Aventis Bio-Services

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

27 October 2003

RE: Docket No. 2003N-0211
Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma

Dear Sir or Madam:

Aventis Bio-Services wishes to thank the FDA for the opportunity to comment on the proposed rule: *Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma.* This proposed rule consolidates labeling standards, and proposes new temperatures for the storage and shipping of Source Plasma and other non-cellular blood components. There are many aspects of the proposed rule that deserve comment.

Consolidation of the Regulations for Labeling Blood and Blood Components

The proposal to move the regulations for labeling Source Plasma from 212 CFR § 640.70 to 21 CFR § 606.121 could have advantages as well as disadvantages. The stated benefit is to move the regulations pertaining to the labeling of blood and blood components, including Source Plasma, into one section of the CFR. While it could be advantageous to have labeling requirements for all blood and blood components in 21 CFR § 606.121, this potential advantage must be balanced with the disadvantage that the relatively straightforward labeling requirements for Source Plasma would now be interspersed into the relatively long and often complex labeling requirements for blood components for transfusion.

While there are similarities between the manufacture of Source Plasma and the manufacture of blood components for transfusion that are prepared from Whole Blood, there are also very significant differences. The differences in the requirements for informed consent, determining donor suitability, the collection process, i.e., plasmapheresis, the immunization of donors, etc., (as reflected in 21 CFR § 640.60 through § 640.76) are significant enough that these requirements are all stated in Subpart G, Source Plasma, rather than being incorporated into the equivalent sections of Subpart A, Whole Blood. Because of these very significant differences, establishments ordinarily collect either Source Plasma or Whole Blood, but not a combination of the two products.

Since Source Plasma is usually manufactured by establishments that manufacture only Source Plasma, keeping the relatively simple labeling requirements for Source Plasma in Subpart G makes these requirements easier to find and follow. In contrast, incorporating these requirements into the lengthy and relatively complex labeling requirements for blood components for transfusion would make compliance more, rather than less, difficult. Keeping the labeling requirements for Source Plasma in Subpart G is also consistent with keeping specific labeling requirements for other blood products (that are markedly different from blood components for transfusion) in the appropriate Subpart, e.g., Subpart H (Albumin), Subpart I (Plasma Protein Fraction) and Subpart J (Immune Globulin) all contain the specific labeling requirements for these products. If the Source Plasma labeling requirements are maintained in 21 CFR § 640.70, then this section should be revised to require labeling statements based on testing for communicable diseases.

Discussion of cautionary statements on labels of products for further manufacture:
The proposed new § 606.121 (c) (10) states that if the product is not intended for transfusion, that the container label should include a statement as applicable:

- Caution: For Manufacturing Use Only
- Caution: For Use in Manufacturing Noninjectable Products Only
- or other cautionary statement as approved by the Director, Center for Biologics Evaluation and Research (CBER)

Given that cautionary statements can be found in other sections of the CFR as well as in other FDA Guidance Documents, it is often difficult to select the proper cautionary statement to use. For example, in the proposed rule the new § 606.121 (c) (12) refers to labeling instructions that are included in § 610.40 (h) (2) (ii) (E), which contains additional cautionary statements for products with reactive test results (and therefore not intended for transfusion). In addition, the September 10, 1991 memo from the FDA entitled *FDA Recommendations Concerning Testing for Antibody to Hepatitis B Core Antigen (anti-HBc)* requires that Source Plasma for use in manufacturing noninjectable products be labeled with the cautionary statement: "Caution: For further manufacture only into in vitro diagnostic reagents for which there are no alternative sources." The same memo also requires that the additional statement "Not tested for Anti-HBc" be added to the label. In the effort to consolidate and simplify labeling requirements, a consolidated listing of cautionary statements (either in the CFR or in an appropriate guidance document) along with a description of when they are to be used, should be considered.

Proposal to Change the Storage and Shipping Temperature for Source Plasma

The proposal to change the storage and shipping temperatures for Source Plasma from -20°C to -30°C, and the proposal to change the shipping temperature for Source Plasma from –5°C to -

15°C, is of special concern, and will have very significant implications for establishments that manufacture Source Plasma.

The proposed new storage and shipping temperatures are based upon the stated supposition that the new temperatures:

1. Will guard against the degradation of the heat labile clotting factors present in plasma
2. Are consistent with published data
3. Represent current industry practice, or what would be industry practice absent existing prohibitions, and do not represent an additional burden
4. Will not have any compliance costs and will not have a significant effect on a substantial number of small entities

Each of these points will be discussed below.

