DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use

Docket No. FDA-2006-N-0040 (formerly Docket No. 2006N–0221)

Final Regulatory Impact Analysis
Final Regulatory Flexibility Analysis
Unfunded Mandates Reform Act Analysis

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Table of Contents

I. Introduction and Summary

A. Introduction

FDA has examined the impacts of the final rule under Executive Order 12866, Executive Order 13563, the Regulatory Flexibility Act (5 U.S.C. 601-612) and the Unfunded Mandates Reform Act of 1995 (Public Law 104-4). Executive Orders 12866 and 13563 direct agencies to assess all costs and benefits of available regulatory alternatives and, when regulation is necessary, to select regulatory approaches that maximize net benefits (including potential economic, environmental, public health and safety, and other advantages, distributive impacts, and equity). The Agency believes that this final rule is not a significant regulatory action as defined by Executive Order 12866.

The Regulatory Flexibility Act requires agencies to analyze regulatory options that would minimize any significant impact of a rule on small entities. 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.

Section 202(a) of the Unfunded Mandates Reform Act of 1995 requires that agencies prepare a written statement, which includes an assessment of anticipated costs and benefits, before proposing "any rule that includes any Federal mandate that may result in the expenditure by State, local, and tribal governments, in the aggregate, or by the private sector, of $100,000,000 or more (adjusted annually for inflation) in any one year." The current threshold after adjustment for inflation is $141 million, using the most current (2013) Implicit Price Deflator for the Gross Domestic Product. FDA does not expect this final rule to result in a 1-year expenditure that would meet or exceed this amount.

B. Summary of Costs and Benefits

This rule sets forth requirements for donor eligibility and donation suitability to ensure the safety, purity, and potency of the blood and blood components used for transfusion or for further manufacture. Costs estimated in this analysis include costs related to the standard operating procedures and bacterial testing requirements for blood collection establishments and transfusion services. The total upfront costs are $16,042,628, and include costs related to the review, modification, and creation of standard operating procedures. The mean annual costs of $892,233 include costs related to the bacterial testing of single units of Whole Blood-derived platelets and speciation of bacterially contaminated platelets. We anticipate that this final rule will preserve the safety, purity, and potency of blood and blood components by preventing unsafe units of blood or blood components from entering the blood supply, and by providing recipients with increased protection against communicable disease transmission. The requirements set forth in this rule will also help to decrease the number of blood transfusion related fatalities that are associated with the bacterial contamination of platelets. The annual value of additional fatalities averted by testing of Whole Blood-derived platelets is estimated to be approximately $27 to $90 million, and the annual value of averted nonfatal sepsis infections is estimated to be $3.19 million to $4.91 million.

II. Regulatory Impact Analysis

A. Costs

On November 8, 2007 (72 FR 63416), FDA published the proposed rule "Requirements for Human Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use" to amend regulations by adding donor eligibility and donation suitability requirements that are consistent with current practices in the blood industry, and to more closely align the regulations with current FDA recommendations and to provide flexibility to accommodate advancing technology. Blood establishments must also establish, maintain, and follow standard operating procedures (SOPs) for the determination of donor eligibility. The final rule provides regulatory standards to support existing practices for assuring donor safety and to assure the safety, purity, and potency of blood and blood products.

This final rule would affect all establishments that collect blood and blood components, including Source Plasma, as well as all transfusion services. The FDA registration database for blood and plasma establishments has records of 416 licensed Source Plasma establishments, and 1,265 licensed blood establishments, for a total of 1,681 licensed blood collection establishments and 680 unlicensed, registered blood collection establishments. In addition, there are approximately 4,961 transfusion services, most of which are not required to register with FDA, that would be impacted by the final rule. FDA estimates that approximately 15 million donations of Whole Blood and apheresis Red Blood cells are collected annually, and 25 million donations of Source Plasma are collected annually.

This rule provides for the establishment of minimum criteria for the assessment of donor eligibility, and the suitability of the donation of blood and blood components. This aspect of the rule is expected to have a minor net impact on blood establishments because it is already usual and customary business practice in the blood industry to assess donors for eligibility, and donations for suitability. FDA retains much of the cost analysis of the proposed rule for application to the final rule. As stated in the analysis for the proposed rule, one of the impacts of the rule will be the one-time review and possible modification of current SOPs that each blood collection establishment would need to conduct.

