American Red Cross

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

RE: Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma; Proposed Rule.
[68 FR 44678-44688, July 30, 2003; Docket No. 2003N-0211]

Dear Docket Officer:

The American Red Cross (Red Cross) appreciates this opportunity to provide public comments concerning the Food and Drug Administration's (FDA or Agency) proposed rule titled "Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma" (Hereafter, referred to as *The Proposed Rule*).

The Red Cross is committed to the safety of donors and patients, and to meet the best interests of the public we serve. The Red Cross, through our 36 Blood Services regions, supplies approximately half of the nation's blood for transfusion needs. The plasma donated by Red Cross' volunteers is recovered from Whole Blood and further processed or fractionated into plasma derivatives. The Red Cross also collects Source Plasma from volunteer donors in relatively small quantities to be fractionated into plasma derivatives.

Red Cross urges the Agency to reconsider the economic and potential safety impact of new storage temperature requirements and proceed to finalize the proposal to simplify labeling requirements. The Red Cross appreciates the Agency's efforts to develop *The Proposed Rule* that will facilitate the implementation of "machine-readable" bar code standards. While optimistic that the Final Rule will achieve this goal, there are a number of complex issues related to new storage temperature requirements proposed that require significant revisions. These new storage temperature requirements represent a significant change that goes beyond current requirements. However, the economic impact of these changes is understated and the additional safety and quality benefits to the public

2003N-0211 C6

are not well supported by the data referenced in *The Proposed Rule*. While we agree with many of the stated requirements given in *The Proposed Rule*, we offer the following comments for your consideration.

Consolidate, Simplify, and Update Container Labels and Instruction Circular Regulations

The Red Cross supports the Agency's effort to combine labeling requirements into one section of the Code of Federal Regulations and remove inconsistencies with ISBT 128. The Red Cross strongly endorses the use of ISBT 128 as a unifying bar code standard for blood and blood products. No other step could help bring about improvements in patient safety as immediately, and as effectively, as the use of standardized bar coding technology. Although "machine-readable bar codes approved by the CBER Director" will further efforts to minimize errors and improve safety, one unifying standard will provide additional benefits to providers, hospitals and patients. One standard will lower the cost of implementation and allow exchange of inventories so that the needs of patients everywhere can be more easily met. Moreover, a unifying bar code standard may help to expedite investigations of unforeseen events. **Any effort to continue momentum toward a Final Rule that facilitates the implementation of ISBT 128 should not be hindered by other complex and unrelated issues commingled in *The Proposed Rule*.**

The Red Cross recommends that the Agency permit an additional initiative to streamline the labeling submission process for ISBT 128 labels originating from on-demand printers. Section II. C. of *The Proposed Rule* states:

> "The proposed revisions discussed in this section of this document are primarily intended to allow for the use of a machine-readable encoded information system, such as ISBT 128. Those changes would allow manufacturers of blood, blood components, and Source components to submit product specific labeling that is consistent with approved labeling formats, such as ISBT 128, to the Director, CBER, for approval without requesting a variance under §640.120."

FDA currently has made certain changes in the label content to facilitate on-demand labeling such as: (1) color of text, (2) placement of anticoagulant wording, and (3) optional use of FDA registration number or another unique facility identifier. On-demand labels are produced either by using a regulated third party label software package or by embedding the label printing specifics within the regulated blood bank software. Since FDA must clear the label software through a 510(k) or other regulatory process, FDA-regulated facilities should be permitted to declare in their license application that labels will be printed using the regulated software. **Red Cross recommends that labeling approval be allowable through either an annual report submission (preferred) (i.e., §601.12 (f) (3)) or a submission that could be implemented before FDA approval (i.e., §601.12 (f) (2)).** Benefits include a less burdensome approach for

both the Agency and blood banks under §601.12 (f) (3) or an expedited implementation time by blood banks under §601.12 (f) (2).

Red Cross also supports and appreciates FDA's efforts to update labeling requirements to be consistent with contemporary terminology and testing practices, such as the change from "Du" to "weak D" and consistency of labeling with revised §610.40 testing requirements.