Point 1 - Degradation of Heat Labile Clotting Factors
Point 2 - Published Data
The published data that are referenced in the proposed rule consist of a single paper reporting the results of a multicenter study of the stability of Fresh Frozen Plasma stored at –20°C, -25°C, -30°C and –40°C for up to 36 months. (Kotitschke, R., "Stability of Fresh Frozen Plasma: Results of 36-Month Storage at -20°C, -25°C, -30°C, and -40°C," Infusion Therapy and Transfusion Medicine, 27:174-180, 2000.)

The study examined the stability of human plasma during storage at -20°C, -25°C, -30°C, and –40°C over a period of two to three years. Plasma collected either by plasmapheresis or prepared from whole blood was pooled, and aliquots of the various pools were sent to the 13 laboratories that participated in the multicenter trial. Aliquots of each pool were tested at the beginning of the storage period, and then again after a defined storage period at a given temperature. Plasma was tested for total protein, Factors VIII, IX and V, fibrinogen, and antithrombin. A sufficient number of tests for these six analytes was performed to allow for statistical evaluation of the results. Plasma was also tested for optical density at 650 nm, thrombin/antithrombin complex (TAT), the prothrombin fragments F1 and F2, Factor VIIa, fibrinogen dimers, IgG, titer of anti-HBs, and C1 esterase inhibitor, however, an insufficient number of number of tests for these analytes was performed to allow for statistical evaluation of the results.

No statistically significant changes resulting from storage for 24 to 36 months at any of the four temperatures were found with the exception of an 11% reduction of Factor IX in plasma stored at -20°C for 24 months. This 11% reduction was shown only for the pool of plasma prepared from whole blood and frozen within 21-24 hours after collection. In contrast, plasma prepared from whole blood and frozen six hours after collection, and plasma collected by plasmapheresis and

frozen four hours after collection, showed a decrease of Factor IX of only 7% and 4%, respectively. Although not mentioned by the authors, these results might suggest that the collection method (whole blood vs. plasmapheresis) and the time to freezing after collection (21-24 hours vs. 6 hours vs. 4 hours) might have an influence on the recovery of Factor IX.

It should be noted that current industry practice is to collect Source Plasma that will be used for the manufacture of coagulation concentrates by plasmapheresis and to freeze the plasma well within fours hours of collection (conditions that resulted in only a 4% decrease of Factor IX when stored for 24 months at -20°C). It should also be noted that industry practice is to store Source Plasma for a maximum of three years after collection. Thus, much of the Source Plasma will be placed into the fractionation process within two years of collection, thus minimizing any protein degradation that might be attributed to prolonged storage at -20°C.

To summarize, the only reduction in plasma proteins reported in this paper was in Factor IX. Even if there had been a statistically significant reduction in the recovery of other plasma proteins, this decrease in activity would be of primary concern when considering units of plasma for transfusion, and of less significance when applied to units of Source Plasma for further manufacture. Since plasma for transfusion is administered directly to patients as individual units with no additional processing, the storage conditions of each individual unit are critical for the maintenance of the plasma proteins in that individual unit. In contrast, units of Source Plasma are pooled prior to fractionation, and, therefore, the storage conditions of any one unit are of less consequence to the final product. In fact, the level of specific proteins in concentrates can be adjusted to predetermined levels. Since the published data do not show a decrease in Factor VIII, or any other proteins, under the conditions of the study, the imposition of a –30°C storage temperature for all Source Plasma based solely upon the reported reduction in Factor IX would be inappropriate. Any potential loss of Factor IX that might be attributable to the existing -20°C storage temperature is already compensated for, and given the overall demand for Factor IX concentrates, is not impacting product availability or patient care.

Point 3 - Current Industry Practice

Current industry practice for Source Plasma that is destined for fractionation into products containing labile proteins that will be marketed in Europe is to freeze Source Plasma that is intended for the recovery of heat-labile proteins at -30°C, and then to store the frozen Source Plasma at -20°C. This is based upon the *European Pharmacopoeia - Human Plasma For Fractionation*, which states:

> PRODUCTION
> "When obtained by plasmapheresis, plasma intended for the recovery of **proteins that are labile in plasma** (emphasis added) is frozen by cooling rapidly at -30°C or below as soon as possible and at the latest within 24 h(ours) of collection."