The burden imposed by this one-time effort to review and, if necessary, modify current SOPs will vary among the 2,361 blood collection establishments, depending on the establishment's existing procedures. For establishments that already have established procedures that conform to the final rule, we estimate that it would take approximately 40 hours of staff time to review the establishment's current SOPs to confirm that the SOPs comply with the regulation. A technical specialist who acts as a regulatory reviewer or manager of quality assurance could perform this process. Based on the total average hourly compensation (including benefits) of $67.64 for medical and health services managers in the healthcare and social assistance industry, as reported by the Bureau of Labor Statistics, the cost would be approximately $2,706 ($67.64 per hour x 40 hours) per establishment (Ref. 1).

For establishments that do not already have procedures that conform to the final rule, we estimate that approximately 60 hours of staff time would be required to align current SOPs with

the provisions of the rule as required under § 606.100(b) (Standard Operating Procedures). As we believe most establishments have SOPs that are consistent with the rule, the extent to which the staff would need to be notified of these updated SOPs would not result in extensive formal training. The cost in this case would be approximately $4,058 ($67.64 per hour x 60 hours) per establishment. Assuming a minimal review is needed at two-thirds of the 2,361 currently operating blood collection establishments, and a more extensive review is conducted by the other one-third, the total one-time cost for the blood industry is estimated to be $7,452,889 [((2/3 x 2,361) x $2,706)) + ((1/3 x 2,361) x $4,058))]. In addition, we estimate that it will take 16 hours for each of the 4,961 transfusion service to review 21 CFR part 606 and modify their SOPs to conform to the final rule. This yields total upfront costs to industry of $5,368,993 (4,961 x 16 x $67.64). Some transfusion services will need to create new SOPs to conform to § 606.100(b)(22) and the cost estimate for such is described later in this section.

There are several requirements that were added to the final rule that were not included in the proposed rule. Of these requirements, there are five that have potential economic impacts. These requirements are in § 610.40-Testing Requirements, § 630.5-Medical Supervision, § 640.21-Eligibility of (Platelet) Donors, § 606.145-Control of Bacterial Contamination of Platelets, and § 606.100(b)(22)-Standard Operating Procedures. Industry currently complies with the first three of these requirements and thus these requirements will not have an economic impact. In addition, any review and modification of associated SOPs would be captured under the economic burden previously described.

Section 610.40 requires testing certain donations for two additional relevant transfusion-transmitted infections, which are West Nile virus (WNV) and Chagas disease. The economic impact is minimal because it is current industry practice to test for WNV and Chagas disease as this testing is already called for in the current AABB (formerly the American Association of Blood Banks standards and FDA guidance documents (Refs. 2 through 5).

Section 630.5(d) requires blood collection establishments to assure that an individual who is currently certified in cardiopulmonary resuscitation (CPR) is located on the premises whenever the establishment is performing collections of blood or blood components. Having trained personnel on site is current industry practice as required in the biologics license application approval process. Thus, FDA believes that this requirement is also consistent with current industry practice.

Section 640.21(c) requires that if a Whole Blood donor has recently ingested a drug that adversely affects platelet function, the unit of platelets must be labeled to identify the ingested drug. This requirement will have a minimal impact on establishments because units are currently labeled.

One of the new requirements being incorporated into the final regulation is the requirement in § 606.145(a) that requires blood collection establishments and transfusion services to assure that the risk of bacterial contamination of platelets is adequately controlled using FDA approved or cleared devices or other adequate and appropriate methods found acceptable for this purpose by FDA. We believe that it is the current practice of blood establishments and transfusion services to test most, if not all, platelet donations for bacterial

contamination. Under this rule, transfusion services may rely on the steps taken by the blood collection establishment to assure that the risk of bacterial contamination of a platelet component is controlled. If the collection establishment did not take steps to control the risk of bacterial contamination, then the transfusion service must do so. Section 606.145(b) through (d) requires that when a blood collection establishment identifies a platelet donation as bacterially contaminated, that establishment must not release for transfusion the product or any other component prepared from the same collection, and must take appropriate steps to identify the organism and determine whether the contaminating organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor. Further, in the event that a transfusion service identifies platelets as bacterially contaminated, the transfusion service must not release the product and must notify the blood collection establishment that provided the platelets. The transfusion service must also take appropriate steps to identify the organism and notify the blood collection establishment of the results of the steps taken to identify the organism. The collection establishment's responsible physician is required to determine whether the contaminating organism is likely to be associated with a bacterial infection that is endogenous to the bloodstream of the donor. We have concluded that the requirements in § 606.145(b) through (d) related to product release, notification of the blood collection establishment and identification of the contaminating organism are currently practiced when blood establishments and transfusion services identify platelets as bacterially contaminated, and SOPs should currently be in place in such establishments.

