Advancing Transfusion and
Cellular Therapies Worldwide

October 19, 2017

Scott Gottlieb, M.D.
Commissioner
U.S. Food and Drug Administration
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Dear Dr. Gottlieb,

AABB is submitting this letter to request that FDA consider reevaluating certain regulations and recommendations that are considered outdated, duplicative, overly burdensome and unnecessary to protect the public health. We believe our request is consistent with the CBER Interim Strategic Plan FY 2017-19 and the agency's efforts to identify future needs and direction. We have identified regulations and recommendations that (1) do not increase safety; (2) are outdated, duplicative, unnecessary or overly burdensome; (3) unnecessarily restrict access to products and technology; or (4) stifle innovation.

AABB is an international, not-for-profit association representing over 6000 individuals and 1000 institutions involved in the field of transfusion medicine and cellular therapies. The association is committed to improving health through the development and delivery of standards, accreditation and educational programs that focus on optimizing patient and donor care and safety. AABB's individual membership includes physicians, nurses, scientists, researchers, administrators, medical technologists and other health care providers.

AABB appreciates its longstanding, constructive relationship with FDA. We are submitting this request in support of FDA's mission to ensure "the safety, purity, potency, and effectiveness" of blood and cellular therapy products, and to protect the public against the threats of emerging infectious diseases and bioterrorism. AABB promotes access to safe, effective products and technologies for transfusion medicine and cellular therapies, and supports the appropriate regulation of products and technologies. Please consider the following:

The new requirements of 21 CFR 630.10 limiting the ability of medical directors to use their clinical discretion when determining donor eligibility via telephonic consultation do not increase safety and are overly restrictive.
§630.10
§630.5

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Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (May, 2015) Available: https://www.gpo.gov/fdsys/pkg/FR-2015-05-22/pdf/2015-12228.pdf

Certain new regulations, in the May 2015 final rule, defining donor eligibility criteria for blood pressure do not increase safety, are overly restrictive, and limit the authority of the medical director to use his or her clinical judgment if a donor's blood pressure falls outside of the newly established range specified in §630.10(f). The preamble to the final rule describes an acceptable process to permit donation if the blood pressure is out of the new range, stating "establishments may permit the donor 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." However, use of this option is severely limited by the new regulations at §§630.5(b)(1)(i)(A) and (c)(1)(i)(A)(*1*) because "the responsible physician is not authorized to delegate this examination and determination of the health of the donor, and must personally perform this examination and determination." Therefore, the responsible physician must be onsite to perform a donor examination prior to donation.

AABB believes that providing the medical director with the discretion to use his or her clinical judgment when evaluating an elevated blood pressure would provide adequate protection for the donor whether evaluated onsite or by telephonic consultation. AABB requests FDA re-visit this issue and consider flexible options to permit medical directors to use telephonic consolation to evaluate such a donor, prevent unnecessary deferrals, and maintain uninterrupted operations.

The new requirements of 21 CFR 630.10 and 630.30 resulting in the destruction blood products, based on a collection error that does not adversely impact product safety, purity, or potency, do not increase safety, and unnecessarily restrict access to products for further manufacture.

§CFR 630.10
§630.30(b)
Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (May, 2015) Available: https://www.gpo.gov/fdsys/pkg/FR-2015-05-22/pdf/2015-12228.pdf

Many collection errors require discard of the blood product to protect the safety of the blood supply. However, certain collection errors captured in the May 2015 final rule have no adverse impact on the recipient of the blood product. AABB believes that discarding a blood product that otherwise meets all transfusion safety criteria does not increase safety; is overly burdensome; and, adversely impacts blood inventory.

