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Blood Products Advisory Committee - c/o William Freas, PhD
Chief, Division of Scientific Advisors and Consultants
FDA/CBER, 1401 Rockville Pike, HFM-71
Rockville, MD 20852

Subj: Albumin Safety – Blood Products Advisory Committee (BPAC) – 3/17/2005

Dear Blood Products Advisory Committee Members:

Thank you for this opportunity to offer my input on the subject of the safety of human albumin. BPAC's consideration of this matter is particularly timely, as there is a particularly high risk of physician misinterpretation of a recently published prospective trial comparing fluid resuscitation with albumin and saline in an unusually heterogeneous study population.

After considering the issues and documentation which follow, I strongly encourage BPAC to recommend that the FDA take the following measures:

1. Remove an August 19, 1998 "Letter to Healthcare Providers" from the FDA website (<http://www.fda.gov/cber/ltr/albumin.htm>), which cautions physicians about the safety of albumin administration in critical care patients, on the basis of a now-discredited meta-analysis by the Cochrane Injuries Group;¹
2. Issue a new "Letter to Healthcare Providers," as well as other public communications as the FDA believes appropriate, which informs physicians of the following:
 - The 1998 Cochrane Injuries Group meta-analysis was undermined by several methodological problems raised by a number of experts in the field.²³ The most serious of these, in my view, was the injudicious decision to include several highly experimental studies in which albumin group subjects were infused with massively higher doses of albumin than is standard medical practice; those subjects experienced a high associated mortality rate, presumably from fluid volume overload.^{4,5}

¹ Cochrane Injuries Group Albumin Reviewers: Human albumin administration in critically ill patients: systematic review of randomized controlled trials. *BMJ* 1998; 317:235-40.

² Erstad BL. Concerns with defining appropriate uses of albumin by meta-analysis. *Am J Health Syst Pharm* 1999; 56:1451-4.

³ Horsey P. Albumin and hypovolaemia: is the Cochrane evidence to be trusted? *Lancet* 2002; 359:70-2.

⁴ Lucas CE, Weaver D, Higgins RF, et al. Effects of albumin versus non-albumin resuscitation on plasma volume and renal excretory function. *J Trauma* 1978; 18:564-70. Investigators infused 150 g/day x 5 days.

- A large prospective randomized trial conducted in Australia and New Zealand⁶ clearly demonstrates that administration of human albumin in critically ill patients requiring fluid resuscitation is not associated with any increased mortality risk over administration of saline solutions. This lack of an association between albumin use and increased mortality risk was supported by a more carefully conducted meta-analysis of 71 patient trials.⁷
- While important for debunking the erroneous conclusions of the flawed Cochrane meta-analysis, **the Australian/New Zealander “SAFE” study was not properly designed nor adequately powered to provide physicians guidance in choosing between the use of albumin or saline in specific clinical populations.** In their conclusion, the SAFE investigators acknowledged this by concluding that “whether albumin or saline confers benefit in more highly selected populations of critically ill patients requires further study.”²
- **The SAFE trial documented an important trend towards improved survival in severe sepsis patients who received albumin (relative risk of death, 0.87; 95% confidence interval (0.74-1.02, P=0.09), suggesting that albumin may confer survival benefit in this specific population.** This finding is consistent with important hemodynamic and oxygen transport function advantages seen in critically ill shock patients who were administered albumin instead of a lactated Ringer’s solution.⁸ Moreover, this result is not surprising in light of a recent landmark study documenting a dramatic 65% reduction in in-hospital mortality in patients with cirrhosis and spontaneous bacterial peritonitis who received a total of 2.5 g/kg of human albumin in addition to the prescribed antibiotic, compared with those who received antibiotic only.⁹

Correcting a misconception: “Albumin and saline should be considered clinically equivalent”

This important albumin group mortality reduction trend is identified in a paragraph on the sixth page of the SAFE report, under the section heading “Subgroup Analyses.” Unfortunately, the SAFE study abstract,¹⁰ *Medscape* reviews¹¹ and other “bottom line” information that reaches thousands of U.S. physicians caring for severe sepsis patients

⁵ Goodwin CW, Dorethy J, Lam V, et al. *Randomized trial of efficacy of crystalloid and colloid resuscitation on hemodynamic response and lung water following thermal injury.* *Ann Surg* 1983; 197:520-31. Albumin group patients received 300-350 g albumin in first 24 hours; equates with an isoosmotic load of 6.0-7.0 L.