We have also concluded that the majority of platelet units are tested for bacterial contamination using FDA cleared devices at least one time prior to transfusion, meeting the requirement in § 606.145(a). There are two types of platelet products: apheresis platelets and Whole Blood-derived platelets. Apheresis platelets are obtained from a single donor by plateletpheresis and can be transfused without pooling because they contain a sufficient number of platelets. Whole Blood-derived platelets are platelet concentrates separated from Whole Blood donations. Whole Blood-derived platelets are pooled to provide a sufficient number of platelets to transfuse to recipients. There are approximately 2 million platelet transfusions administered annually in the United States. Of these, about 1.74 million are apheresis platelets and 0.26 million are pools of Whole Blood-derived platelets with each pool composed, on average, of five single units of Whole Blood-derived platelets.

Consistent with the AABB consensus standard, apheresis platelets are currently subject to testing by the blood collection establishment using a culture-based method before they are distributed to transfusion services. Thus, we do not expect this new requirement will alter testing practices for blood establishments distributing apheresis platelets. Whole Blood-derived platelet testing practices will be minimally affected by this rule. There are approximately 260,000 Whole Blood-derived platelet transfusions per year. Of these, 164,000 are pooled shortly after collection and tested at the collection establishment before distribution using a pre-storage pooling system for Whole Blood-derived-platelets. This system requires bacterial testing as part of the instructions for use according to 21 CFR 606.65(e) which states, "supplies and reagents shall be used in a manner consistent with instructions provided by the manufacturer." Therefore, we conclude that all 164,000 pooled platelet doses are tested for bacterial contamination. The remaining approximate 96,000 pooled platelet doses of Whole Blood-derived platelets are not processed using the pre-storage pooling system and are pooled at the transfusion service prior to

transfusion. Therefore, these units would be subject to point of release testing. Consistent with data publicly presented in 2012 (Ref. 6) we believe that it is current practice that all of these 96,000 pooled platelet doses are tested at the transfusion service using an FDA approved rapid test.

However, a transfusion service may intend to release for transfusion a platelet component derived from a single unit of Whole Blood without pooling for use in a pediatric patient or neonate. We are not aware that blood collection establishments typically subject such components to testing by culture-based methods, in part because the volume of the sample required for currently available culture tests would significantly deplete the volume of the component. For such single units of Whole Blood-derived platelet components, § 606.145 would require the transfusion service to take steps, such as the performance of an FDA-cleared rapid test, to assure that the risk of bacterial contamination is adequately controlled. Based on AABB standards, we would expect that these collections would also be tested for bacteria. However, we are not aware of data on testing of these donations and are uncertain whether these single donations of Whole Blood-derived platelets are being tested. According to the National Blood Collection and Utilization Survey, there were 1.1 million Whole Blood-derived platelets collected in 2011 (Ref. 7), and we estimate that approximately 1 to 3 percent may be released as single units for transfusion and may not currently be subject to bacterial testing. Accordingly, we estimate that at most, 11,000 to 33,000 platelet collections per year may not be tested currently and would be subject to point of release bacterial testing of platelets. Based on the testing algorithm of the point of release test which requires repeat testing on initial positive results, the total number of tests would range from 11,146 to 33,348. At an estimated cost of approximately $40 for each test, the bacterial testing requirement will yield an annual maximum cost ranging between $445,840 ($40 x 11,146) and $1,337,520 ($40 x 33,438). Further, under § 606.145(c), if any of these single unit Whole Blood-derived platelets are identified as bacterially contaminated, the transfusion service must take steps to identify the contaminating organism. Given that the rapid bacterial tests have a repeat reactive rate of 0.548%, between approximately 61 (11,146 x 0.548%) and 183 units (33,438 x 0.548%) will be considered positive and then be cultured at a cost of $45 per culture test for a total cost of $2,745 to $8,235. Approximately 3 to 10 donations will test positive on culture tests (0.03% of total number of units), and will require speciation. At an estimated cost of $85 per speciation, the annual cost of the speciation requirement will range between $255 and $850.

Section 606.100(b)(22) concerning standard operating procedures requires establishments to have procedures for the processes (SOPs) used to control the risk of bacterial contamination of platelets. As discussed previously, we believe that all blood establishments and most transfusion services currently have SOPs in place to control the risk of bacterial contamination consistent with the requirements in § 606.145. In addition, according to current AABB standards, blood banks and transfusion services should have methods (1) to limit, and (2) to detect or inactivate bacteria in all platelet components, and detection methods shall either be approved by the FDA or validated to provide sensitivity equivalent to FDA-approved methods (Ref. 8). Thus, this additional requirement will have a minimal impact on blood collection establishments that are currently complying with the new requirements in § 606.145 or those transfusion services that are AABB members or AABB accredited because it is current industry practice to keep such procedures and processes for testing blood and blood components.