AABB strongly supports compliance with FDA regulations for donor eligibility under §§630.10 and 630.15, while also respecting the value of life-saving products donated by altruistic volunteers. The May 2015 final rule, §630.30(b) "expressly prohibits an establishment from releasing an unsuitable donation for transfusion or further manufacturing use". Clearly, if applied to a donation deemed unsuitable due to the donor's increased risk for a relevant transfusion-transmitted disease, such as HIV, the destruction of the product is necessary to protect the transfusion recipient. These regulations also require the destruction of a blood product based on a collection error that does not pose a risk if transfused to a patient. For example, blood products inadvertently collected early, even 1 day prior to the required 56-day period between donations, are deemed unsuitable donations because the donor was not yet eligible to return for donation.

Thus, a safe, pure and potent blood product must be destroyed as unsuitable in the same manner as a product that would be at risk for disease transmission.

If this punitive approach is intended as a deterrent, the destruction of a life-saving blood product that meets all criteria for safety, potency or purity, is an ineffective and not easily justified. AABB recommends that FDA consider alternatives that offer protection to donors while permitting the use of a suitable blood product. This can be safely implemented if, for example, a blood collection establishment demonstrates an adequate quality system to monitor the rate of collection errors, with evidence of an acceptable error rate. At the time of FDA inspection, quality records could be available to provide evidence of adequate process control.

AABB has shared data with FDA illustrating the low rate error rate and the resulting discard of suitable collections in a sampling of blood collection establishments. It is clear that an acceptable error rate results in the unnecessary destruction of large number of blood products. We request that FDA consider soliciting public comments on effective approaches and enforcement mechanisms.

The regulatory storage requirements applicable to frozen plasma are outdated, overly restrictive, and do not increase safety.

§640.34
§640.69(b)
§640.74
Changes to an Approved Application: Biological Products: Human Blood and Blood Components Intended for Transfusion or for Further Manufacture; Guidance for Industry. (December, 2014) Available: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM354668.pdf

AABB continues to be interested in a change to FDA's interpretation of the regulations requiring Source Plasma to be placed in a freezer within 2 hours of collection. The decades old requirements specifying the freezer temperatures and time limit necessary to ensure adequate time for the freezing process, were developed prior to the use of "blast" freezers. Blast freezers, commonly used today, accelerate the controlled freezing process to achieve a frozen product in less time, permitting a change in practice that achieves the intended goals for product quality without the 2-hour limit.

We have shared in discussions with CBER that it is rarely possible to collect and expedite transport of blood from a collection site to the component manufacturing laboratory to ensure the 2-hour time limit for placement in the freezer. This obsolete requirement negatively impacts the business operations of blood collection establishments by limiting the number of collections that can be prepared and sold to plasma fractionators for further manufacture. In addition, these overly restrictive requirements for the early steps of processing by the collection establishment exceed the product specific requirements of the plasma fractionators purchasing this plasma for further manufacture into a final product. In general, plasma intended for manufacture into injectable products is frozen immediately. The term "immediately" is arbitrary and outdated, as other countries have implemented a more flexible twenty-four-hour requirement. It is important to recognize that each plasma fractionator stipulates adequate collection, processing, storage, and distribution steps to support the quality, purity and potency of a final product through the contract with the collection establishment.

AABB supports CBER's plans to update the regulations related to this issue. Based on the merits of this request, AABB suggests that FDA consider expediting the update of related regulations and definitions as a regulatory priority. We request that FDA provide relief from obsolete restrictions to permit practices that are consistent with the long established worldwide practice for freezing plasma within 24 hours, and remove excessive restrictions to provide for conformance with collection and handling requirements already mandated by fractionators in the contract with collectors to ensure the quality of the final product.

The recommendation to test donor units for syphilis is outdated, does not increase safety, and is overly restrictive.

