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

RE: DOCKET NO. 2004D-0462, Comments for Draft Guidance for Industry: Criteria for Safety and Efficacy Evaluations of Oxygen Therapeutics as Red Blood Substitutes

Hemosol has been one of the pioneering leaders working since 1985 in an effort to bring to market a human hemoglobin based oxygen therapeutic which would serve several important clinical needs. Hemosol welcomes the publication of this most current Guidance document as a timely response to many major developments in this field in the past near-decade. Below Hemosol first offers some general comments to the Guidance document, and these are followed by section specific comments.

General Comments

As clearly noted within the "Scope of Recommendations" FDA has been collaborating with industry and other interested parties since before 1990 on several prior versions of the guidance document focused on the evaluation of oxygen carriers or oxygen therapeutics. Over this more than 15 year period FDA has had the unique opportunity to engage in detailed discussions and reviews of a significant body of scientific and clinical trial data related to this new class of therapeutic agents that have the untapped potential to offer important, and in many cases life-saving, medical benefits. Although considerable information regarding oxygen therapeutic products has been published over the years, there remains an even larger body of data that has been submitted to the FDA in confidence by several product sponsors. Therefore FDA, unlike other individual sponsors, has had the unique privilege to review this extensive history of published and confidential scientific and medical knowledge. Not only does FDA have the most comprehensive body of scientific knowledge related to this class of products in the world, but FDA has also actively planned and directed product and clinical development through the review and approval processes related to IND and BLA submissions. Hence FDA is in possession of detailed knowledge about the outcome of some of the directed developmental steps and procedures.

As one of the development leaders in this area, Hemosol is disappointed that the current guidance document presented for review and comment offers only limited and very general direction. There is almost nothing new in this current version since the development of the Guidance document first published in 1997. Hemosol believes that additional important and specific guidance should be included in the current draft Guidance, taking into account the vast amounts of knowledge resident within CBER since 1997. Hemosol believes that FDA has an important opportunity and responsibility to be more specific in stating recommendations in all areas of the product development cycle covered within this revised guidance document. The overall goal of this guidance document should be to provide sufficient and specific direction to industry in order to facilitate the development of this important new product that will benefit targeted patient groups.

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FDA, within Section C Efficacy Considerations, rightly acknowledges that red blood cells, as a regulated therapeutic biopharmaceutical, have not been subjected to the rigors of well-controlled clinical trials as required for new products. Although some of the adverse effects of red blood cell transfusions are presented, the Guidance does not completely list all the significant known risks of red blood cell transfusions. Moreover, Hemosol also believes that an additional comment should be added to the Guidance regarding the intermittent and unpredictable safety risks from the lack of available (or compatible) red blood cells for transfusion. The development of safe and effective alternatives to red blood cell units, such as the products envisioned in this Guidance, should be given the best opportunity to succeed and this can only occur with the active participation and leadership of the FDA in setting clear and specific direction.

Hemosol offers the following additional comments per Guidance document section as published for comments on October 28, 2004. The comments are restricted to those that refer to hemoglobin based oxygen therapeutics.

Hemosol Section Specific Comments

I. Purpose and Rationale

Hemosol agrees with the potential benefits identified for an oxygen therapeutic that includes universal compatibility, immediate availability and long-term storage. As FDA's standard of comparison for safety is an allogeneic RBC unit, then for further balance this section should be expanded to include additional potential benefits based on the avoidance of the documented labeled risks of allogeneic red blood cells. These added important medical benefits would include:

- Reduced transmission of blood borne pathogens
- Reduced immune suppression
- Elimination of adverse consequences of typing and crossmatching errors
- Avoidance of TRALI
- Avoidance of graft versus host reaction
- Avoidance or reduction in frequency of major and minor transfusion reactions

In addition it would be appropriate for this guidance document to acknowledge that HBOC preparations enable immediate oxygen delivery which does not occur with allogeneic RBC units due to the depleted 2,3-DPG levels and HBOC preparations have a well defined product consistency relative to hemoglobin content per unit and product volume.

Consideration of these benefits should also be part of the risk/benefit analysis between transfusions of red cells and oxygen therapeutics.

II. Scope of Recommendations

The first sentence of this paragraph is explicitly directed to the use of oxygen therapeutics as red blood cell substitutes. Hence, comparison of oxygen therapeutics to the safety and efficacy of stored red cells is directly relevant for this indication, but may not be appropriate for other indications. As other possible indications are mentioned elsewhere in the guidance, this section should be expanded to include those indications which are based on medical benefits other than as a red blood cell substitute.

Paragraph 1, line 7, refers to the workshop entitled "Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Cell Substitutes" which was held on September 27-28, 1999, as "in part" the basis of this Guidance document. It is understood that the Guidance document, when finalized, will represent the current thinking of the FDA and the scientific consensus on this topic. Interested parties would gain added assistance and insight into FDA's views by the inclusion of a more comprehensive reference list which FDA has relied upon for the development of this 2004 document.

