America's Blood Centers

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October 14, 2003

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

Re: **Docket No. 2003N-0211**, Proposed Rule: Revision to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma

Dear Docket Officer:

America's Blood Centers (ABC) appreciates the opportunity to comment on the Food and Drug Administration's proposed rule revising the labeling and storage requirements for blood and blood components. For your information, America's Blood Centers is North America's largest network of non-profit, community blood centers. Seventy-six member blood centers operate more than 500 collection sites in 45 U.S. states and Quebec, Canada, and provide nearly half of the United States, and nearly one-quarter of Canada's volunteer donor blood supply. ABC blood centers serve more than 150 million patients and provide blood products and services to more than 3,300 hospitals. All ABC member centers are licensed by FDA.

The proposed rule, *Revision to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma* consolidates and clarify a number of labeling issues regarding Plasma products. ABC and its members congratulate and thank the FDA for proposing these forward- thinking changes and look forward to implementing many of the labeling changes included in this rule.

The consolidation of labeling requirements in one section will simplify and enable compliance in these areas of blood component manufacturing. The changes to the rule allowing the use of code ISBT-128 labeling without having to apply for numerous waivers not only reduces the paperwork burden but will improve patient safety by enabling patient identification and blood unit identification and tracking.

However, a careful review of the proposed rule by ABC and its members has identified some apparent contradictions within the document to the stated purpose by FDA. We have the following major recommendations:

ABC requests that FDA revise the proposed rule to retain Fresh Frozen Plasma (FFP) as a blood component with a 12 month storage period when maintained at -18C or below, or—based on the studies cited by the FDA—extend the storage period for FFP stored at -20C or below to 24 months.

ABC also requests that the labeling change requiring that the results of all communicable disease tests be placed on the label be removed and that this section be re-worded to indicate that communicable disease tests performed on a sample from the donor of the unit are listed in the current *Circular of Information*.

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We believe that specific collection, freezing, and storage conditions that may be more restrictive for plasma intended for further manufacture and fractionation should continue to be part of the contract between the buyer and the seller.

We are also providing comments to some of the more technical aspects of the rule and requesting consideration of our suggested changes in the final rule.

Storage Time and Temperature for Non-Cellular Blood Components. FDA proposes changes in the storage temperature and shipment of blood and blood components in order to "to provide consistency with data published in Europe." FDA also states that "this approach is intended to reduce the burden on industry by minimizing the number of times blood container labels must be revised and reordered."

FDA is proposing to revise § 640.34(g)(2) to clarify that frozen plasma must be stored at appropriate temperatures to ensure product potency and clarify individual unit test results by making sure that, "...Communicable disease agents provided the units are appropriately labeled to indicate all test results."

In the background section FDA states: "We have determined that the current requirements for storage and shipping temperature should be updated to ensure potency of the blood components over time and to provide more flexibility in inventory management... The proposed changes are consistent with published data and current industry practices."

The proposed change in storage temperature for FFP and cryoprecipitated AHF (cryo) would have an immediate and negative impact on many ABC members. We are not aware of "current industry practices" requiring FFP to be stored at less than -25C other than recommendations by the Council of Europe in its *Guide to the Preparation, Use and Quality Assurance of Blood Components 9th edition, January 2003*. And to the contrary, the American Association of Blood Banks (AABB) **Standards for Blood Banks and Transfusion Services**, considered to be the industry standard for the US, specifies storage of FFP and cryo at -18C.

The Council of Europe *Guide, 9th edition,* does address Labeling and Storage Guidance (page 69), but the emphasis is on freezing rate, not storage temperature. The *Guide* describes the plasma eutectic point as -23C (page 76), but we believe that the glass transition temperature (Tg) is the critical factor— not the eutectic point. While the Tg of FFP may not have been reported for *all* collection systems, most investigators have studied the Tg of albumin and plasma proteins. In this case, two Glass Transitions have been observed, a low one at -80°C and a higher one at -10°C (References 1 and 2).