STORAGE

"Store and transport plasma at or below -20°C (emphasis added); the plasma may still be used for fractionation if the temperature is between -20°C and -15°C for not more than a total of 72 h(ours) without exceeding -15°C on more than one occasion as long as the temperature is at all times -5°C or lower."

It should be noted that the storage temperature of -20°C as specified in the *European Pharmacopoeia - Human Plasma For Fractionation* is already harmonized with the storage temperature of -20°C as specified in 21 CFR § 610.53.

Industry may meet the European requirement to initially freeze Source Plasma at -30°C by placing the plasma in:

- Flash freezers that freeze a unit of Source Plasma to -30°C within a stated period of time, **or**
- Walk-in freezers that are capable of maintaining -30°C or colder

Thus, the walk-in freezers in establishments that utilize flash freezers will only have to maintain the harmonized -20°C storage temperature. Generally speaking, these freezers will not be capable of consistently maintaining a storage temperature of -30°C.

Even when a walk-in freezer is used for the initial freezing of the plasma at -30°C, the freezer might not be capable of consistently maintaining a -30°C storage temperature. The European requirement to initially freeze plasma at -30°C is imprecisely stated, in that the plasma must be frozen by cooling rapidly at -30°C or below as soon as possible and at the latest within 24 hours after collection. It should be noted that at least in some cases, the European requirement has been interpreted (by industry as well as the regulatory authorities) to mean that plasma, that is maintained at -30°C or colder for at least 10 hours out of the first 24 hours after the plasma is first placed into the freezer, meets this requirement. Walk-in freezers that have been deemed as acceptable in meeting this requirement would not necessarily be capable of consistently maintaining -30°C to meet the requirements of the proposed rule. The acceptance of this interpretation may be in the spirit of the statement from the *European Pharmacopoeia - Human Plasma For Fractionation:*

"Preservation of factor VIII in the donation depends on the collection procedure and the subsequent handling of the blood plasma. With good practice, 0.7 IU/ml can usually be achieved, but units of plasma with lower activity may still be suitable for use in the production of coagulation factor concentrates. The aim of good manufacturing practice is to conserve labile proteins as much as possible."

Point 4 - Compliance Costs

Introduction:
The proposed change to a -30°C storage temperature for Source Plasma would require several very significant changes, and these changes would have major and far-reaching operational and economic impact.

Almost all plasmapheresis centers contain one or more walk-in freezers for the storage of Source Plasma. In addition, as described above, it is common practice, at least in some Source Plasma Establishments, to carry out the initial freezing of Source Plasma using a flash freezer. Depending upon when the plasma is placed into the flash freezer, the flash freezer may also be used for short-term, i.e., overnight storage, of the Source Plasma.

After initial freezing, the frozen plasma is transferred to walk-in freezers for prolonged storage at -20°C. Almost all of the walk-in freezers currently in use were designed and built to maintain at least -25°C in order to ensure the currently required storage temperature of at least -20°C. Although some of the existing freezers may be able to maintain a temperature of -30°C, this is often beyond the designed operating range and will likely result in premature equipment failure and/or increased maintenance and operating costs.

Proposed Rule – Analysis of Impacts
The proposed rule states that:

> "The agency believes that these requirements (proposed storage and shipping temperature – clarification added) reflect current industry practice and do not impose an additional burden. 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. Because the agency believes these proposed rule amendments have no compliance costs, the agency certifies they will not have a significant economic impact on a substantial number of small entities."

Aventis Bio-Services disagrees with this assumption. Compliance with the proposed rule will result in substantial costs in the following areas:

Replacement or modifications to freezers in plasmapheresis centers:
As already stated, the majority of freezers currently in use, and that the agency assumes are already capable of maintaining –30°C, are not capable of consistently maintaining this temperature. These freezers will require either expensive renovation or replacement in order to meet the requirements of the proposed rule. Increased insulation and new, more powerful compressors will be required in almost all cases. Conversion to ammonia-based systems, which

are more costly and represent additional safety and environmental concerns, may also be required. Replacement or renovation costs are estimated to be at least $30,000 per freezer, which could, depending upon the number of freezers, represent a total cost of millions of dollars. It should also be noted that if implementation of the final rule were required within the stated six months, the industry-wide demand for new freezers and related equipment would almost certainly outstrip the supply.

