PPTA
Plasma Protein Therapeutics Association

December 21, 2004
Reference No. FDAA04028 **Via E-Mail**

Jesse Goodman, MD, MPH
Director
Center for Biologics Evaluation and Research
Food and Drug Administration
1401 Rockville Pike
Rockville, MD 20852

Dear Dr. Goodman:

Thank you and your staff for meeting with us on December 13, 2004. We appreciate the opportunity to discuss issues affecting the plasma therapies industry. In that meeting, Mr. Jan Bult, President, Plasma Protein Therapeutics Association (PPTA), mentioned that PPTA would submit a letter to the Center regarding albumin. PPTA has been closely monitoring the peer-reviewed fluid therapy literature including the article describing the results of the Saline vs. Albumin Fluid Evaluation (SAFE) trial, appearing in the May 2004 issue of the *New England Journal of Medicine* (1).

The SAFE trial was a randomized, double-blind, multicenter study that compared the fluid resuscitation effect of albumin or saline on mortality. A total of 6997 patients in 16 Australian and New Zealand intensive care units (ICU) received either 4 percent albumin or 0.9 percent sodium chloride for fluid resuscitation over the 28-day study period. The primary endpoint was 28-day all-cause mortality. In the albumin group there were 726 deaths and in the saline group there were 729 deaths; the relative risk of death was 0.99, the 95 percent confidence interval was 0.91 to 1.09 and P=0.87. The authors concluded that the administration of either 4 percent albumin or normal saline for fluid resuscitation in ICU patients results in similar clinical outcomes at 28 days. It is important to realize that this study was a safety study; a trial to evaluate efficacy or equivalence would require different study design and sample-size calculations.

These data prove clinically that albumin is a safe therapy and clearly refute the findings of a meta-analysis from the Cochrane Collaboration (2) which was the subject of a 1998 Dear Doctor letter from the Food and Drug Administration (FDA). That meta-analysis raised questions regarding the safety of human albumin administration in critically ill patients but has been widely criticized due to methodological flaws (3-6). Furthermore, a subsequent meta-analysis of Wilkes and Navickis (7) could not replicate the finding of excess albumin-associated mortality reported by the Cochrane investigators. In fact, the results of the SAFE trial corroborate the conclusions of this second and more rigorous meta-analysis.

147 Old Solomons Island Road · Suite 100 · Annapolis, MD 21401 USA
tel: 202.789.3100 · 410.263.8296 · fax: 410.263.2298 · e-mail: ppta@pptaglobal.org · www.pptaglobal.org
PPTA Offices in Washington · Annapolis · Brussels · Tokyo

In light of these new data, PPTA believes that the continued presence of the 1998 Dear Doctor letter on the FDA web site does not serve the best interest of optimal fluid therapy and may indeed encourage the overuse of crystalloid and artificial colloid solutions that may entail greater risks than those of albumin (8,9). Consequently, PPTA would like to request the removal of the Dear Doctor letter from the FDA web site. Since the Cochrane meta-analysis has gained wide notice at least in part from the imprimatur of the FDA Dear Doctor letter, PPTA further believes that some remedial action on the part of FDA would be appropriate. We would therefore like to request additionally that a notice be displayed on the FDA web site containing information about the recently published SAFE study results. Suggested language for the notice would be the following:

SAFE Study

A randomized, double-blind, multicenter trial comparing the effect of 4% albumin administration with normal saline use on mortality in critically ill patients was published in May 2004 (SAFE Study Investigators: A comparison of albumin and saline for fluid resuscitation in the intensive care unit. N Engl J Med 2004; 350:2247-2256). The trial investigators concluded that albumin or normal saline administered for fluid resuscitation results in similar clinical outcomes at 28 days. Further details may be found at:

http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?cmd=Retrieve&db=pubmed&dopt=Abstract&list_uids=15163774

Thank you very much for your consideration of these requests. Should you desire any further information supporting the requests, PPTA would be happy to provide it. With the holiday season upon us, I would like to take this opportunity to wish you a happy and successful New Year. I will follow up on this issue with you by phone early in 2005. In the meantime, if you have any questions please feel free to contact me at 202-789-3100, ext. 2115.

Sincerely,

Mary Gustafson
Senior Director, Global Regulatory Policy

cc: Jay Epstein, MD, Director, OBRR, CBER, FDA

References

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4. Erstad BL: Concerns with defining appropriate uses of albumin by meta-analysis. Am J Health Syst Pharm 56:1451-1454, 1999

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8. Schaadt J: Oxygenator thrombosis: an international phenomenon. Perfusion 14:425-435, 1999

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