regulatory mechanism for a plasma product intended for manufacturing use that is collected under the umbrella of whole blood donation requirements than to attempt to define such a product by exceptions to the requirements for Source Plasma."

Proposed 21 CFR § 640.65 Plasmapheresis

§ 640.65 Plasmapheresis (b)(1)(i) Except as provided under § 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 immunodiffusion test or an equivalent test to determine immunoglobulin composition of the plasma or serum, must be performed on the sample.

(2)(i) Except as provided under § 630.25 of this chapter, the accumulated laboratory data, including tracings of the plasma or serum protein electrophoresis pattern, if any, the calculated values of each component, and the collection records must be reviewed by the responsible physician as required in § 630.5 of this chapter within 14 calendar days after the sample is drawn to determine whether or not the donor should be deferred from further donation. If a determination is not made within 14 calendar days, the donor must be deferred pending such a determination. The responsible physician must sign the review. If the protein composition is not within normal limits established by the testing laboratory, or if the total protein is less than 6.0 grams per deciliter of plasma sample or more than 9.0 grams per deciliter of plasma sample, or the comparable level for a serum sample, the donor must be deferred from donation until the protein composition returns to acceptable levels. Reinstatement of the donor into the plasmapheresis program when the donor's values have returned to acceptable levels must first be approved by the responsible physician.

Preamble Requests, p. 63431

No additional request for information

Recommendation

For § 640.65 (b) (1) (i), **PPTA** reiterates comments made on proposed § 630.15(b) (3).

For § 640.65 (b) (2) (i), **PPTA** recommends that the review time for determination remain at 21 days. The current 21 day allowance is needed to ensure adequate time for testing, return of test results to the laboratory and medical review. FDA should note

that Canadian health authorities recently changed their requirement from 14 days to 21 days Please see attachment 2 for a copy of C.04.407(3) of the *Canadian Food and Drug Regulations*.

I. § 640.69 General Requirements

Proposed 21 CFR §640.69 (e) Restrictions on distribution

Establishments must ensure that Source Plasma donated by paid donors not be used for further manufacturing into injectable products until the donor has a record of two suitable donations within the last 6 months.

Proposed § 640.69 (f) Hold

Source Plasma donated by paid donors determined to be suitable for further manufacturing into injectable products must be held in quarantine for a minimum of 60 days before it is released for further manufacturing.

Preamble Requests, p. 63431

FDA is soliciting comments and supporting data on whether other requirements other than what is proposed in proposed 21 CFR § 640.69 would achieve the same goal of voluntary initiatives described in the report entitled, "Blood Plasma Safety: Plasma Product Risks Are Low if Good Manufacturing Practices are Followed" (September 9, 1998). Also, the Agency is soliciting comments on whether these provisions should also apply to Source Plasma from paid donors collected for manufacture into noninjectable products.

Recommendation

PPTA recommends that FDA remove the proposed 21 CFR § 640.69 (e) and (f) from the Final Rule. Plasma protein therapies are safe and effective under the current FDA requirements. PPTA appreciates FDA recognizing the voluntary PPTA Standards. However, it must be recognized that the PPTA Standards Program layers additional standards to an already effective regulatory framework to allow PPTA members an additional margin of safety.

In its proposal, FDA selected only two elements of a comprehensive Standards Program, the Qualified Donor standard and the 60 day-hold standard for plasma donations. In order for a plasma center to be certified under PPTA's International Quality Plasma Program (IQPP), it must follow the entire voluntary standards program and be audited against the criteria in the Standards. PPTA has recently compared IQPP certified plasma centers against the FDA's registration and product listing data base. According to the Center for Biologics Evaluation and Research's (CBER) Blood Establishment Registration Database, there are 384 Plasmapheresis Centers. PPTA

represents 96.6% of those registered. Those plasmaspheresis centers that are not IQPP-certified or pending certification and do not follow our standards include blood establishments that presumably list Source Plasma collected under infrequent programs and facilities that collect for research, specialty or for diagnostic use. PPTA is willing to discuss the specific results of this comparison with CBER personnel.

The entire PPTA Standards program is reviewed periodically for effectiveness. The ability to evaluate the program and change if necessary ensures that the Standards remain meaningful and valuable. In addition, it allows the industry to respond quickly to changes in the environment. PPTA has a strong track record for successfully managing this process. Adoption of current PPTA Standards in regulation will remove flexibility and serve as a disincentive to the development of new standards (or the adoption of new technologies) that would increase the supply of scarce life-saving plasma derived therapies with the existing or an enhanced safety profile. The lack of flexibility of the regulatory process is demonstrated by the over ten years that it took FDA to publish this proposed rule. Because of the time it took to publish the proposed rule, the rationale for inclusion of some proposed requirements has become outdated and outmoded. For example, FDA bases the inclusion of these two elements of the PPTA voluntary standards on the GAO report ‘‘Blood Plasma Safety: Plasma Product Risks Are Low if Good Manufacturing Practices Are Followed’’ (September 9, 1998), which is now 10 years old and was published prior to universal adoption of NAT testing.

