



**BLOOD PRODUCTS ADVISORY COMMITTEE**  
82<sup>nd</sup> Meeting — March 17<sup>th</sup>, 2005  
Gaithersburg Holiday Inn, 2 Montgomery Village Avenue  
Gaithersburg, MD 20877

**Topic I. Safety of Albumin Revisited**

**ISSUE:**

FDA seeks advice from the Committee whether a recently published study has resolved earlier concerns over the safety of albumin in critically ill patients.

**BACKGROUND:**

On July 25, 1998, the *British Medical Journal* published a meta-analysis completed by the Cochrane Injuries Group that studied administration of human albumin to critically ill patients (*BMJ* 1998;317:235-40). Their analysis, comprising 30 randomized trials, revealed an excess overall mortality of 6 % (95% confidence interval 3% to 9%) for patients with hypovolemia, burns, or hypoproteinemia who received albumin instead of (or in addition to) crystalloid solutions. Specifically, the relative risk of death was 1.46 (95% confidence interval 0.97 to 2.22) for hypovolemia, 2.40 for burns (1.11 to 5.19), and 1.69 (1.07 to 2.67) for hypoproteinemia in the albumin treatment arm. The authors of this study concluded that albumin administration may increase mortality in critically ill patients.

One month later, FDA issued a Dear Doctor letter that highlighted these findings. It urged physicians to “exercise discretion in use of albumin ...based on their own assessment of these data” (<http://www.fda.gov/cber/ltr/albumin.htm>).

When these results from the *British Medical Journal* were presented before a BPAC meeting in September 1998, several Committee members voiced concern over the quality of studies included in the Cochrane Group’s meta-analysis. Industry responded by sponsoring additional meta-analyses. For example, Wilkes and Navickis (*Ann Intern Med* 2001;135:149-164) claimed that the Cochrane Group had omitted relevant trials, combined heterogenous populations (e.g., adults and high-risk neonates), and paid inadequate attention to critical design issues such as blinding, treatment allocation, crossover, different treatment regimens, and endpoints. In their

own meta-analysis, Wilkes and Navickis found an overall relative risk of mortality of 1.11 (0.95 to 1.28) in the albumin treatment arm. The authors concluded that since the confidence interval for relative risk “crossed” 1.00 and thus, did not reach statistical significance ( $p < 0.05$ ), their study “should serve to allay concerns regarding the safety of albumin”.

In an accompanying editorial (*Ann Intern Med* 2001;135:205-208), Cook and Guyatt pointed out that while the results from the study by Wilkes and Navickis were not statistically significant, the point-estimate — the best estimate of the true effect of treatment — showed an increase in the relative risk for death of more than 10% overall and up to 76% in various subgroups. They underscored that fact that, “Point estimates that suggest harm and confidence intervals that include important increases in mortality cannot allay concerns about the potentially harmful effects of albumin.” The authors also noted that while this study had many strengths, it was limited by some of the same weaknesses noted by Wilkes and Navickis in their critique of the Cochrane Group’s meta-analysis, as well as those *not* noted by them, e.g., transfusion thresholds.

In 2004, the SAFE study was published (*N Engl J Med* 2004;350:47-56). This was the first large (6997 subjects), multicentered (16 hospitals), controlled (normal saline), randomized, *blinded* mortality study to compare albumin with normal saline in ICU patients requiring fluid resuscitation due to hypovolemia. It is worth noting that cardiac surgery, liver transplantation, and burn patients were excluded from the trial and that the experimental arm was 4% albumin, rather than 5% albumin which is used routinely in the United States. Results of this study showed that the relative risk of death was 0.99 (0.91 to 1.09), leading the authors to state that in ICU patients, “Use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.” The clinical importance of the SAFE study was recently highlighted by a letter to FDA from the Plasma Protein Therapeutics Association (*December 21, 2004 letter to Jesse Goodman, MD, MPH, Director, Center for Biologics Evaluation and Research, Food and Drug Administration*)

#### Questions for the Committee:

1. Have data from the SAFE study resolved the safety concerns that were raised in the meta-analysis by the Cochrane Group for
  - a. critically ill patients in general?
  - b. subgroups of critically ill patients with burns, hypovolemia, or hypoproteinemia?