

January 19, 2004

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

From: Robert M. Winslow, MD  
Sangart, Inc. and the University of California, San Diego

Re: "Guidance for Industry. Criteria for Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes"

The Blood Division should be congratulated on production of this very extensive and very helpful guidance document for the development and clinical testing of potential new "Oxygen Therapeutics." My comments are few.

1. Section III. B. Safety Considerations

- a. I believe the sentence, "For hemoglobin-based oxygen carriers, the recommended testing scheme is based on the hypothesis that one cause of toxicity involves the interaction of oxygen radicals or iron with cellular metabolism," gives an unbalanced emphasis on potential toxicity. There is no question that cell-free hemoglobin can act as an oxidant, and potential harmful effects have been demonstrated in vitro and in cell culture. However, I am not aware of data supporting the hypothesis that this is a principle, or even important source of *clinical* toxicity. Instead, both preclinical and clinical trials with hemoglobin-based solutions since 1949 have shown a clear pattern of physiological effect: elevated systemic and pulmonary pressure, reduced cardiac output and bradycardia. This triad correlates with arteriolar vasoconstriction and reduced tissue oxygenation. The mechanism of this effect is still not completely clear, although as you point out later, progress is being made and hypotheses have been offered including NO scavenging and hyperoxic vasoconstriction. In the absence of universal agreement on this issue, I believe FDA should require clear demonstration whether this triad has been eliminated, including relevant animal studies, with controlled volume status, comparing test article with purified (or stroma-free) hemoglobin to serve as a positive control. Clinical trials with any product that has not solved this problem should not be encouraged

2. Section III. B.3.b. Bacterial Translocation

- a. The connection between the architectural changes in intestinal microvilli and the danger of bacterial translocation may be overstated.

3. Section III C.

- a. This section should be careful not to equate optimal properties of red blood cells (hemoglobin level, P50, for example) with cell-free oxygen carriers. A wealth of data now indicate that the mechanisms of oxygen transport for cellular vs. acellular oxygen carriers are very different, and no assumptions should be made about measures of potency. Rather, sponsors must develop their own measures of potency and be prepared to defend the rational for their use. P50 and hemoglobin levels are not sufficient (or even relevant) measures of potency. The goal of these products is to oxygenate tissue, and the surrogates used for red blood cells must not be assumed to apply to cell-free solutions. Insofar as O<sub>2</sub> content is used as a marker for efficacy, any measure of in vivo O<sub>2</sub> content must account for any loss of O<sub>2</sub> capacity due to heme oxidation.

4. Section III C.

- a. FDA should be aware that its recommendations reach beyond the developed world. In many parts of the world blood is either not available or unsafe. Therefore, FDA should consider that showing safety and efficacy equivalent to blood may be sufficient for approval.