Specific comments to the FDA proposal follow:

“Restrictions on distribution” – The language of the proposed requirement mimics the PPTA Qualified Donor Standard. The PPTA Qualified Donor Standard was established to provide an additional donor history evaluation and acceptable test results prior to using a donation from a donor and to eliminate the one-time only donor since studies have shown that this donor for both blood and plasma has higher viral marker rates. Although reasons for this are not known definitively, one explanation is that the donor may be a test seeker.

Although the Qualified Donor Standard was developed over ten years ago, PPTA has evaluated this standard on a periodic basis and believes the Qualified Donor Standard continues to add value. However, PPTA believes it is more beneficial to keep this as an Industry Standard to allow for continued flexibility and responsiveness to changing technology and increasing knowledge of donor management. Furthermore, it is inappropriate to add the qualifier “paid.” The Qualified Donor Standard adds value in any frequent donation program.

PPTA objects to the use of “paid” as a modifier to Source Plasma in any context, whether in proposed new regulations or other documents. The plasma industry expects much of its donors in terms of commitment to donation and the time it takes to fulfill that commitment. For this commitment, PPTA member companies compensate their donors. The voluntary compensated donor should not be made to feel less worthy,

considering the donors' irreplaceable contribution to the health and well being of others. Donation of blood and plasma should be encouraged. With the competition for philanthropy in its various forms, it is often necessary to reward donors. FDA's current black and white definitions of "paid" and "volunteer" work against recognizing the need to provide incentives to encourage donation. PPTA does not understand how FDA differentiates between money for donation and a "gift card" for donation. PPTA is providing examples of current donor incentives to show FDA how the line between the current terms is blurred and to encourage FDA to open discussion and research into the use of incentives to encourage donations and stop discriminatory labeling of donations. Copies of recent advertisements and news articles are included in Attachment 3.

"Hold" - The Industry Standard for a 60-day inventory hold was established over ten years ago, prior to NAT testing. At that time the 60-day hold added significantly to the safety of the plasma manufacturing pool as was acknowledged by the GAO report ''Blood Plasma Safety: Plasma Product Risks Are Low if Good Manufacturing Practices Are Followed'' (September 9, 1998).

Since that time NAT testing has been introduced. As a result, regulations and industry standards include use of NAT at the donation and/or pool level testing. The window period for a virus to be present in plasma before detection is greatly reduced with NAT testing, since NAT detects the viral particles. NAT testing ensures that the viral load in the plasma is below the detection of the NAT test; this is very different than viral load in plasma prior to the appearance of antibody. PPTA has reaffirmed in its review of its Standards that the industry will maintain the 60-day inventory hold as part of its current practices to continue adding a margin of safety. However, introduction of the 60-day inventory hold into regulations should require the Agency to prove that the 60-day inventory hold is necessary to assure the safety of plasma protein therapies.

In addition to comments above, PPTA notes that the proposed regulation, as written, is a requirement for the collector as a release test for the plasma not as a manufacturing requirement prior to use of the plasma in manufacturing, as is the case for the PPTA voluntary standard. The proposed regulation would be unduly burdensome on plasma collectors as they would have to store the plasma at the collection center during the 60-day inventory hold period or provide "quarantine" labeling. The PPTA standard for 60 day hold provides the manufacture the flexibility to determine the most appropriate place for storage. It is not a quarantine. It is a normal step in the manufacturing process. Quarantine implies the material is in question and needs to be secured until a full investigation can be completed. There is nothing irregular about the plasma in the 60 day hold; it is simply sitting in inventory as part of the standard process. There are legitimate reasons to place material into quarantine and doing so for all plasma will add confusion and weaken the exiting quarantine system.

Collector quarantine and interim labeling are impractical and would add substantial cost to the manufacture of plasma for fractionation without increasing the safety of the current plasma protein therapies. Regarding storage on site, due to freezer space constraints, most collection centers have to ship material out on at least every two weeks and many on a more frequent basis. To require a freezer sized to hold 60 days of material would be very costly. A freezer for a two week inventory can typically run between $100,000 to $200,000 dollars each. Regarding "quarantine" labeling, use of an interim label would add cost, increase the probability of errors, and increase the probability of temperature fluctuations during the labeling operations. It also would dilute the value of the term "quarantine" as currently used and understood.

The preamble to the proposed rule asks if the proposed regulation should be extended to plasma for manufacture into non-injectable products. PPTA opposes this inclusion, as we object to the inclusion of the restrictions in the regulations for plasma for manufacturing into injectable products, as stated above.

If FDA wishes to acknowledge the acceptability of PPTA's voluntary standards program, there is precedent for doing so. Precedent for such reference can be found in 21 CFR 606.100 (d). The SOP regulations cite the manuals for organizations (e.g., ARC and AABB) as appropriate to meet the requirements for an SOP. This approach allows PPTA the continued ability to respond quickly to changing needs in the Standards.