III. Background Discussion

A. General

The guidance states that purified hemoglobin is "obtained from sources including outdated human blood..." Although outdated RBC units have been the dominant source for human hemoglobin it is not necessary to restrict human hemoglobin source to outdated units. The guidance should be written to allow for other sources such as non-expired RBC units, and such language should not lead to an interpretation from this guidance that outdated RBC units or recombinant hemoglobin are the only source of human hemoglobin FDA would consider acceptable.

B. Safety Considerations

The comment on the potential toxicity due to interaction of oxygen radicals or iron with cellular metabolism is presented as a hypothesis, and Hemosol believes, is overstated as a mechanism of toxicity when compared to other potential mechanisms of hemoglobin side effects. There has never been a convincing demonstration that this mechanism is important *in vivo* for hemoglobin therapeutics, in either an animal model or in humans. On the other hand, the interaction of hemoglobin with NO clearly results in physiologic effects in humans and animals.

FDA acknowledges that there are some safety issues related to "hypothetical toxicities that have not been demonstrated experimentally or clinically". Taking into consideration FDA's extensive review of several clinical studies submitted by multiple sponsors, FDA should be in a position to remove comments that propose "hypothetical toxicities" or to further amplify the probable and clinically important mechanisms of toxicities.

It would benefit sponsors if statements regarding safety concerns could be supported with appropriate literature references that would permit the industry to distinguish the reported adverse effects observed with the use of products manufactured under GMPs with known purity and characteristics, from those of earlier, inadequately purified and characterized materials produced mostly in academic laboratories.

FDA clearly notes in this section that unmodified hemoglobin (MW 64kDa) should not be present in the final product and should be eliminated to the maximum extent possible. Therefore, it would benefit the manufacturers of hemoglobin-based oxygen carriers to know a more quantitative level of removal or conversely the maximum level of unmodified hemoglobin that is acceptable to FDA. As FDA understands, complete (100%) removal is nearly impossible, and the manufacturing requirements needed to reduce the percentage to or near zero can reach a point which is unfeasible for a commercial product.

1. Vasoactivity

Hemosol generally agrees with the statements in this section. However, an objective assessment of the total database accumulated on this topic strongly suggests that the primary mechanism for hemoglobin vasoactivity is the "scavenging" of NO by hemoglobin that has mostly extravasated into the intravascular space. The involvement of adrenergic and/or endothelin pathways is likely to be less important, in many tissues and may well be a secondary consequence of the interaction with endothelial cell function or with the NO pathway.

The statement regarding a vascular inflammatory response "progressing to multi-organ failure" is speculative, and not supported by convincing published evidence. It is important to note that "vasoconstriction" does not equate to tissue ischemia, if cardiac output and organ blood flow are maintained. Hemosol's extensive experience with preclinical studies using Hemolink has not uncovered or documented any evidence of "multi-organ failure" caused by Hemolink. Within human clinical trial experience, Hemosol documented less than a handful of multi-organ failure reports in treatment and control subjects which were attributed by principle investigators to be caused by other clinical factors unrelated to the administration of a oxygen therapeutic. Preclinical testing by Hemosol of multi-dose toxicity in cumulative doses greatly exceeding the total body hemoglobin content has not shown any evidence of multi-organ failure, and we suspect that this would be the case of all other commercial developers' product.

FDA should further clarify the scientific basis for this section and include detailed suggestions regarding the acceptable animal models for evaluating the vasoactivity effect and any measurements related to the inflammatory responses that lead to multi-organ failure.

2. Cardiac Toxicity

No specific comments to offer for this section, although it would be appropriate to note that the microscopic pathology detected, presumably in reference to studies done with crosslinked 64 kDa product, was not accompanied by any detectable functional sequelae.

3. Gastrointestinal Toxicity

a. Discomfort

No specific comments to offer for this section.

b. Bacterial Translocation

No specific comments to offer for this section.

4. Pro-inflammatory Activity

The reported early *in vivo* evidence of thrombotic lesions and prothrombotic activity with disseminated intravascular coagulation was observed in rabbits infused with incompletely purified hemoglobin containing phospholipid components (White et al.: Toxicity of human hemoglobin solution infused into rabbits. J Lab Clin Med 108:121-31; 1986; White CT et al.: Synergistic toxicity of endotoxin and hemoglobin. J Lab Clin Med 108:132-37; 1986), and has not been confirmed in experiments with fully purified lipid-free hemoglobin preparations. Therefore this potential toxicity issue is not relevant to appropriately prepared and highly purified hemoglobin solutions.

5. Oxidative Stress

Hemoglobin can clearly act as an oxidant under some circumstances and it may act as an antioxidant under other conditions. Much of the experimental evidence suggesting oxidant injury by hemoglobin is derived from observations of "cytotoxicity" in *in vitro* exposure of cells in culture to hemoglobin products in systems lacking the normal antioxidants present *in vivo* (Yeh L-H and Alayash AI: Redox side reactions of hemoglobin and cell signaling mechanisms. *J Internal Med* 253:518-26; 2003). The potential protection afforded by the many natural antioxidants present in blood and tissue, is not tested in *in vitro* systems. Moreover, the effects demonstrated *in vivo*, such as those on intestinal mucosal and vascular integrity, and the protective effects of the antioxidant selenite, are highly hemoglobin product specific (Baldwin AL et al.: Sodium selenite reduces hemoglobin-induced venular leakage in the rat mesentery. *Am J Physiol* 284:H81-91; 2003; Baldwin AL et al.: Differential effects of sodium selenite in reducing tissue damage caused by three hemoglobin-based oxygen carriers. *J Appl Physiol* 96:893-903; 2004). Thus, Hemosol believes that the *clinical* significance of the oxidation potential of HBOC's still remains speculative, unless supported by direct clinical evidence. At least some of the enzyme increases cited in this paragraph as being the result of oxidant injury may have alternative explanations, and be coincidental without causal connection. It is recommended that FDA provide further references that provide more direct evidence of oxidative stress.