§CFR 610.40
Guidance for Industry: Recommendations for Screening, Testing, and Management of Blood Donors and Blood and Blood Components Based on Screening Tests for Syphilis. (September, 2014) Available:
https://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm411780.htm
Requirements for Blood and Blood Components Intended for Transfusion or for Further Manufacturing Use; Final Rule (May, 2015) Available: https://www.gpo.gov/fdsys/pkg/FR-2015-05-22/pdf/2015-12228.pdf

AABB has long considered the requirement to test blood donors for syphilis to be outdated, unnecessary and overly restrictive because industry experience shows that, for over thirty years, there has not been a documented case of transfusion-transmitted syphilis. In the May 2015 Final Rule, FDA stated "We also solicited comments with supporting data on whether to discontinue the requirement for testing for syphilis, and we indicated that we might drop the requirement for syphilis testing if sufficient data were submitted (72 FR 63416 at 63422) …We have retained requirements for syphilis testing of blood and blood components for transfusion, since we did not receive data sufficient to support their elimination."

This spirochete has not been shown to survive during component storage, and viable spirochetes are not present in blood donors with confirmed antibody-positive test results which is consistent with the absence of documented reports of transfusion-transmitted syphilis over decades. The decision to "continue the requirement to test donations for evidence of syphilis" until data is provided, also results in the unnecessary deferral of blood donors due to false positive test results.

For these reasons, we question whether syphilis testing remains a valuable safety measure. AABB requests that FDA:

- Revisit the regulatory strategy, including the September 2014 guidance, and
- Pursue an evidence-based approach to update and remove these requirements.

The current statistical quality control plan is overly burdensome and does not increase safety.

§606.160
§211.192
Guidance for Industry Pre-Storage Leukocyte Reduction of Whole Blood and Blood Components Intended for Transfusion (September, 2012) Available:

https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM320641.pdf

Currently, conformance to product standards must be assessed by a statistically valid method, as required in §211.160(b). In the absence of a validation method (plan) provided by the manufacturer, blood establishments must use a "statistically valid plan based on 95% confidence that more than 95% of the components will meet the recommended results."

The agency's current recommendations for such a statistically valid plan, outlined in the September 2012 Guidance, are overly burdensome. The 2012 recommendations required a marked increase in quality control (QC) activities, are not necessary to increase safety and place a significant burden on all blood collection establishments. For example, under Table A of the hypergeometric sampling plan, a center collecting 40 products per month must perform QC testing on 31collections (75% of collections must be tested). Following the same example, a center with 1000 collections per month must perform QC testing on 60 collections. A wide range of component preparation processes, that are validated and well controlled by the establishment, require QC testing for to be repeated each month. This constitutes a tremendous burden on resources. The examples above demonstrate the large numbers of tests that are required in multiple product categories, the resulting financial burden for all, and the notable burden for those with fewer monthly collections. Additionally, these QC measures can require the use of complex testing technology, such as flow cytometry, creating a scenario where a physician's order for patient testing that is necessary for diagnosis and treatment, must compete for the same resources needed for testing a large number of QC samples within tight time frame.

Once validated to achieve the expected high degree of product conformance and safety, the process should not require additional extensive testing each month to re-validate a proven process. AABB suggests FDA revisit these recommendations and consider soliciting public comments to identify alternative processes for effective quality assurance for successfully validated and controlled processes.

The current donor deferral policy related to the risk of transmission of Creutzfeldt-Jakob Disease and Variant Creutzfeldt-Jakob Disease is outdated, overly burdensome and does not increase safety.

§630.3
§610.40
"Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products" (May 2010, Updated January 2016) Available: https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/UCM307137.pdf

AABB commends CBER for plans to update guidance recommendations in 2017. We believe the outdated recommendations can be safely removed and revised for the 2016 guidance, "Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products."

The 2016 donor deferral recommendations for potential exposure to Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) do not reflect current science. Specifically,

the basis for deferral does not consider the current evidence related to a shorter latency period than initially understood. The overly restrictive donor deferral recommendations have a substantial negative impact on the military blood system due to the travel of military members throughout the United Kingdom. Despite the absence of vCJD cases in the U.S. military and Department of Defense personnel over many years, these personnel continue to be ineligible for donation. This negative impact is also felt outside the Armed Services Blood Program because veterans and active duty personnel would be motivated to respond to the needs of community blood centers but remain deferred. Additionally, the policy is confusing, and difficult to interpret and enforce due to donors' and their families' non-consecutive travel.