Proposed 21 CFR § 640.72(a) Records

(a)(2)(i) For each donor, a separate and complete record of initial and periodic examinations, tests, laboratory data, and interviews as required in §§ 630.10 and 630.15 of this chapter and §§ 640.65, 640.66, and 640.67, except as provided in paragraph (a)(2)(ii) of this section. (ii) Negative results for testing for evidence of infection due to relevant transfusion-transmitted infections required in § 610.40 of this chapter, and the volume or weight of plasma withdrawn from a donor need not be recorded on the individual donor record if such information is maintained on the premises of the plasmapheresis center where the donor's plasma has been collected. (3) The original or a clear copy of the donor's written statement of understanding for participation in the plasmapheresis program or for immunization. (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.

Preamble Requests, p. 63431

No request for additional information

Recommendation

PPTA seeks Agency clarification on whether the requirement, within proposed § 640.72(a) (3), for a copy of the donor's written statement of understanding be maintained, would meet the electronic records requirements of Part 11. Also, proposed § 640.72(a) (4) requires responsible physician documentation. We refer to comments made earlier within section VII, on proposed § 630.3(h) regarding the duties of the responsible physician and seek clarification of this term as stated previously.

Proposed 21 CFR § 640.73 Reporting of Donor Reactions

(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.

Preamble Requests, p. 63431

No request for additional information

Recommendation

PPTA recommends the following changes be made "When a complication of source plasma collection is confirmed to be fatal, the Director of the Center for Biologics Evaluations and Research shall be notified by telephone, facsimile, express mail, or electronically transmitted mail as soon as possible. A written report of the investigation shall be submitted to the Director within 7 days after the fatality by the collecting facility. Follow-up reports shall be submitted as indicated."

The report of fatalities related to collection of blood or plasma is covered in two parts of the 600 series of the CFR. Section 606.170 covers "blood collection" while section 640.73 covers "source plasma collection". The wording used in the two parts is different. FDA does not propose to change the wording used in 606.170; therefore, we believe the wording in 640.73 should be the same as that in 606.170. Currently, source plasma establishments follow both sections. Consistency would be helpful to assure appropriate reporting. The use of the phrase "which, in any way, may be" in 640.73 leads to lack of clarity as to the fatalities that should be reported. The wording in 606.170 is clearer and assures the Agency will deal only with fatalities confirmed to be related in some way to the procedure, whether caused by it or not. Fatalities after the donor leaves the establishment that result from various diseases or mishaps cannot be clearly related to the procedure and should not be reported unless there is some reasonable basis to link the fatality to the procedure.

Proposed 21 CFR § 640.73 (b)
(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 § 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 Requests, p. 63432

No request for additional information

Recommendation

PPTA recommends 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. For vaccine adverse events, there is already a reporting system in place - the Vaccine Adverse Event Reporting System (VAERS), which has been developed under 21 CFR 600.81. Currently, blood components, including Source Plasma and immunizing 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 PPTA recommends that this exemption be continued.

PPTA is actively participating in AABB's Donor Biovigilance Working Group that is working towards a system aimed at capturing and analyzing data regarding adverse events associated with donating blood or plasma. PPTA believes that the work completed by this group will provide a valuable service in surveillance of donor adverse events and expanding current regulatory requirements for reporting may hinder the important voluntary work being undertaken at this time.

Proposed 21 CFR § 660.31 Eligibility of Donor

Donors of peripheral blood for Reagent Red Blood Cells must meet all the criteria for donor eligibility under §§ 630.10 and 630.15 of this chapter.

Preamble Requests, p. 63432

FDA is interested in receiving comments on limiting donor eligibility determination requirements to donation collected in the United States for use in the manufacture of Reagent Red Blood Cells.

Recommendation

PPTA recommends that FDA not include the proposed requirements in the final rule as the additional requirements of meeting criteria for donor eligibility under § § 630.10 and 630. 15 would impose an unnecessary restriction on the collection of whole blood that is used in manufacturing of in vitro diagnostic devices. These products are not used for transfusion and are further processed for reagent use only. These proposed regulations could adversely impact the number of donors for these products. With the short expiration dating for these products, a large inventory of donors is necessary to allow production of the required cells for the US market. A reduction in the number of these donors could potentially cause a shortage of reagent red blood cells used in transfusion services.

Proposed 21 CFR § 1270.3 Definitions

(b) *Blood component* means a product containing a part of human blood separated by physical or mechanical means.

Preamble Requests, p. 63432

No request for additional information

Recommendation

PPTA refers to comments made previously in section I above on § 606.3(a).

PPTA appreciates the opportunity to comment on the Proposed Rule. Should you have questions concerning these comments, please direct them to me at the Association.

Respectfully submitted,

Mary Gustafson
Vice President, Global Regulatory Policy
Plasma Protein Therapeutics Association

Attachments:

1. FDA letter dated April 18, 2005
2. C.04 407(3) of Canadian Food and Drug Regulation
3. Miscellaneous news articles and advertisements related to donor incentives