In the proposed rule, the FDA has changed the storage parameters for FFP, Cryo, and Plasma cryo depicted to 24 months at -25 and 3 months at -18C. Making this type of change to a blood product without either a PLA or data from any US licensed manufacturer seems unprecedented. This change effectively de-licenses Fresh Frozen Plasma stored at -18C for 12 months and reduces the storage period to 3 months—without any known complaints regarding the efficacy of this product.

The references offered by FDA in the proposed rule do not appear to support the changes being suggested. The first reference, "Degradation Products of Factor VIII Which Can Lead to Increased Immunogenicity", identifies a 40 kda peptide fragment in some batches of factor VIII concentrate. This peptide fragment was associated with the possible formation of a potential inhibitor. The formation of the potential inhibitor was associated with different types of source material but is not directly related to storage temperatures or freezing rate. The authors' only conclusions are: "the problem of inhibitor potential can be avoided if appropriate preventive measures are taken." It is not apparent from this article that storage at -25C is an appropriate measure.

The second reference, "Stability of Fresh Frozen Plasma: results for 36-Month Storage at -20C, -25C, -30C and -40C", supports the extension of the storage time of FFP held at -20C from 12 to 24 months, based on the conclusion: "Thus FFP may be stored -20C for 2 years or at -25C, -30C, and -40C for three years without any detectable changes in the sensitive plasma proteins." Although the investigators did not test any FFP at –18C, they did test this product at -20C, and concluded that the plasma proteins were stable. The data and conclusions from this article would support extending the storage period for FFP to 24 months at -20C but not shortening it to three or requiring colder storage at -25C in order to lengthen the shelf life.

FFP is frozen and transfused to treat patients bleeding from a loss or reduction of many coagulation factors and plasma proteins, never for the replacement of Factor VIII. We believe that modifying the storage conditions based solely on the cited references is unwarranted for the clinical indication for which FFP is transfused, without additional data or studies.

If proposed changes in storage times and temperatures for non-cellular products represent an effort by FDA to ensure that FFP can be converted to recovered plasma and meet the manufacturer's specifications, ABC would recommend that these specifications be left in the contractual arrangement between the buyer and the seller. In this regard, we would like to point out that the contracts for purchase of source plasma or recovered plasma collected for the express purpose of fractionation into factor concentrates are very specific about the pre-freezing storage conditions, freezing rates, and storage temperatures for the plasma.

ABC agrees that harmonization with European standards, reflected in the Council of Europe's Guide to the Preparation Use and Quality Assurance of Blood Components, is desirable in many cases, but this should be accomplished based on objective data. Absent scientific evidence that the proposed changes in storage times and temperatures will improve the purity, potency or efficacy of FFP, the significant burden on the blood banking organizations and hospitals of implementing such a change argues against its adoption.

Compliance Costs Significant. In the proposed rule FDA states that "In general, the agency believes that the proposed rule will have no compliance costs, because any requirements are either industry practice or would be industry practice absent existing prohibitions. Because the agency believes these proposed rule amendments have no compliance costs, the agency certifies they will not have a significant impact on a substantial number of entities." We disagree. An informal survey of ABC members revealed the following regarding the financial impact of the proposed rule:

Many Freezers have limitations:

- Factory alarm settings will need to be changed by Service technicians at a cost of $500.00 to $1000.00 per freezer
- Some older freezers cannot be set for -25 or colder reliably and would have to be replaced forcing centers to purchase new freezers
- One collection agency estimated that most of its 52 customers would have to purchase new freezers

In Addition, Process limitations, which are very difficult to estimate with precision, could add major financial impacts

Managing multiple inventories also adds cost. as well as complexity:

- Increased error rates in labeling, shipping, expiration, and disposition

- Increased outdate from conversions when shipping from a center to a hospital

Relabeling a Potential Problem. The proposed rule does not address the storage life of a product that is moved from -25C storage to a hospital with a -18C degree freezer. Would the FFP have to be re-labeled with three month expiration from the time it is placed at -18C or would it retain the remainder of its 24 month shelf life? Re-labeling a frozen product is always difficult; labels don't stick, errors can be made when transcribing an ABO and RH, and the original or new expiration date.