Validation of freezers in plasmapheresis centers:
The revalidation of each plasmapheresis center walk-in freezer at -30°C could cost in the vicinity of $1,000 per freezer. As also mentioned above, the flash freezers that are used for freezing the plasma may also be used for overnight storage of the plasma. These flash freezers have been validated to provide overnight storage at -20°C, and the proposed rule would require that these freezers be revalidated at -30°C, also at a cost of approximately $1,000 per flash freezer. Validation costs would also include the purchase of additional data loggers, for, again, if implementation of the final rule is required within the stated six months, the validation schedule that would be necessary to revalidate all freezers would require more equipment than is currently available. Validation costs would also include the actual cost of gathering and analyzing the data, preparation of reports, etc. Total validation costs would easily exceed $100,000.

Increased energy costs in plasmapheresis centers:
Lowering the temperature from an average of -25°C (for freezers that currently meet the -20°C storage temperature) to at least -35°C to -40°C (required to meet the proposed -30°C storage temperature) would also increase energy consumption by at least 20% to 30%. The colder temperature would also result in more frost accumulation, and this in turn would lead to higher costs for defrosting of equipment and for maintenance.

Increased costs in plasma storage warehouses:
In addition to the walk-in freezers in the plasmapheresis centers, some Source Plasma Establishments also maintain plasma storage warehouses that consist of walk-in freezers (of approximately 400,000 cubic feet) capable of holding in excess of 500,000 L of Source Plasma. It is common practice to maintain these freezers at a temperature well in excess of the required -20°C, e.g., at -30°C or colder. This temperature is necessary to provide an adequate buffer in order to ensure that the temperature does not exceed -20°C. A 10 degree buffer is entirely reasonable in order to prevent the relabeling in excess of 500,000 units of Source Plasma as Source Plasma Salvaged as would be required by 21 CFR § 640.7, in the event that the plasma was subjected to two episodes of the temperature becoming warmer than -20°C but colder than -5°C. Experience has shown that a -30°C set point would result in no excursions above -20°C, but in many excursions above -30°C each year. Due to the length of time that plasma may be held in this freezer (a minimum of 60 days for the voluntary inventory hold period), every excursion above

-30°C would result in an automatic request for an exemption (under 21 CFR § 640.120) to 21 CFR § 640.76. This would dramatically increase the workload for industry as well as for the FDA.

Because of the quantity of plasma stored and the potential consequences of any temperature excursions above -30°C, the proposed rule would mandate that plasma storage warehouses maintain at least -40°C in order to maintain an appropriate temperature buffer. This would require modifications to these freezers that could cost in the vicinity of $500,000 to $600,000 per freezer. In addition, the colder temperature would increase energy costs, by at least 20% to 30%, as already described. It would also cost in excess of $10,000 to revalidate a freezer of this type at -40°C.

The lower temperature would also have an impact on the type, maintenance and service life of equipment e.g., the power forklifts, that are used in the plasma storage warehouses.

Environmental Health and Safety Concerns:
As already described, in order to ensure a product temperature of -30°C, a freezer set point of approximately -40°C would be necessary. In addition to the costs already mentioned, there are significant costs and concerns about safety that come into play at this reduced temperature.

The discussion of these issues will focus on a plasma storage warehouse, as described above. The size of these freezers (up to 400,000 cubic feet) and the nature of work performed in these freezers, e.g. moving and retrieving pallets loaded with cartons of Source Plasma using powered (and occasionally manual) forklifts, presents a worst-case scenario in terms of discussing concerns related to cold stress and cold injury. However, the same issues and concerns also apply to every walk-in freezer in every plasmapheresis center.

In order to ensure proper air circulation, and therefore a constant temperature throughout such a large freezer, it is necessary to have several powerful fans in these freezers – in at least one of these freezers there are seven fans that blow cold air (approximately -30°C) at approximately 20 mph down each aisle of the freezer. The significance of these conditions will be described below.

The American Conference of Governmental Industrial Hygienists (ACGIH)® is a private, not-for-profit nongovernmental corporation, whose members are industrial hygienists and other occupational health and safety professionals dedicated to promoting health and safety in the workplace, and to the administrative and technical aspects of occupational and environmental health. ACGIH® has proposed guidelines, known as Threshold Limit Values (TLVs®), for use by industrial hygienists in making decisions regarding safe levels of exposure to various physical agents found in the workplace. The TLVs® represent scientific opinion that is based on a review of peer-reviewed scientific literature by committees of experts in public health and related sciences. The TLVs® are based solely on health factors, and no consideration is given to

economic or technical feasibility. Although the TLVs® are not designed to be used as standards, ACGIH® believes that TLVs® can be considered by regulatory bodies as valuable input into the risk characterization process. OSHA has the ability to reference these TLVs® since there is no comparable OSHA regulatory standard in effect. Thus, even with the above mentioned limitations, the TLVs® provide useful guidelines for determining the impact of the proposed rule on worker safety issues.

The 2003 TLVs® for Cold Stress, *Table 2. Cooling Power of Wind on Exposed Flesh Expressed as Equivalent Temperature* (Reference 1) characterize a dry bulb temperature of -30°C with a wind speed of 20 mph, which has an equivalent temperature of approximately -55°C, (current conditions), as "INCREASING DANGER – Danger from freezing of exposed flesh within one minute." In contrast, a dry bulb temperature of -40°C with a wind speed of 20 mph, which has an equivalent temperature of approximately -71°C, (proposed rule conditions) is characterized as "GREAT DANGER – Flesh may freeze in 30 seconds." The TLVs® generally recommend that under conditions characterized as Great Danger, that non-emergency work should cease.

The *TLVs® Work/Warm-up Schedule for a 4-Hour Shift* (Reference 1, Table 3) suggests that for a dry bulb temperature of -30°C with a 20 mph wind (current conditions), the recommended schedule for a 4-hour work period is a maximum work period of 30 minutes with 5 breaks or warm-up periods (of 10 minutes) in a warm location, and an extended break, e.g., lunch, at the end of the 4-hour work period, in a warm location. If the dry bulb temperature were decreased to -40°C with no adjustment to the wind speed, the TLVs® recommend that "Non-emergency work should cease." Thus, only if the fans in the freezer were shut off whenever anyone was working in the freezer, would work be permitted, and this would be at the schedule recommended for the current conditions, i.e., a maximum work period of 30 minutes with 5 breaks or warm-up periods (of 10 minutes) in a warm location, etc.

The TLVs® for the current conditions, as well as for the conditions under the proposed rule in this type of freezer, are summarized in the following table.

Explanation	Approximate Dry bulb temperature	Approximate Wind speed	Approximate Equivalent temperature	Risk Category	Suggested maximum work period and number of 10 minute breaks per 4 hour shift
Existing conditions	-30°C	20 mph	-55°C	Increasing Danger[1]	30 minutes of work 5 breaks
Proposed rule – temperature adjustment only	-40°C	20 mph	-71°C	Great Danger[2]	Non-emergency work should cease
Proposed rule – temperature and wind speed adjustment	-40°C	No wind	-40°C	Increasing Danger[1]	30 minutes of work 5 breaks
1 - Increasing Danger = Danger from freezing of exposed flesh within one minute					
2 - Great Danger = Flesh may freeze within 30 seconds					

Thus, a mechanism to stop the flow of air whenever anyone is working in the freezer would have to be implemented, likely at considerable cost. Of even greater significance, however, is the fact that reduced air circulation for prolonged periods of time could lead to uneven temperatures and to temperature excursions above -30°C within the freezer. As mentioned above, in a freezer of this size, every excursion above -30°C would result in an automatic request (under 21 CFR § 640.120) for an exemption to 21 CFR § 640.76. Again, this will dramatically increase the workload for industry as well as for the FDA. Even with no air flow, special PPE and work controls including constant supervision or use of the buddy system, frequent rest breaks in heated areas, minimization of sitting or standing, etc., would be necessary in order to ensure worker safety.

It should be noted that a dry bulb temperature of -40°C was used in this discussion. If the actual dry bulb temperature in any given freezer falls below -42°C, even with no wind, the TLVs®, recommend that non-emergency work should cease. It must be remembered that these same work controls would have to be implemented in almost every freezer in every plasmapheresis center.

PPE that protects all exposed skin would be costly, and would hamper the ability of staff to perform in this environment and to exert the care that is expected in a GMP environment. Errors due to staff hurrying because they are uncomfortable in this extremely cold environment, or encumbered by bulky and uncomfortable PPE, are likely to increase, and will be costly to correct, especially in terms of lost product.

Revisions to SOPs:
Standard operating procedures (SOPs) would also have to be revised to reflect the requirements of the proposed rule. Procedure revisions, and then the training required to implement the revised procedures, could cost in the vicinity of $15,000.

Proposed shipping temperature:
Because of the existing requirement (in the *European Pharmacopoeia - Human Plasma For Fractionation*) to store and transport plasma at or below -20°C, many of the trailers that are currently in use to transport Source Plasma are already validated to maintain a shipping temperature of -20°C, and this new shipping temperature would not be expected to impose an additional burden. However, the proposed rule would state (21 CFR § 640.76 (b)) that <u>any</u> temperature deviation above -15°C requires that the Source Plasma be labeled as Source Plasma Salvaged. (Existing 21 CFR § 640.76 (b) states that <u>any</u> temperature deviation above -5°C requires that the Source Plasma be labeled as Source Plasma Salvaged.) The existing -5°C shipping temperature has not presented a major problem because of the approximately 15 degree buffer that currently exists. However, the proposed shipping temperature of -15°C will provide only a five degree buffer, and therefore temperature excursions above -15°C will be frequent. This will result in a substantial increase in requests for an exemption (under 21 CFR § 640.120) to 21 CFR § 640.76. As already mentioned, this will dramatically increase the workload for industry as well as for the FDA.

Discussion of requirement to relabel Source Plasma as Source Plasma Salvaged:
If the shipping temperature is changed to -15°C, 21 CFR § 640.76 (b) should be amended to allow an exemption to the requirement to relabel Source Plasma as Source Plasma Salvaged for a temperature excursion above -15°C, but below -5°C, for at least 72 hours. As mentioned above, this currently does not exist, and this lack of an exemption will impose a burden, since shipping temperatures are more difficult to control, and temperature excursions will, and do, occur. This requested exemption would be consistent with the existing exemption for storage temperatures permitted in § 640.76 (a)(2). It should also be noted that the temperature permitted for this requested exemption (-5°C) would be the same temperature as is currently required for the routine shipment of Source Plasma. An allowance for a temperature excursion not to exceed -5°C would also be consistent with the requirements in the *European Pharmacopoeia - Human Plasma For Fractionation,* which allows for a temperature excursion during storage and/or transport up to -5°C for up to 72 hours.

As an additional note, § 640.76 (a)(2) should be definitively clarified to indicate if the phrase "one episode of storage temperature warmer than –20°C and colder than –5°C for not more than 72 hours" is really intended to mean that only <u>one</u> temperature excursion, no matter how brief, is exempt, or if the phrase is intended to mean that several temperature excursions, as long as they

do not exceed a total of 72 hours, are exempted from the requirement to relabel the Source Plasma as Source Plasma Salvaged. Various interpretations of this requirement are currently in use. Similarly, this concept should also be addressed in § 640.76 (b) if an exemption were to be permitted during the transport of Source Plasma. With the proposed lower storage and shipping temperatures, allowing only a single temperature excursion is overly restrictive, and will result in large quantities of Source Plasma either being relabeled as Source Plasma Salvaged, or held under quarantine as requests for an exemption to 21 CFR § 640.76, filed under 21 CFR § 640.120 are prepared and then processed by the FDA.

We respectfully also request that the regulatory requirement to relabel Source Plasma as Source Plasma Salvaged be reviewed. There are no regulatory restrictions on the use of Source Plasma Salvaged for fractionation, and the purpose of relabeling the plasma is to notify the plasma derivative manufacturer that a temperature excursion has occurred. With the increased use of automated data transfer systems, alternative methods of notification of temperature excursions are possible, and may provide as high, or an even higher, degree of control of the notification process than the relabeling of every unit of Source Plasma.

Summary of compliance costs:
As has been described, compliance costs for the proposed rule could be in the vicinity of several million dollars for a typical Source Plasma Establishment. Costs will include both conversion costs, which would have to be expended in a relatively short period of time (depending upon the time allowed for the implementation of the final rule), and the ongoing costs. Although the costs as described are only preliminary estimates, they are presented to show that the proposed rule will in fact have very significant compliance costs.

Concluding remarks:
As can be seen, the proposed -30°C storage temperature and the proposed -15°C shipping temperature would have a significant operational and economic impact on a substantial number of small entities. In today's environment, all partners in the healthcare system, including patients, providers, industry, and regulators, have a responsibility to ensure that every dollar that is spent on health care is wisely spent, and provides real value to the patient. It could be argued that the dollars that would be spent on complying with the proposed storage and shipping temperatures would not pass this test.

Again, thank you for the opportunity to comment on this proposed rule. Please do not hesitate to contact me if you have any questions regarding these comments.

Sincerely,

Robert J. Kratzel, Ph.D., M.B.A.
Director, Regulatory Affairs

References:

(1) 2003 TLVs® and BEIs® Based on the Documentation of the Threshold Limit Values for Chemical Substances and Physical Agents & Biological Exposure Indices. 2003, American Conference of Governmental Industrial Hygienists.