Red Cross would like to request that the Agency consider more flexibility in terms of what may be placed on a tie tag for autologous donations. According to the current regulations and *The Proposed Rule*, a tie tag may be used to convey the identity of unexpected antibodies and to show the donor/recipient identification, the date of the donation and the statement "For Autologous Use Only." In *The Proposed Rule*, the ABO/Rh designation has been removed as an acceptable donor/recipient identifier on the tie tag, but must be reflected on the "For Autologous Use" label on the container. Since the "For Autologous Use" label applied to the container currently cannot be system-generated with an ABO/Rh designation, the ABO/Rh designation must be hand-written on this label. Red Cross suggests that a system-generated ABO/Rh label could be applied to the tie tag, to replace the current practice of writing the ABO/Rh result on the tag and the "For Autologous Use" label. Use of a computer system-generated ABO/Rh label on the tie tag eliminates the need for hand-written information and would reduce the likelihood of human error and improve patient safety.

Scientific Analysis of Proposed Changes in Storage Requirements for Certain Blood Components

The Red Cross supports efforts to preserve the stability of known and yet-to-be discovered blood components that are heat labile through implementation of new storage temperature requirements based on sound science. *The Proposed Rule* provides only one scientific reference to support colder temperature requirements for Fresh Frozen Plasma (FFP) [i.e., "Stability of Fresh Frozen Plasma: Results of 36-month Storage at -20^{0}C, -25^{0}C, -30^{0}C, and -40^{0}C," Kotitschka, et.al (Infus. Ther. Transfus. Med 2000:27; 174-190)]. **The Red Cross has reviewed that reference carefully since it is being used as a basis for *The Proposed Rule* that will have a dramatic economic and operational impact on blood collection establishments and hospital transfusion services.**

The Red Cross provides the following comments about the design, execution, and conclusions of the study in this single reference. The study may have been adequately designed in concept, but was not executed to the full extent of the design. The study contains significant flaws relative to a typical stability study for a biological product as defined by the Agency and International Conference of Harmonization (ICH) Final Stability Guidance.

Quoted from the scientific study:

> "Comparison of the stability of 3 FFP's during storage at 4 temperatures over a period of 3 years is based on an assessment of the determinations of 14 analytes by 13 participants of a multi-center study..."

This statement implies a collection of a complete data set for all FFP batches for the complete set of analytes from each of the centers for the full stability period at all temperatures. If this were true, the study would have been of considerable magnitude. However, compared to the study design stated by the authors, there are major gaps in the data presented in this CY2000 publication.

In their discussion, the authors of the DGTI[1] study recognize the gaps in the data, so it is puzzling why they would base their confidence in their conclusions on the full study design. The execution of the study design was incomplete in many ways:

1. **Not all FFPs were tested in all centers.** In fact, almost all of the data reported in the article are only from four to seven laboratories, and no single data set shown is from all 13 centers.

2. **Not all temperatures were tested in all centers.** Statistical variance testing to show differences with temperature came only from three to six labs, with no data shown for -30^0C. Moreover, these data do not show statistically significant differences in the stability of some plasma proteins for up to 36 months when stored at -20^0C, -25^0C, -30^0C, and -40^0C. These findings do not support the article's broad conclusion.

3. **Not all time points were tested in all centers.** The authors state that they do not show data for nine, 12, and 18 months (*"...since no deviations in these values were found..."*), although the article uses these data as the baseline for claiming stability at 24 and 36 months. The authors did report six month data in a previous publication.

4. **Not all analytes were tested at all centers.** In fact, only six of the 14 analytes had sufficient data points to be considered statistically relevant. This considerably reduces the intent of the study design and does not support the authors' general statements on the total number of analytes tested.

5. **There were wide variances in the results.** Even the total protein values, which should be stable over time, show a high degree of variability. It is not clear if the variations are between laboratories or within laboratories since the data in the report are grouped together. For purposes of monitoring stability, it is necessary

[1] Deutsche Gesellschaft für Transfusionsmedizin und Immunhämatologie (DGTI)

to distinguish test method variations from true product changes.

6. The authors rationalize the high degree of variation seen in some results as 'outliers' and values skewed by *"...small data sets due to limited participation of centers."* However, this rationale conflicts with the authors' later statements that *"...another advantage of the results of our study lies in the fact that these results were obtained by a number of participants in a multi-center study, conferring additional validation to the data obtained."*

7. **None of the test methods are indicated to be sensitive or specific for stability-indication of the target plasma protein.** It is not clear from the article if the test methods were validated for their intended use, as required by ICH and FDA for stability studies. The authors do state that the laboratories followed quality assurance practices, but it is not clear if this includes method validation for stability studies.