Impact on Blood Supply. We did not see any comment in the proposed rule regarding the impact of changing storage times and temperatures on supply.

> **We request that FDA assess the potential impact of reducing the storage time at -18C from 12 to 3 months on the availability of AB FFP. Given the scarcity of AB donors, and the barriers to universal adoption of -25C storage, ABC members are concerned about the very real possibility of an inadequate AB plasma supply should the storage time be reduced to three months.**

Problems with Low Temperature Storage in PVC Containers. It has become quite apparent that PVC is not the plastic of choice for low temperature storage as pointed out in a recent *Transfusion* article (reference 3). In that regard, Canadian blood establishments recently changed the storage temperature of FFP from -30C to -20C. Prior to the change, the Canadian Red Cross had received a number of complaints about breakage and brittle bags. Information from Héma-Québec, an ABC member, indicates that there have been no complaints about efficacy of the product since the storage temperature was raised to -20C. The proposed rule does not address validation studies of the currently used PVC bags for storage at -25C or colder even though there are numerous reports and studies indicating their inappropriateness for storage at low temperatures.

> **We believe it would be inappropriate to arbitrarily lower the storage temperature of FFP without appropriate validation studies to assess the impact of storage at lower temperatures on bag breakage rates.**

Test Results on Labels. In the proposed rule FDA also states that it intends to, "...address as many labeling changes as possible at one time, thereby limiting the number of times establishments must revise container labels." However, we believe the requirement to place the test result for each communicable disease on the label would accomplish exactly the opposite goal. Providing the result of each infectious disease test is problematic and contrary to the direction that labeling has been going—which is to simplify the label. As the number of tests performed continues to increase, the move toward placing information about all tests performed on blood and blood components in the circular of information (which is part of the label) has provided collection centers with a much simpler and more flexible method of meeting labeling requirements without the expense of constantly changing labels.

Moreover, with respect to recovered plasma labels, fractionators have their own requirements for documentation, including a form with each shipment that identifies the tests performed and states that all tests are negative. Printing, purchasing, reviewing, and maintaining quality control for labels is expensive and time consuming. The documents accompanying a shipment could be more easily modified as new tests are added and other tests are deleted. Revising and discarding labels contributes to a negative financial impact for this rule. If FDA is concerned about contracts that would allow the shipment of positive units for further manufacture, it would make more sense to label only the positive units or continue the current method of noting positives on the shipping form.

CFR Specific comments. We also have the following comments in specific sections of revised rules:

606.121(c)(8)(ii): The statement refers to the "Circular of Information" but 606.122 refers to the "Instruction Circular". The wording should be consistent from section to section.

606.122(e): Requires the "Instruction Circular" list every test for "infectious agents" performed on the product. Instead, we recommend that 606.121(c)(11) be revised to require the label to bear a statement "See Circular of Information ...results of infectious agent testing" or 606.121(c)(8)(ii) be revised to include the statement.

610.53(c): Same comment as 600.15, above. In addition, the table should also address Plasma, Cryoprecipitate Removed.

We appreciate the opportunity to comment on this proposed rule and look forward to further dialogue if needed.

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1. Chang B., Randall C. Use of Subambient Thermal Analysis to Optimize Protein Lyophilization. Cryobiology 1992;29:632-656
2. Carpenter, JF. and Chang, B.S. Lyophilization of biopharmaceutical products. In "Biotechnology issues in Pharmaceutical process Engineering Vol. 2" (Avis, K. and Wu, V. eds.) 1992, 199-264
3. Hmel PJ, Kennedy A, Quiles JD *et al*.Physical and thermal properties of blood storage bags: implications for shipping frozen components on dry ice. Transfusion 2002; 42:836-846

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Comments to **Docket No. 2003N–0211**, Proposed Rule: Revision to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma