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Plasma Protein Therapeutics Association

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Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

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

Dear Sir or Madam:

PPTA is pleased to provide these comments on the Food and Drug Administration's (FDA's) Proposed Rule entitled, "Revisions to Labeling and Storage Requirements for Blood and Blood Components, Including Source Plasma" (hereinafter "Proposed Rule"). The Plasma Protein Therapeutics Association (PPTA) is the international trade association and standards-setting organization for the world's major producers of plasma-derived and recombinant analog therapies. Our members provide 60 percent of the world's needs for Source Plasma and protein therapies. These include clotting therapies for individuals with bleeding disorders, immunoglobulins to treat a complex of diseases in persons with immune deficiencies, therapies for individuals who have alpha-1 anti-trypsin deficiency which typically manifests as adult onset emphysema and substantially limits life expectancy, and albumin which is used in emergency room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to assuring the safety and availability of these medically needed life-sustaining therapies.

PPTA's comments highlight several areas of impact by the Proposed Rule.

- First, PPTA examines the scientific basis utilized by FDA as a foundation for the Proposed Rule.
- Second, the economic costs associated with compliance will be discussed, summarizing the findings of a PPTA survey of the plasma industry.
- Discussed next are the proposed labeling changes and the regulatory contraction recommended by FDA.
- Other associated issues, such as worker safety and environmental impacts, conclude PPTA's comments.

The Proposed Rule's Scientific Basis

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PPTA would first like to address the difficulty regarding the scientific basis used for the Proposed Rule. FDA cited Kotitschke, Morfeld, et al, (2000) as providing adequate

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scientific basis; the article, however, does not illuminate any difficulties within the plasma industry.

First, the Kotitschke article may not have a direct application to plasma for fractionation or fractionated plasma products. Indeed, the article appears to be focused on plasma used for transfusion, a procedure which differs from collection of plasma for fractionation. In summary, it may be difficult to extrapolate the results reported in the paper and apply them to the fractionation industry

Essentially, the article sought to determine human plasma's stability at different temperatures, ranging from –20°C to –40°C over two to three years. Of all the protein levels examined, no statistically significant changes could be found at any temperature, save an 11% reduction in Factor IX (which, in this single instance, had been stored at –20°C for two years.) This particular sample had not been withdrawn using plasmapheresis and was frozen 21-24 hours after collection. The industry standard is that plasma be derived through plasmapheresis and placed in a freezer within thirty minutes of collection. Because no other significant changes could be detected in any other sample, it would be more reasonable to hypothesize that the lower level of Factor IX in this one sample was due to the collection method and the time to freezing. Conditions similar to industry practice presented in the article showed a 4% (and not statistically significant) decrease in Factor IX levels. There were no statistically significant decreases in any other protein levels. Since the published data do not show a decrease in any other proteins, the imposition of a –30°C storage temperature for all Source Plasma based solely on the reported reduction in Factor IX would be inappropriate. It would therefore seem unreasonable to mandate a lower storage temperature based on a single sample from only one type of the many proteins separated from plasma from a method that is not analogous to industry practice.

While PPTA favors reasonable regulations that protect the patient population, there is no loss of Factor IX efficacy given current industry practice. Essentially, this particular temperature issue is a matter of product yield. Given the insignificant differences found in the study, the apparent differences in yield are not significant. The level of specific proteins in concentrates can be adjusted to predetermined levels. The rather academic, isolated loss of Factor IX in the Kotitschke article has no impact on product availability or patient care and the study provides no information demonstrating an improvement in the quality of plasma derivatives manufactured from plasma stored at –30°C.

The Proposed Rule and Projected Economic Impact

PPTA devised a straightforward instrument designed to collect any data that the plasma industry might have with regards to the economic impact that the Proposed Rule might have in terms of the temperature standards. The hypothesis tested with the instrument was the FDA's statement that the Proposed Rule has "no compliance costs and will not have a significant effect on a substantial number of small entities." (Part VI.) The FDA

also stated that "these [temperature] requirements reflect current industry practice and do not impose an additional burden." (Part VI.)