⁶ SAFE Study Investigators. A comparison of albumin and saline for fluid resuscitation in the intensive care unit. *N Engl J Med* 2004; 350:2247-56.

⁷ Wilkes MM, Navickis RJ. Patient survival after human albumin administration: A meta-analysis of randomized, controlled trials. *Ann Intern Med* 2001; 135:149-64.

⁸ Shoemaker WC and Wo CC. Circulatory effects of whole blood, packed red cells, albumin, starch, and crystalloids in resuscitation of shock and acute critical illness. *Vox Sang* 1998; 74(Suppl 2):69-74.

⁹ Sort P, Navasa M, Arroyo V, et al. Effect of intravenous albumin on renal impairment and mortality in patients with cirrhosis and spontaneous bacterial peritonitis. *New Engl J Med* 1999; 341:403-9.

¹⁰ Transcribed verbatim in Appendix 1.

¹¹ Transcribed verbatim in Appendices 2 and 3.

focus only on *overall* outcome findings that lump together all clinical populations. These variously include severe sepsis, postoperative recovery, ARDS and a large, generally much younger and healthier trauma population -- for whom saline resuscitation is the standard of care in the U.S. (no published studies have ever suggested a survival or other important health outcome benefit for albumin in an unselected trauma population).

There is no specific mention of the important mortality reduction trend in sepsis in the study abstract or other major communications to the physician community.

A statement in *Medscape Medical News* attributed to a SAFE study investigator (S. Finfer) also exposes a problematic blurring of the distinction between safety and efficacy in this study:

Dr. Finfer told Medscape that the results provide the first “evidence that one fluid is not safer than the other in terms of mortality.” Of patients who received albumin, 28-day mortality was 20.9% while the 28-day mortality in the saline group was 21.1%. “So we can answer the question about difference: there is no difference,” he said. With 7,000 patients, the study was powered at 90% to detect a 3% difference in mortality.

In addition to providing evidence that colloids and crystalloids are equally effective...

In evaluating the safety of one anti-inflammatory drug (e.g. a cox-2 inhibitor) against another, mortality is certainly a legitimate safety endpoint to evaluate because it is an obviously unintended adverse event which is unrelated to the therapeutic objective. But in this unselected heterogeneous mix of patients, whose only commonality happens to be that they were admitted to the ICU, albumin and saline were administered specifically to avoid complications of hypoperfusion that could lead directly to patient death.

Just as mortality is not a “safety” endpoint in an assessment of alternative drug regimens for advanced colorectal cancer, mortality is clearly not a “safety” endpoint in a randomized trial of albumin and saline for resuscitation of severe sepsis or ARDS or hemorrhagic trauma. As in the example of colorectal cancer, mortality is not a unrelated or unexpected outcome. Mortality happens to be the very outcome the physician is hoping to avoid by administering resuscitative fluids – thus the mortality endpoint is properly a measure of the comparative efficacy of these two interventions. The same can be said of end-organ failure, mechanical ventilation days, ICU days and the like – all direct measures of efficacy. The SAFE trial evaluated these efficacy parameters in a number of distinct critically ill populations, each with distinct baseline patient characteristics and pathophysiology. Aggregating any of these key health outcome measures across these populations is not methodologically sound.

Thus, Dr. Finfer’s comment to reporters that “our study provides evidence that albumin and saline should be considered clinically equivalent treatments...in a heterogeneous population of patients in the ICU”¹² is not valid: one cannot reach a single conclusion

¹² Appendix 2.

about a key efficacy measure after combining results of a distinct patient population A (e.g. generally elderly hypotensive patients with severe sepsis and serious comorbidities), some other *entirely different* population B (e.g. generally younger, previously healthy hypovolemic acute trauma patients), a third yet-different population C, etc. That these very disparate populations all happened to be physically placed in the hospital ICU is not a justification for treating them as a homogenous group for purposes of evaluating the efficacy of alternative resuscitative fluids.