In addition, we estimate that the approximately 40 percent of transfusion services are AABB members and would be expected to follow the voluntary standards for testing, speciation, and notifying the blood establishment. Of the remaining 60 percent of the transfusion services that are not AABB members, we estimate that 50 percent would need to create new SOPs for bacterial testing and speciation of platelets consistent with § 606.100(b)(22). Of the 4,961 transfusion services, 1,488 may be impacted by this requirement. We estimate that the time required to create a new SOP is 16 hours, at an average hourly labor cost of $67.64. This yields a cost burden of $1,610,373 (1,488 x 16 x $67.64) for each new SOP. Accounting for the two new SOPs that must be created for testing and speciation, the total one-time cost associated with this requirement is $3,220,746.

Table 1. Summary of Total Costs

Type of Cost	Upfront Costs	Annual Costs		
		Low	Mid	High
Review and Modification Standard Operating Procedures (blood collection establishments)	$7,452,889			
Review and Modification Standard Operating Procedures (transfusion services)	$5,368,993			
Creation of New Standard Operating Procedures (transfusion services)	$3,220,746			
Bacterial Testing of Whole Blood-derived Single Unit Platelets (transfusion services)		$445,840	$891,680	$1,337,520
Bacterial Speciation of Whole Blood-derived Single Unit Platelets (transfusion services)		$255	$553	$850
Total Costs	$16,042,628	$446,095	$892,233	$1,338,370

B. Benefits

This rule will help ensure the continued safety of the nation's blood supply. As described in the preamble to this rule, the assessment of eligibility of donors and the suitability of donations will help prevent unsafe units of blood or blood components from entering the blood supply. This rule will also protect the health of donors and will preserve the safety, purity, and potency of blood and blood components. The requirements set forth in this rule are intended to

increase the safety of all blood and blood components by providing recipients with increased protection against communicable disease agents.

The gravity of the disease risks associated with blood and blood components is widely recognized. For example, the risk of transfusion transmission of human immunodeficiency virus (HIV), the virus that causes AIDS, has decreased significantly over the last two decades due to donor screening and testing, but continues to be of concern. Human T-lymphotropic virus, types I and II, were identified in the early 1980s. These viruses are known to be transmitted by transfusion. Infection with these viruses is associated with tropical spastic paraparesis, adult T-cell leukemia/lymphoma, and some inflammatory disorders (Ref. 9).

Hepatitis B virus (HBV) is a major cause of acute and chronic hepatitis, cirrhosis, and hepatocellular carcinoma worldwide and also is known to have been transmitted by transfusion. The Centers for Disease Control and Prevention (CDC) estimates that 1.2 million Americans are chronically infected with HBV. Approximately 15 to 25 percent of people with chronic Hepatitis B develop serious liver problems, including liver damage, cirrhosis, liver failure, and liver cancer. Every year, approximately 3,000 people in the United States die from Hepatitis B-related liver disease. Although the number of new cases of Hepatitis B has decreased more than 80 percent over the last 20 years due, in part, to childhood vaccination, currently an estimated 40,000 people become infected each year (Ref. 10). Prior to the development of hepatitis screening tests, transfusion-related risks were significantly higher.

Prior to 1992, when widespread screening of the blood supply began in the United States, Hepatitis C was commonly spread through blood transfusions. Blood donor screening for HCV has reduced transfusion-associated transmission to less than one in 1.6 million transfused units of blood (Ref. 11). The CDC estimates approximately 17,000 new HCV infections occur annually in the United States and that 3.2 million Americans have been infected with HCV. Chronic Hepatitis C infection can result in long-term health problems, including liver damage, liver failure, and liver cancer that result in the need for a liver transplant. Approximately 12,000 people die every year from Hepatitis C-related liver disease (Ref. 12).

The rule will also require testing for WNV. WNV infection was first recognized in 2002, as a potentially fatal transfusion transmissible infection. Since implementation of WNV screening assays in 2003, thousands of infections in blood recipients were prevented. In November 2009, FDA issued final guidance recommending year-round use of WNV nucleic acid test (NAT). In 2012 and 2013, blood establishments reported 748 and 422 positive donations, respectively, that were interdicted. The WNV outbreak in 2012 was the largest reported since the 2002/2003 outbreaks resulting in a total 5,674 reported cases, including 2,873 neuroinvasive diseases and 286 deaths. The 2013 outbreak was also intense resulting in 2,374 reported cases including 1,205 neuroinvasive diseases and 114 fatalities. Testing for WNV by NAT is now a routine practice in blood establishments.