Current plasma industry practice, in accord with FDA and European standards for the collection of plasma by plasmapheresis, is a –20°C storage temperature. Rapid cooling at –30°C or lower freezing temperature as soon as possible, or within 24 hours after collection, is required by the European Pharmacopeia (EP) Monograph for plasma intended for the recovery of proteins that are labile. The requirements for the storage of plasma at –20°C for all plasma collected by plasmapheresis as required by both the US Code of Federal Regulations (CFR) and EP Monograph are harmonized today under the existing regulations. The Proposed Rule alters the current –20°C storage temperature to a –30°C storage temperature and therefore would create disharmony between the US CFR and EP Monograph plasma storage temperature requirements. In addition, not every United States based plasma supplier participates in the European plasma market. These particular suppliers may not freeze product at the –30°C temperature, and the Proposed Rule would force these entities to install completely new equipment or purchase new facilities. Some of these entities may choose to leave the business rather than attempt such recapitalization, given the current economic climate. Indeed, even with flash-freezers that are able to obtain the –30°C freezing temperature, these same devices cannot store product at that temperature. The European standard also mandates a –30°C freezing temperature for labile products, but not as a blanket provision for all plasma.

As our research discovered, the economic impact in terms of transition and upkeep to the Proposed Rule's new standards would be severe. Virtually all of the plasma industry's freezing and refrigeration units would either need retrofit, or, more often, complete replacement. The conservative, estimated industry-wide total impact is $70 million. This figure is derived from different categories:

1. Approximate total cost associated with hardware upgrade/setpoint changes.
2. Approximate total cost of revalidating freezers after upgrade.
3. Approximate total cost of updating SOPs and training new staff.
4. Approximate total cost of maintaining a –40°C set point in all new freezers.
5. Best estimate of excursions expected per year under the new requirements.

PPTA asked the plasma collection industry, the plasma fractionation industry, and large plasma warehouses/transporters to comment on the above issues. Industry participants agreed that in order to ensure a plasma storage temperature of –30°C, a setpoint of –40°C was agreed on as a reasonable target, with an alarm point of –32°C warning of a potential excursion. In comparison, current practice has setpoints of –27°C or –28°C with an alarm point of –25°C or –23°C to maintain the regulatory standard of –20°C for plasma storage.

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The industry's primary freezer engineering consists of a single cooling system. This single system is made up of one condenser and one evaporator which are, when run at maximum capacity, capable of a "suction" temperature of –40°C, which translates to a maximum lowest temperature of –35°C within the freezer box. To ensure compliance with the Proposed Rule, the current engineering design would have to be upgraded with a two-stage condenser and evaporator, with a "suction" temperature of –60°C and theoretically capable of a –50°C temperature, if all other factors involved with freezer temperature remain constant (i.e., no mechanical or utility failures). Without a two-stage system, a single condenser freezer could not maintain the Proposed Rule's standard and would maintain the current –20°C temperature requirement. Many smaller freezers do not have the size capacity to accommodate a two-stage system and would have to be scrapped and replaced. Another difficulty with such replacement, as alluded to below as well, would be hardware availability for equipment upgrade and maintenance.

With 450-500 freezers in question (widely varied in size, capacity, current temperature, and other factors), we estimate that the approximate industry-wide cost to upgrade freezers with a lower set point would be approximately $29 million. Of course, some facilities already have newer equipment, which would mean a lower expenditure. The majority of facilities, however, indicated that they would need not only new compressors to maintain the lower temperature, but also entirely new freezer boxes and re-engineered refrigeration systems. Estimates of the price of a single upgrade, either by buying new or by re-engineering current equipment, ranged from $30,000 to $90,000 *per unit*. One of our members had already purchased equipment capable of maintaining the Proposed Rule's requirements, and supplied an invoice and receipt for $77,000 for a single unit. Ancillary comments noted that while some of the new freezers on the market are theoretically capable of –50°C temperature, this has not stopped excursions from occurring above the –30°C proposed standard. With an average of over $70,000 per unit, with hundreds of units to be replaced or upgraded, the cost of compliance dramatically increases, and the Proposed Rule does indeed have significant compliance costs.

Addressed below are further concerns, in that the proposed standard would require new coolant systems, which do not employ widely available refrigeration technology. Instead, the current technology and refrigeration methods may need to be switched to an ammonia-based system, which is not only far more expensive, but represents further environmental and occupational hazards. An ammonia-based cooling system also has a plethora of different regulations in continental Europe, inconsistent with current U.S. regulations and any attempt at harmonization.

Industry-wide revalidation costs exceeded $1 million, with estimates ranging from $100-$50,000. These revalidation costs range widely according to the business type. Some businesses may have trained refrigeration experts or engineers on site, while others would have to retain external consultants, with attending fees, travel costs, and so on.

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The situation with upgrading training and SOPs is similar, with a total industry wide cost exceeding $100,000.

Industry-wide total expected increase in operating cost is nearly $4 million, representative of an expected 20-30% increase over the current operating costs. Estimates include the upward surge in energy consumption. As mentioned above, one respondent to our survey had completed an installation with the new freezer, and one-month electrical costs surged by 30%. We estimate that the total yearly increases for maintenance and utility expenditure would be 25-30% over what is the current monthly expenditure.