Lumping together findings from such dissimilar populations might be acceptable if limited to *unexpected adverse events* not associated with the intended effect of the treatments. But mortality is a *common* event whose rate may be *directly* associated with the very dissimilar physiological effects of albumin and saline. Those dissimilar effects might be important in one clinical setting, while not in another. In the SAFE trial, the strong statistical trend toward improved survival in severe sepsis, but not in non-brain injured trauma patients, are suggestive of precisely this type of scenario.

Making “further study” a reality in our lifetimes – and the lifetimes of sepsis patients

While the SAFE investigators reflexively call for “further study” to prove or disprove the strong mortality reduction trend they identified in sepsis patients resuscitated with albumin, it is highly unlikely that such a trial will be completed in the near future.

This is regrettably the case for the same reason that the “colloid-crystalloid debate” has dragged on for several decades: albumin is a very low-priced, costly-to-produce commodity that yields minimal profitability for manufacturers.¹³ Individually or collectively, manufacturers of this product simply cannot justify the cost of sponsoring an adequately designed and powered trial. Of course, there is also no patient or professional “advocacy group” to champion more research to resolve this “albumin-versus-saline in sepsis” question. (The 16-center SAFE trial was realized only through a remarkable collaborative effort involving the Australian/New Zealand Intensive Care Society Clinical Trials Group, the University of Sydney, the Australian Red Cross Blood Service, a large domestic albumin manufacturer and financial support aggregated from a number of regional and national health agencies in Australia and New Zealand).

A fast, efficient and relatively inexpensive option is for the SAFE study investigators – with support as needed from domestic and/or U.S. health agencies – to extend the SAFE protocol itself to specifically enroll additional severe sepsis patients as required to achieve a statistically significant result.

Of approximately 750,000 sepsis cases each year in the U.S., an estimated 225,000, or roughly one in three, are fatal.¹⁴ The SAFE study identified a very important potential

¹³ The current retail price per liter of 5% albumin is less than \$75 (source: FFF Enterprises, Temecula, CA; www.fffenterprises.com)

¹⁴ Linde-Zwirble WT, Angus DC, Carcillo J, et al. Age-specific incidence and outcome of sepsis in the U.S. *Crit Care Med* 1999; 27(Suppl 1):A33.

survival benefit associated with albumin resuscitation in the severe sepsis population. Remarkably, this potential mortality reduction benefit is on a similar order to the much-heralded benefit of a newer and significantly more costly intervention: recombinant activated protein C (drotrecogin alfa activated; *Xigris*[®]).¹⁵

If we assume that the sepsis mortality reduction trend documented by the SAFE investigators is eventually borne out, a comparison with findings from the 1,690-subject, Eli Lilly-sponsored PROWESS trial of drotrecogin alfa activated should awaken the interest of critical care specialists, federal health and research officials and other healthcare policy makers:

<i>Study</i>	<i>Randomization – n</i>	<i>Mortality (%)</i>	<i>Risk reduction per 100 patients treated</i>	<i>Treatment cost</i>	<i>Nominal cost per life saved</i>
PROWESS	<i>Xigris</i> – 850 Placebo – 840	<i>Xigris</i> – 24.7% Placebo – 30.8%	6.1 lives	\$9,800	\$160,000
SAFE	4% albumin – 603 0.9% saline – 615	Albumin (30.7%) Saline (35.3%)	4.6 lives	\$150*	\$3,300

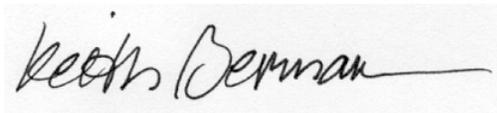
*Assumes a mean of approximately 2 liters of 5% albumin at a hospital-level cost of \$75/liter

I believe it would serve the public health interest for the SAFE investigators to extend their trial specifically to address the severe sepsis population in the ICU, and resolve this unanswered “safety” question.

Failing that, BPAC should urge the FDA and the National Institutes of Health to orchestrate and finance a well-designed and adequately powered “Albumin vs. Saline Resuscitation in Severe Sepsis” trial.

“Further study” is needed urgently for the sake of many thousands of patients worldwide at risk of death from severe sepsis.

Sincerely,



Keith Berman, MPH, MBA

Disclosure: I consult for FFF Enterprises, a leading U.S. distributor of plasma products and other biotherapeutics.

¹⁵ Bernard GR, Vincent J-L, Laterre P-F, et al. Efficacy and safety of recombinant human activated protein C for severe sepsis. *New Engl J Med* 2001; 344:699-709.

Appendix 1

New Engl J Med 2004 May 27; 350(22):2247-56

A comparison of albumin and saline for fluid resuscitation in the intensive care unit.

Finfer S, Bellomo R, Boyce N, et al; SAFE Study Investigators.

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BACKGROUND: It remains uncertain whether the choice of resuscitation fluid for patients in intensive care units (ICUs) affects survival. We conducted a multicenter, randomized, double-blind trial to compare the effect of fluid resuscitation with albumin or saline on mortality in a heterogeneous population of patients in the ICU.

METHODS: We randomly assigned patients who had been admitted to the ICU to receive either 4 percent albumin or normal saline for intravascular-fluid resuscitation during the next 28 days. The primary outcome measure was death from any cause during the 28-day period after randomization.

RESULTS: Of the 6997 patients who underwent randomization, 3497 were assigned to receive albumin and 3500 to receive saline; the two groups had similar baseline characteristics. There were 726 deaths in the albumin group, as compared with 729 deaths in the saline group (relative risk of death, 0.99; 95 percent confidence interval, 0.91 to 1.09; $P=0.87$). The proportion of patients with new single-organ and multiple-organ failure was similar in the two groups ($P=0.85$). There were no significant differences between the groups in the mean (\pm SD) numbers of days spent in the ICU (6.5 \pm 6.6 in the albumin group and 6.2 \pm 6.2 in the saline group, $P=0.44$), days spent in the hospital (15.3 \pm 9.6 and 15.6 \pm 9.6, respectively; $P=0.30$), days of mechanical ventilation (4.5 \pm 6.1 and 4.3 \pm 5.7, respectively; $P=0.74$), or days of renal-replacement therapy (0.5 \pm 2.3 and 0.4 \pm 2.0, respectively; $P=0.41$).

CONCLUSIONS: In patients in the ICU, use of either 4 percent albumin or normal saline for fluid resuscitation results in similar outcomes at 28 days.

Appendix 2

[Medscape – Critical Care Medpulse]

Albumin, Saline Comparable for Fluid Resuscitation in ICU

NEW YORK (Reuters Health) May 26, 2004 - Whether saline or albumin is used for fluid resuscitation in the ICU setting seems to have no effect on survival or other clinical endpoints, according to a report published in the May 27th issue of The New England Journal of Medicine.

The best fluid to use for resuscitation has remained unclear due in large part to a lack of adequately powered randomized trials examining this topic. In the absence of such trials, clinicians have relied on evidence from meta-analyses, which have yielded conflicting results.

To hopefully settle this issue, Dr. Simon Finfer, from the ANZICS Clinical Trials Group in Carlton, Australia, and colleagues conducted a randomized trial involving nearly 7000 patients in 16 ICUs in Australia and New Zealand. Known as the Saline versus Albumin Fluid Evaluation (SAFE) study, subjects received either 4% albumin or normal saline for fluid resuscitation in the ICU.

During the 28-day study period, mortality in each group was nearly the same--726 deaths in albumin group compared with 729 in the saline group. Moreover, the proportion of patients who experienced organ failure in each group was similar.

The groups were also comparable in terms of length of ICU and hospital stay, days of mechanical ventilation, and days of renal-replacement therapy.

"Our study provides evidence that albumin and saline should be considered clinically equivalent treatments for intravascular volume resuscitation in a heterogeneous population of patients in the ICU," the authors state. However, further studies are needed to determine if either might be advantageous in a highly selected patient subgroup, they add.

In a related editorial, Dr. Deborah Cook, from McMaster University in Hamilton, Canada, comments that authors' "study has raised the bar for future trials by using multidisciplinary implementation strategies and Web-based management and by demonstrating excellent protocol adherence in thousands of patients. The SAFE study is not only a landmark trial; it is also a milestone for the discipline of critical care medicine."

N Engl J Med 2004;350:2247-2256,2294-2296.

Appendix 3

[Medscape Medical News]

No Difference in Mortality Between Colloid, Crystalloid IV Fluid Resuscitation

Feb. 24, 2004 (Orlando) — Fluid resuscitation is a cornerstone of intensive care therapy, yet for years there has been little agreement about the best fluid to use — crystalloid or colloid. Now, results of a 7,000-patient placebo-controlled study suggest that there is no difference in 28-day mortality between patients resuscitated with albumin or saline.

Simon Finfer, MBBS, MRCP, FRCA, is a senior staff specialist in intensive care at Royal North Shore Hospital in Sydney, Australia, and lead investigator of the Saline versus Albumin Fluid Evaluation (SAFE) trial. He presented the study results at a late-breaking clinical trials session here at the 33rd Critical Care Congress, the annual meeting of the Society of Critical Care Medicine (SCCM).

Dr. Finfer told Medscape that the results provide the first "evidence that one fluid is not safer than the other in terms of mortality." Of patients who received albumin, 28-day mortality was 20.9% while 28-day mortality in the saline group was 21.1%. "So we can answer the question about difference: there is no difference," he said. With 7,000 patients, the study was powered at 90% to detect a 3% difference in mortality.

J. Christopher Farmer, MD, professor of medicine, pulmonary, and critical care medicine at the Mayo Clinic in Rochester, Minnesota, told Medscape that the "crystalloid-colloid debate has been going on for three or four decades...but nobody has been able to do a study that is this large and this well designed so that it weeds out bias. What is really different about this trial is that it is so well done that it is amazing — to meet the enormous logistical challenge of running a 7,000-patient trial at so many ICUs and collect all the data in just 18 months. The bottom line is that this is a very clean set of data."

Dr. Farmer was not involved in the study, but he chaired the late-breaking clinical trials session and he is a cochair of this year's congress. He is also the series editor of supplements to *Critical Care Medicine*.

In addition to providing evidence that colloids and crystalloids are equally effective, the study also "debunked another myth: the three-to-one ratio," said Dr. Farmer. He said it has been universally accepted that it takes three times as much crystalloid volume to resuscitate. But Dr. Finfer said that the actual ratio was 1.38 L saline to 1 L albumin. "On average, the patients received an average of 1,200 mL albumin/day and 1,600 mL saline during the initial four days," Dr. Finfer said.

Data were available on 3,473 patients randomized to albumin and 3,460 patients randomized to saline. Dr. Finfer noted that the 16-center study had "closed the books" in October so "we have only completed the analysis to answer the mortality question."

Nonetheless, he did note that while there was no overall difference in survival, there was a slight difference in trauma and head trauma patients that favored saline. Trauma patients resuscitated with albumin had a 1.36 risk for death, so "there was a slight excess death."

The average age of patients in both groups was 58 years; 1,424 of the albumin-treated patients were female as were 1,376 of the saline patients.

Dr. Finfer said an essential part of the study was the use of specially designed packaging and tubing. Both albumin and saline were packaged in cardboard sleeves that disguised their contents and the intravenous (IV) tubing was tinted green so that it was impossible to detect a color difference. Dr. Farmer agreed that this unique blinding technique successfully eliminated bias.

Timothy G. Buchman, MD, PhD, professor of surgery, anesthesiology, and medicine and chief of the burn, trauma, and critical care section at Washington University School of Medicine in St. Louis, Missouri, told Medscape that "perhaps the most common therapy we deliver in intensive care — more common than vents, more common than antibiotics — is the administration of IV fluids."

The results of the SAFE trial indicate that "a caring and competent clinician can make a good choice using either albumin or saline as he or she thinks appropriate," Dr. Buchman said. Dr. Buchman, who was not involved in the study, is the president of SCCM.

But Dr. Farmer said that he thinks most clinicians will opt for crystalloid fluids since "they cost just pennies compared to colloids, which are purified human protein products and thus carry some antigenic risk."

The study was supported by the Australian and New Zealand Intensive Care Society Clinical Trials Group, the Institute for International Health at the University of Sydney, the Australian Red Cross Blood Service, and CSL Limited of Melbourne, which manufactured the IV fluid products used in the study.

SCCM 33rd Annual Congress: Late-Breaking Topics — "Does Albumin Kill? Results of a Randomized Control of 7,000 Patients." Presented Feb. 22, 2004.

Reviewed by Gary D. Vogin, MD