While the risk of transfusion related transmission of viral diseases such as HIV and hepatitis has steadily decreased over the last decade, the risk of transmission of bacteria from platelet transfusions continues to cause great concern. Platelet transfusions are typically needed to prevent or treat bleeding in individuals undergoing chemotherapy for cancer, following major

trauma, during or after surgery, and in patients who are not able to produce platelets. Bacteria-contaminated platelets can cause sepsis, a life-threatening infection in the bloodstream that can spread to multiple organs and is the leading infectious cause of patient fatalities associated with platelet transfusion. Testing of platelets for bacterial contamination prior to transfusions may prevent contaminated units from reaching patients and is a potentially life-saving measure.

The risk of bacterial contamination in platelets is one of the leading infectious risks of blood transfusions. Approximately 2 million platelet products are transfused annually in the United States and an estimated 1/1000-platelet products are contaminated by bacteria at collection. Platelet components are uniquely vulnerable to bacterial outgrowth because of their room temperature storage and are associated with a higher risk of sepsis and related fatality than other transfusible components. Non-fatal adverse reactions from blood transfusions are not currently required to be reported to FDA. However, the number of transfusion related fatalities reported to FDA is small in comparison to the total number of transfusions. In Fiscal Year 2013, two deaths associated with bacterial contamination of platelets were reported to FDA. There were a total of 19 fatalities associated with bacterial contamination of platelets reported to FDA from Fiscal Year 2007 through Fiscal Year 2013. , . However, the number of fatalities reported to FDA is believed to be underestimated due to the passive nature of the reporting mechanism. The current estimate of the total fatalities from bacterially contaminated platelets is approximately 10 to 20 cases per year in spite of the early culture of the units (Refs. 13 and 14). Platelet culture has reduced sepsis cases from bacterially contaminated platelets by about 50% (Ref. 13) leading to a reduction of the cases from about 400 cases per year prior to bacterial testing to about 200 cases per year following the introduction of the early culture test. Further, platelet culture has reduced fatality cases from transfusion of bacterially contaminated platelets by 75% (Ref. 13); therefore, the annual number of averted fatalities by performing bacterial testing is currently estimated to be between 30 (10 x 0.75/0.25) and 60 cases (20 x 0.75/0.25). Considering that 11,000 to 33,000 single units of Whole Blood-derived platelets are estimated to be transfused annually in the United States and do not undergo bacterial testing, and that the rate of bacterial detection by rapid testing is about 1/3,000 platelet units, we have estimated that testing of single units of Whole Blood-derived platelets will prevent about 3 to 10 additional cases of transfusion of bacterially contaminated platelets annually in neonates. Multiplying the average number of fatalities by the value of a statistical life (VSL) yields the estimated value of fatalities averted each year resulting from compliance with the bacterial contamination testing requirement. The VSL can be interpreted as the expected present value of the gain in consumer surplus from a reduction in risk and the value that we use is derived by the National Center for Environmental Economics of the Environmental Protection Agency. Using a VSL of $9 million, the annual value of additional fatalities averted by testing of Whole Blood-derived platelets is estimated to be approximately $27 to 90 million. In addition to the benefits from reduced fatalities, the rule would reduce medical expenditures for those who would otherwise acquire nonfatal sepsis infections. Data from the Healthcare Cost and Utilization Project (HCUP), a nationally representative sample of hospital discharges, suggest that sepsis related hospitalizations are associated with mean costs ranging between $15,944 and $24,533, depending upon the severity of the case. Using an estimate of 200 sepsis cases related to bacterially contaminated platelets per year, the annual estimated benefit of averted nonfatal sepsis infections range from $3.19 million to $4.91 million.

Due to advances in donor screening, improved testing, and changes in transfusion medicine practices, the risks associated with blood transfusion continue to decrease. The requirement that, for each donation of blood or blood component, blood collection establishments maintain standards for donor eligibility and blood and blood component donation suitability significantly reduces the risk of morbidity and mortality associated with diseases such as HIV HBV, HCV, HTLV, WNV, and syphilis, as well as the risk associated with the bacterial contamination of platelets. Such standards also reduce the attendant costs of these diseases.

III. Regulatory Flexibility Analysis

FDA has examined the economic implications of the final rule as required by the Regulatory Flexibility Act. If a rule will have a significant economic impact on a substantial number of small entities, the Regulatory Flexibility Act requires agencies to analyze regulatory options that would lessen the economic effect of the rule on small entities. Because the costs associated with this rule are expected to be minimal, this final rule would not impose a significant economic impact on a substantial number of small entities.

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