Maintenance costs on the new freezers are also expected to be high. Documentation shows more than $200 a month extra in freezer maintenance (beyond utility costs) *per unit*. The new designs, in order to meet the –40°C or lower temperature, requires an anteroom for entering the freezer; some respondents replied that space will not be available in the current facilities, necessitating a new physical plant. These new, expanded designs require special compressors that run at a higher rate and are therefore more prone to failure. As mentioned above, the new compressor design is highly specialized, with only a handful of distributors nationwide. An equipment failure could result in a catastrophic cascade of lost product, due not only to a temperature excursion and subsequent thawing but also an inability to procure replacement parts and/or the technical expertise necessary to affect a repair. While costs due to normal wear and tear, mechanical flaws, and other problems encountered in the ordinary course of use with these devices are hard to estimate, PPTA expects the increased maintenance costs to be in the range of $10 million.

Some industry respondents were confident that the current systems, if retrofitted to meet the Proposed Rule's temperature standards, would not have cold-air excursions. Unfortunately, the majority of the freezer operators projected everything from occasional excursions to daily excursions. While industry currently makes use of requested exemptions under the applicable regulations at 21 CFR §640.120, FDA may expect a dramatic upsurge in the number of requested excursion exemptions. Several respondents noted that there would be enough excursions to "ruin" the products under the new regulatory mandate, with an expected cost exceeding $10 million due to product that would not be viable under the new regulatory requirements. Other respondents estimated 200-300 excursions expected per year, with subsequent extreme difficulty in continuing operations.

The plasma warehousing and transport area of industry would also be severely affected and would pass costs on to the source and fractionation industries as well. These passed costs are not reflected in the above survey results. The warehouses expect a 30-50% increase in power, labor and personal protective equipment (PPE), and maintenance costs. The warehouses use exceptionally large freezer rooms that would cost $500,000-$600,000 each for upgrade.

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The Proposed Rule, Labeling, and Regulatory Consolidation

Previous PPTA comments, such as on the FDA's Proposed Rule regarding bar coding of products, have endorsed fluid regulations that allow technological improvement with a minimal regulatory burden. PPTA is cautious regarding FDA's labeling proposals in the current Proposed Rule, as combining the regulatory language for both Source Plasma and blood may not be the most efficient regulatory method.

The Proposed Rule made numerous suggestions with regard to labeling, and also made a significant attempt at consolidating the regulatory language. While we applaud these efforts, we would like to point out some potential areas of difficulty.

PPTA agrees with FDA that the current form of regulations can be cumbersome at times due to labeling requirements being spread throughout different sections. PPTA is concerned that incorporating the Source Plasma requirements into the regulatory passages for blood and other blood products may increase the difficulty in identifying the applicable labeling requirements. For example, regulatory section length is further subdivided and substantially extended, making Source Plasma requirements more difficult to find. A more feasible alternative would be to follow FDA's initial idea by compiling the regulatory requirements for labeling into a single section, but focus a subsection dedicated to the requirements specific to Source Plasma.

The Occupational and External Environments Under the Proposed Rule

Beyond the labeling requirements and the Proposed Rule's temperature impact on the economics of the industry, PPTA would like to comment on the lower temperature's impact on plasma center workers. The Occupational Health and Safety Administration (OSHA), the National Institute of Occupational Safety and Health (NIOSH), and the American Council of Government Industrial Hygienists (ACGIH) all consider –25°C and colder to be an "extreme cold" environment. As such, many occupational health specialists consider temperature to be a physical hazard akin to particulate matter, falls, and radiation.

As mentioned above, a –30°C storage requirement would necessitate an environment much colder, such as –40°C, in order to minimize excursions. The freezers would have to be set with an alarm point of –32°C or colder to ensure this. Because the current temperatures are held at the borderline of an "extreme cold" environment under the NIOSH and other guidelines, the Proposed Rule would clearly put workers within the protected category envisioned by the occupational health experts.

Vasoconstriction helps retain core body temperature. The offshoot to this is that it lowers extremity and skin temperature, increasing the risk of frostbite. Manual dexterity begins to lessen, and dexterity is lost more quickly in direct proportion to the level of cold temperatures. Gloves, of course, help to lessen heat loss but also preclude any

work of fine motor skills, which could increase product loss through breakage. Beyond these initial health problems, frostbite, trenchfoot, and hypothermia are all very real concerns (OSHA Fact Sheet No. 98-55). Heart disease has also been linked to repeated cold-temperature exposure (CDC/NIOSH Topics: Occupational Heart Disease).