AABB looks forward to review of the updated guidance, as listed on the July 2017 update to the CBER Guidance Agenda.

Requiring a Prior Approval Supplement for the collection of Source Plasma is overly restrictive and is not necessary to increase safety.

§601.12(c)

The requirement for submission of a Prior Approval Supplement (PAS) under §601.12 to collect source plasma for further manufacture from healthy donors with high titer antibodies is unnecessary if the establishment is currently licensed for the collection of infrequent, healthy donors. For example, the collection of Source Plasma from normal, healthy donors, with a high titer antibody for specific disease state (and not targeting disease state or IgM), can be achieved by submission of Changes Being Effected in 30 days (CBE-30) under §601.12(c) with reasonable assurance the licensed establishment follows a safe and adequate process that simply warrants a label approval. The lengthy PAS process for this type of routine plasma collection using an established protocol is disproportionate to the level of change being reported.

AABB requests FDA consider removing this overly restrictive application of the regulations to permit licensed facilities to submit a CBE-30 for the collection of Source Plasma from infrequent, healthy, donors for collection of high titer antibodies.

The Premarket Submission requirements for transfusion medicine software are outdated and overly burdensome.

21 CFR, Part 807

"Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices" (May, 2005) Available:
https://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm089593.pdf

"Guidance for Industry: Blood Establishment Computer System Validation in the User's Facility" (April, 2013) Available:
https://www.fda.gov/downloads/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm078815.pdf

We do not agree with FDA's description of the May 2005 guidance as the "least burdensome approach" to documentation provided in premarket submissions for "software devices regardless of the means by which the software is delivered to the end user, that is, whether factory-installed, installed by a third-party vendor, or field-installed or -upgraded". AABB believes this outdated and overly burdensome regulatory process is not necessary for effective regulation for all transfusion information systems (software)

and blood establishment computer systems (BECS). Specifically, AABB suggests that FDA expand exemptions for the excessive documentation and reporting requirements (such as found in §807.87, Information required in a premarket notification submission, §807.81, When a premarket notification submission is required, §807.92, Content and format of a 510(k) summary, and §807.93, Content and format of a 510(k) statement because they are no longer necessary based on current industry practices using well established validation processes implemented since 2005.

There are a limited number of options available in the US for software and BECS. The investment of resources required for Premarket Notification Procedures to achieve 510(k) clearances for transfusion medicine/blood bank/blood donor software stifles innovation, further limiting enhancements and access to such systems. The software that has been cleared often has limited functionality and flexibility to support advancements in the industry. The clearance process and resulting limitations placed on this blood bank software exceed the burden of corresponding safety measures placed on similar systems in other areas of laboratory medicine. In addition, changes to software to enhance performance require re-submission to FDA. By contrast, Laboratory Information Systems have much more advanced functionality than transfusion software but face less burdensome regulatory oversight.

Given the rigorous validation that is performed when implementing transfusion systems and software recommended in the April 2013 guidance, AABB encourages FDA to re-evaluate the broad scope of the regulations, to update the applicable definitions, and/or provide exemptions to permit a less burdensome approach. AABB supports a less restrictive approach that would update and narrow the scope of requirements while providing adequate protections, promote innovation, and improve access to products with increased functionality and flexibility.

AABB looks forward to working with FDA to continue advancing the safety of blood and cellular therapy products. If you have any questions or would like additional information, please contact Sharon Carayiannis, Director, Regulatory Affairs, at 301-215-6542 or SCarayiannis@aabb.org.

Sincerely,

Mary Beth Bassett

Mary Beth Bassett
President
AABB