

January 21, 2004

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

From: Peter Keipert, PhD
Sangart, Inc.

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

General Comments

In general, this Guidance Document is a significant improvement of the previous version. A lot more detail has been provided that will be most helpful for companies that are early in their development efforts. However, because this document is so specific in many instances, it is more important that FDA clearly defines what products are being referred to, as many items may be only relevant to one particular class of oxygen therapeutic (i.e., Hb solution versus PFC emulsion).

Generally, there are many cases where the FDA refers to 'evidence' without providing any references from peer-reviewed literature. When sponsors make claims about their product, FDA always insists that relevant literature is cited. Hence, specific claims in this Guidance Document about 'known' side effects or 'evidence' of unwanted characteristics of either Hb or PFC-based oxygen carriers should be properly referenced with published literature that is available to the scientific community.

Section III B. Safety Considerations

- a. Line 1. Recommend changing "...largely unresolved safety-related problems..." to "...incompletely understood safety-related issues..." as this more fairly describes the current status of the field, and it is not yet known whether all of these are real 'problems' or just issues that need further study to elucidate mechanisms.

Section III C. Efficacy Considerations

- a. Page 8 (#2. Perioperative Indication). The purpose or implied message of the last (second) paragraph in this section is unclear. Is this intended to suggest that a sponsor will be required by FDA to run additional trials in unstable or trauma patients, even if a company pursues a purely "elective surgery" indication in a specific surgical patient population, and the product label clearly indicates that the product has NOT been evaluated in critically ill or unstable patients or in trauma? This should be clarified in the Guidance Document, and it would be helpful for FDA to provide some specific guidance as to how much additional clinical data would suffice, e.g., a supportive Phase 2 study, as opposed to a large Phase 3 trial.

- b. Page 9 (#3. Trauma). The latter half of the first paragraph on Page 9 suggests that a ‘noninferiority’ claim for an oxygen therapeutic compared to blood transfusion might not qualify for running the trial under the exception of informed consent. However, FDA should clarify whether a noninferiority claim could be used for approval of an oxygen therapeutic that was compared against transfusion of blood in an appropriately designed trial that was performed with full informed consent?

Section IV A. Preclinical Evaluation

- a. Page 10, Characterization of the Product. This section is confusing, as it does not specify whether the list of proposed characterizations is for Hb or PFC-based products. In fact, the majority of the items a. through j. is only relevant for Hb-based products. It would be easier to interpret if two lists were provided, each specific to either Hb or PFC-based products.
- b. Page 13, 1st paragraph. The recommendation to perform a study in primates to evaluate cardiac toxicity should specify that this is for Hb-based products.

Section IV B. Clinical Evaluation

- a. 1. General, Page 14, 4th paragraph. This section indicates that FDA is “recommending” clinical studies that include safety and efficacy in both trauma and elective surgery. While this may be desirable, it may be too expensive and time consuming for a company that is only seeking a specific surgical indication. Hence, FDA should provide some guidance as to whether it is possible to potentially get an approval without having parallel trauma studies, provided that the safety profile is excellent and that the risk-benefit is clearly in favor of using the product for the indication that was studied.
- b. 2. Elective Surgery, Page 15, 2nd paragraph. The recommendation by FDA to “...conduct concentration/dose toxicity trials to determine the maximum tolerated dose of an oxygen therapeutic...” is troublesome, as this is generally done in preclinical GLP toxicology studies in a variety of animal species. Most IRB or Ethics Committees would probably not approve a study in which the intent is to escalate dosing until acute drug-dependent toxicity is documented. The appropriate dose of a drug that can be shown to be efficacious in Phase 3, should be selected based on having an adequate safety margin below the toxic doses that have been established/demonstrated in preclinical toxicology studies. Also, the reference to use “...non-linear mixed-effects modeling...” is something that will be unfamiliar to most readers, and an appropriate reference should be provided.
- c. 2. Elective Surgery, Page 16, 1st paragraph. It would be helpful to provide more specific statistical guidance as to what FDA means when they say that they “...are willing to accept a modest level of uncertainty....” when comparing safety equivalency between an oxygen therapeutic and red blood cells.