8. Two of the four temperatures chosen (i.e., -20^{0}C and -25^{0}C) are both within the range of variability allowed by the ICH guideline on stability testing for products stored at –20^{0}C. Since each center stored its own stability samples, it is not clear if the four different temperatures reflect single storage conditions in individual centers, or if each center had four different storage chambers. If the centers each had four different conditions, it would require verification of the documentation of freezer temperature recordings in each participating DGTI laboratory to verify if the operational distinction between -20^{0}C and -25^{0}C was actually achieved for the duration of the study.

Red Cross believes the intended power of the DGTI study is significantly reduced by the lack of participation of the testing centers in the full study design. There are major gaps in the data sets that would be considered unacceptable to meet the intentions of current ICH and FDA stability protocols. There is a high degree of variability in the results that makes the analysis of the limited data reported in the article difficult to interpret.

Red Cross would support initiatives by FDA or the Department of Health and Human Services (HHS) to allocate resources or provide funds to conduct an adequate stability study at Red Cross' Holland Laboratory and other participating blood banks. Information gained through a sound scientific study can be used by the Agency for future rulemaking regarding storage requirements. The ideal situation would be to design a comprehensive new study to evaluate the stability of FFP, Cryoprecipitate and Source Plasma for known plasma proteins using the study parameters specified in the current Stability Guidance documents. In order to evaluate stability trends, it would be necessary to assure the collection of the full data sets as designed in the protocol. It would also be necessary to confirm that the test methods used are suitable for the quantitative measurement of stability of their target plasma proteins. While such a study would demonstrate the stability characteristics of the starting raw materials for the

analytes tested, it might still be necessary for each manufacturer to design and implement appropriate stability studies for the specific plasma proteins produced. The purification of proteins out of the complex plasma environment can have a significant impact on the stability of the purified plasma products, which would not be predictable from general stability studies on Cryoprecipitate, FFP or Source Plasma.

Red Cross believes the proposed temperatures are not in alignment with current ICH and FDA ranges for frozen biological products. The temperature range specified for frozen products in ICH Q1A (R2) "Stability Testing of New Drug Substances and Products" (February, 2003), which applies to biological and biotechnological products [per ICH Q5C: Stability Testing of Biotechnological/ Biological Products (July 1996)] and is endorsed by the FDA is: -20^0C +/- 5^0C.

Thus, the operational range of -15^0C to -25^0C is considered by ICH as the acceptable range of normal operational variation for the validated temperature control of freezer chambers to maintain the target storage temperature. The proposed change from -18^0C or colder to -25^0C or colder as the target storage temperature is within the specified ICH range for frozen storage conditions.

In addition, the proposed differences in storage temperatures based on expiration dates of 3 months (i.e., -18^0C to -25^0C) versus 24 months (i.e., -25^0C or colder) do not seem appropriate unless the 24 month storage temperature is intended to be considerably colder than -25^0C (e.g., -40^0C) to allow this extended storage time. Red Cross fails to see the connection between the data in the DGTI study and the proposed storage requirements.

The Red Cross urges the FDA to consider changing the storage temperatures of FFP and cryoprecipitate to -20^0C +/- 5^0C to match the frozen storage range specified by the ICH stability guidance documents. The reasons for this recommendation are:

1) The Agency is also proposing changes that require the manufacturer to determine the appropriate storage conditions to maintain the stability and potency of specific plasma products they manufacture (§640.34 and §640.54). In compliance with current ICH and FDA guidance documents, most new stability data collected on frozen biological products will be generated at -20^0C +/-5^0C.

2) In order to provide maximum comparability, FFP and Cryoprecipitate should be stored under the same storage conditions used for stability protocols on final plasma-derived products.

3) By harmonizing the FFP and Cryoprecipitate storage conditions to the ICH temperatures for frozen biological products, the FDA would allow manufacturers to establish and validate a single temperature range for the storage of frozen raw material as well as frozen final plasma-derived products.

4) The ICH temperature range of -20^0C +/- 5^0C is already accepted by the FDA and other international regulatory bodies as an appropriate range for the controlled storage of frozen biological and biotechnological products.

5) The scientific study conducted by DGTI, although flawed in several technical aspects noted in this comment letter, supports the storage of FFP at -20^0C or colder for up to 36 months.

Proposed temperature changes for storage and shipping of Source Plasma and Salvaged Source Plasma from -20^0C to -30^0C and -5^0C to -15^0C, respectively

It is not clear why the FDA is proposing a change from -20^0C to -30^0C for storage of Source Plasma. The referenced DGTI study does not provide evidence to suggest that the activity of the tested plasma proteins differs from -20^0C to -30^0C over 24 months.