Workers who use tobacco or caffeine may be at higher risk for cold-related health problems in the proposed extreme cold environment. Asthmatics or people with other respiratory problems will suffer from bronchospasm and mucosal disorders. Occupational safety and health organizations have noted that cold environments also vastly increase the risk of repetitive stress injury. (NYCOSH, SEMCOSH).

As an example, discussion of these issues will focus on the plasma storage warehouse. The warehouse consists of a single freezer of approximately 380,000 cubic feet that has seven large fans that blow air down each aisle of the freezer at approximately 20 mph. The size and the nature of work performed in this freezer, 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. Conditions at plasmapheresis centers may actually be of greater concern, because staff at plasmapheresis centers will require further training to familiarize themselves with the risks encountered in an extreme cold environment to which they are unaccustomed.

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 (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, *Table 2. Cooling Power of Wind on Exposed Flesh Expressed as Equivalent Temperature* [hereinafter "Indices"]) characterize 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) as "GREAT DANGER – Flesh may freeze in 30 seconds." In contrast, 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), is characterized as "INCREASING DANGER – Danger from freezing of exposed flesh within one minute." 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* (Indices, 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 (i.e., no wind), should 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, and an extended break, e.g., lunch, at the end of the 4-hour work period, in a warm location.

The TLVs® for the current conditions, as well as for the conditions under the Proposed Rule, 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, at considerable cost. However, reduced air circulation

for prolonged periods of time could lead to uneven temperatures and temperature excursions above -30°C within the freezer. Virtually *every* excursion above -30°C would result in an automatic request (under 21 CFR § 640.120) for an exemption to 21 CFR § 640.76, since Source Plasma is held in the plasma storage warehouse for the bulk of the 60-day inventory hold storage period.

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 maximum 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, according to the TLVs®, the risk category would be characterized as "Great Danger." It must be remembered that these same controls would have to be implemented in almost every freezer in every plasmapheresis center.

In addition, ACGIH® recommends that staff that are routinely exposed to air temperatures below -24°C with wind speeds less than 5 mph, or air temperatures below -18°C and wind speeds above 5 mph, should be medically certified as suitable for such exposures, i.e., that they are not suffering from any disease, or taking any medications, that interfere with normal body temperature regulation or that reduces tolerance to work in cold environments. This would involve the medical certification of hundreds of employees.

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, will increase and will be costly to correct. PPTA would also like to point out that while ACGIH and NIOSH recommendations are not binding with the force of law, the Proposed Rule's lower temperature values open the door to severe injury. Flowing from the increased likelihood of injury is a proportionately increased possibility of litigation, Workers' Compensation claims, and disability insurance claims.

Added concern is not restricted to impact on the working environment, but the environment at large. With the lowered temperatures come increased utility bills, as noted above –even in a completely overhauled system. Special handling requirements for maintenance and regular use come into play as a result of using an ammonia-based system for refrigeration. Other external environmental impacts come about as a result of disposal of obsolescent refrigerant, compressors, and freezer boxes. European standards for ammonia-based systems require different levels of security and engineering within buildings containing such systems, and may represent further harmonization difficulties.

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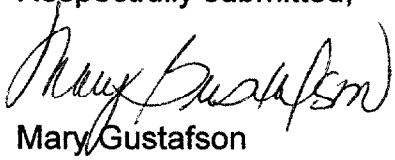
Conclusion

The article cited by FDA [Kotitschke, Morfeld, et al, (2000)] as providing an adequate scientific basis to justify a –30°C plasma storage temperature requirement has been inappropriately applied to Source Plasma for further manufacture. It is stated in the Proposed Rule that a –30°C plasma storage requirement is intended to harmonize with EU requirements and is in line with current industry practice. PPTA has presented information demonstrating that the Proposed standard of plasma storage at –30°C is not current industry practice and does not conform with current EU plasma storage requirements. The Proposed Rule, if enacted, will lead to significant industry expenditures to comply with the Proposed Rule without a public health benefit. Furthermore, no data have been presented to demonstrate an improvement in the quality of plasma derivatives manufactured from plasma stored at –30°C. The recipients of plasma-derived therapies will receive no added benefit from this Proposed Rule. Given the lack of data to demonstrate an improvement in the quality of plasma derivatives produced from plasma stored at –30°C, the significant costs associated with meeting the Proposed Rule that would be incurred by industry are not justified. The existing US CFR regulations that provide harmonized plasma storage requirements (–20°C) between the US CFR and the EP Monograph should not be altered.

PPTA appreciates the opportunity to comment on this Proposed Rule. Should you have any questions regarding these comments or would like additional information, please contact PPTA. Thank you for your consideration.

Respectfully submitted,



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