In order to harmonize with the ICH temperature conditions for frozen products as recommended for FFP and cryoprecipitate, Red Cross suggests that the FDA allow Source Plasma and Salvaged Source Plasma be maintained frozen at -20^0C +/-5^0C under segregated conditions.

Proposed Cost Analysis and Time Permitted to Implement New Storage Requirements Are Understated

The Red Cross believes that the cost of implementing the proposed new temperature requirements for certain blood products will be significant and require more time allowances. Section III. Analysis of Impact states:

> "In general, the Agency believes the proposed rule will have no compliance costs, because any requirements are either industry practice or would be industry practice absent existing prohibitions."

Red Cross urges the Agency to fully evaluate the cost of implementation to understand the impact of *The Proposed Rule* on blood banks. Red Cross has over 900 freezers, including 125 walk-in freezers. Temperature specification changes are not accomplished by a manual change to a thermostat. Temperature changes must be done according to current Good Manufacturing Practice.

Actual temperature set-points typically includes an additional "buffer" ranging from 5 ^{0}C to 10 ^{0}C colder to prevent alarms and prevent adverse impact to product due to temperature excursions caused by normal fluctuations due to operational processes (e.g., opening controlled storage equipment to remove or replace inventory). Therefore, a temperature specification of -25 ^{0}C or colder would need to have an actual temperature set-point ranging from – 30 ^{0}C to -35 ^{0}C or colder in order to provide adequate assurance of a -25 ^{0}C environment.

Any temperature setting of -30 ^{0}C or colder would require major capital expenditures including: (1) changing all freezers from a single-stage compressor system to two- stage compressor system, (2) enhancing facility-wide electrical capacity to support the new equipment, (3) purchasing more emergency generators to support higher energy-consuming storage equipment, and (4) hiring engineering firms to perform surveys to retrofit existing facilities and equipment to meet new requirements. Compliance-related costs would have to include revision of procedures and training, validation of new equipment, revalidation of existing equipment and shipping containers system-wide.

Red Cross' engineers estimate energy consumption costs for new walk-in storage equipment alone would triple in dollars under conditions stated in *The Proposed Rule.* On-going operation costs are projected to increase 5%-10% system-wide. Red Cross believes shipping costs would double since only half as much product could be shipped per box due to the need for additional refrigerant in the shipping container. Alternatively, Red Cross would have to redesign validated shipping containers to new specifications and requirements.

Red Cross believes *The Proposed Rule* potentially adds risk to the blood supply if temperature requirements change from -18^{0}C to -25^{0}C or colder. Red Cross' engineers indicate that two-stage compressor freezer systems are: (1) less efficient than one-stage compressor systems, (2) prone to breaking-down more frequently resulting in higher maintenance costs and lost inventory, (3) require greater labor resources to perform additional quality control activities, and (4) larger and heavier which may adversely impact already limited facility space and structural capacity, among other challenges.

Red Cross currently utilizes most of the available electrical capacity at each facility. Red Cross' engineers advise that most Red Cross' facilities would therefore have to be closed down for at least one week to upgrade electrical wiring and transfer panels. Start-up activities including revalidation of equipment and operational processes may further delay normal operations.

Red Cross believes that time allowances are insufficient to meet the new storage temperature requirements. Section VIII. Proposed Effective Date states:

> "The agency is proposing that any final rule that may issue based upon this proposed rule become effective 180 days after the date of publication in the Federal Register."

If the decision was made to retrofit existing facilities to meet lower temperature requirements in *The Proposed Rule*, Red Cross' engineers estimate that it would take more than five years and, at a conservative estimate, $75 - $95 million dollars, to just retro-fit 125 walk-in freezers. Additional time may be required to upgrade emergency generators, transfer panels, and the other stand-alone freezers.

Inventory Management Impact

Red Cross would need to significantly alter our inventory management practices until facility modifications are made to achieve lower storage temperatures. Red Cross would wish to avoid the complexities of maintaining and tracking two different inventories created by different storage temperatures and different expiration dates. Significant inventory management adjustments would be needed to change products with a one-year expiration date to a three-month expiration date. Red Cross would strongly consider a single expiration date of three-months for frozen plasma products if *The Proposed Rule* is implemented as stated to minimize the potential for errors due to maintaining two inventories. However, Red Cross is concerned about creating supply shortages, since such a short-dated inventory would need to be kept at a minimum. Hospitals may be impacted by a reduction of availability of FFP or Cryoprecipitate for patients in need. Clearly, Red Cross would need to produce less plasma for transfusion or move it more quickly into inventory for fractionation. Production of FFP by apheresis would need to be severely curtailed if not used for transfusion, since this product cannot currently be converted for further manufacture.

A significant percentage of Red Cross' plasma product inventories are older than three months at any given time. The proposed reduction in expiration date would mean that 18% of total frozen product in current inventory could not be used based on October, 2003 data. In other words, 20,434 products would not be useable for transfusion purposes.

Total Frozen Product	# Product	Percentage
Total units in Inventory	115,341	
Units in Inventory 0-90 days old	94,907	82%
Units in Inventory Greater than 90 days old	**20,434**	**18%**
Cryo-reduced Plasma		
Total units in Inventory	18,137	
Units in Inventory 0-90 days old	13,609	75%
Units in Inventory Greater than 90 days old	4,528	**25%**
Cryoprecipitate (without 1st Stage Cryo)		
Total units in Inventory	28,165	
Units in Inventory 0-90 days old	23,345	83%
Units in Inventory Greater than 90 days old	4,820	**17%**
Cryoprecipitate (with 1st Stage Cryo)		
Total units in Inventory	38,384	
Units in Inventory 0-90 days old	33,564	87%
Units in Inventory Greater than 90 days old	4,820	**13%**

FFP	# Product	Percentage
Total units in Inventory	45,925	
Units in Inventory 0-90 days old	37,769	82%
Units in Inventory Greater than 90 days old	8,156	**18%**
Plasma from Pheresis		
Total units in Inventory	12,895	
Units in Inventory 0-90 days old	9,965	77%
Units in Inventory Greater than 90 days old	2,930	**23%**

If a three month expiration date for transfusable plasma were adopted, Red Cross would also no longer be able to stockpile FFP for use in extraordinary situations, like the West Nile Virus (WNV) epidemic of the past two years. Red Cross stockpiled FFP during the pre-West Nile Virus season, in order to provide this plasma to areas that experienced epidemic numbers of cases of WNV during the season for this virus to be active. This FFP had to be retained longer than 6 months, in order to avoid the WNV active period and provide sufficient inventories for impacted regions. Future needs for stockpiled plasma, due to WNV or the appearance of large numbers of cases of other potentially transfusion-transmitted diseases such as dengue, Japanese encephalitis, and St. Louis encephalitis, could not be met with a reduced three-month expiration date.

Red Cross believes that the Agency would need to provide different product codes for products with the same name, but maintained in different storage conditions, if blood banks had to implement *The Proposed Rule* as stated and choose to maintain two separate inventories. Otherwise, Red Cross believes it would be impossible to manage inventories without significant risk of errors. If Red Cross chooses to produce and store frozen products at only one temperature, imports from other blood collection establishments would still require the use of separate product codes to manage them.

Conclusion

Prior to issuance of *The Final Rule*, Red Cross recommends that the Agency conduct a workshop to discuss initiatives relating to storage requirements and to provide a forum for additional scientific exchange of information. Red Cross reiterates, however, that the beneficial labeling proposals should be finalized separately while the storage and shipping requirements are considered further.

The coordination of all FDA-proposed frozen storage conditions to the single, internationally-recognized ICH temperature range of -20^{0}C +/- 5^{0}C will allow manufacturers to establish one validated freezer chamber condition to hold all plasma products (i.e., FFP, Cryoprecipitate, Source Plasma, or Salvaged Source Plasma) under segregated conditions. This temperature is supported for storing FFP for up to 24 months by the DGTI study referenced by the FDA.

Compliance with the current and proposed temperature conditions requires the establishment of multiple freezer chambers with subtle temperature differences. However, Red Cross' engineers advise that engineering specifications to maintain the distinctly different, but very close, target temperatures are a significant challenge for blood banks to achieve.

Additionally, the use of single-temperature validated freezer chambers would allow the controlled storage of multiple biological products, providing maximum operational flexibility for manufacturers, while maintaining their facilities in compliance with current Good Manufacturing Practice.

The Red Cross appreciates this opportunity to provide public comments on *The Proposed Rule*. If you have any further questions or require follow-up, please contact Barbara M. Peoples, Director, Technical Policy and Promotions at 202-303-5212 (phone) or PeoplesB@usa.redcross.org (e-mail), or Joel C. Harder, Senior Associate, Technical Policy and Promotions at 202-303-5942 (phone), 202-303-0106 (fax) or HarderJ@usa.redcross.org (email).

Sincerely,

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Vice President
Regulatory Compliance and Quality Systems;
and Chief Compliance Officer