6. Pancreatic and Liver Enzyme Elevation

While there is clinical evidence of some adverse effects on the pancreas by at least some hemoglobin solutions in some patients, attribution to an oxidative mechanism is at least debatable.

7. Endotoxin Synergy with Hemoglobin

No specific comments to offer for this section, other than to note that the enhanced lethality is controversial (e.g., Hoyt DB et al.: Resuscitation with pyridoxalated stroma free hemoglobin: tolerance to sepsis. *J Trauma* 21:93842; 1981).

8. Neurotoxicity

No specific comments for this section.

C. Efficacy Considerations

The use of hematocrit as a surrogate endpoint for clinical benefit in patients treated for chronic (non-surgical) anemia is well-established. Although it is correct that the "knowledge of the effects of hemoglobin-based oxygen therapeutics on hematocrit is not well established", there is preliminary non-clinical and clinical data demonstrating that hemoglobin-based oxygen therapeutics have a stimulatory effect on erythropoiesis. Therefore, FDA should not determine at this time that hematocrit is not suitable as an acceptable surrogate endpoint for these products because of the possible positive effects of these products on erythropoiesis and hematocrit. FDA should also determine what other measures of effects would be acceptable to demonstrate a clinical benefit in chronic anemia (i.e. chemo-induced anemia).

1. Local Effects/Regional Perfusion

No specific comments for this section

2. Perioperative Indications

Hemosol appreciates the recommendation that a delay in allogeneic RBC transfusion would not provide added levels of safety and therefore a measurable sustained avoidance is needed. However any level of avoidance is important as there are important risks associated with allogeneic transfusions previously noted. Therefore to set a minimum of a two RBC unit avoidance to demonstrate efficacy is arbitrary, unless supported by clinical evidence.

This section would also benefit by FDA providing more definition to their views on what situations would constitute an unstable patient in surgical settings

3. Trauma

No specific comments for this section

IV. Recommendations

A. Preclinical Evaluation

1. Characterization of the Product

No specific comments for this section.

2. Animal Safety Testing

This recommendation is under the heading of preclinical studies. Since most HBOCs in development are based on human Hb, immunological testing for immune responses to human hemoglobin in non-human species is problematic as one would expect such responses would be elicited. Hemosol would support that immune responses should be part of the safety assessment that is fulfilled during controlled human clinical trials. Should FDA continue to recommend preclinical evaluation, then more specific comments within the guidance relative to appropriate models and test species should be included.

3. Use of Animal Models in Toxicity Testing.

Within this section (3c) there is a recommendation to use a model designed to produce reperfusion injury. It is important for FDA to provide further description or definition as to what would be acceptable to FDA, particularly in view of the recent review of the experimental studies used on these products (Buehler PW and Alayash AI: Toxicities of hemoglobin solutions: in search of in-vitro and in-vivo model systems. Transfusion 44:1516-30; 2004).

4. Important Observations in Animal Tests

FDA should include a listing of the most important "effects" and what models are acceptable ones for use in investigating microvascular circulation and endothelium effects.

Within this section FDA states that measurements of reliable markers of oxidative damage be included in animal studies. See earlier comments (5. Oxidative Stress) on the oxidation potential of hemoglobin based products. In addition, as FDA prescribes "reliable markers" be used; there should be added detail and discussion as to what are acceptable reliable markers and in what testing models or circumstances.

The draft indicates the need to use a battery of renal functional tests to evaluate appropriately the possible nephrotoxicity of oxygen therapeutics. This recommendation appears to be unwarranted, in that nephrotoxicity has not been found in clinical and experimental testing of highly purified modified hemoglobin products. Moreover, it would be noted that direct pressure measurements are not useful in detecting renal arteriolar vasoconstriction, and that relative changes in creatinine clearance may still be useful in detecting changes in GFR, when tubular secretion of creatinine is not complete.

FDA has noted in this document that both pigs and monkeys are susceptible to the myocardial lesions associated with administration of hemoglobin-based oxygen carriers. Since non-clinical studies with monkeys are more difficult to perform (due to a limited number of facilities capable of performing these studies, increased costs associated with studies in monkeys compared to pigs, and limited availability of monkeys for terminal studies), FDA should suggest that these studies be performed either in pigs or monkeys and not limit studies to monkeys as currently written.

Not all indications for the use of hemoglobin-based oxygen carriers involve clinical settings where the risk of stroke is increased or head trauma is present. Therefore, FDA should qualify the recommendation regarding the need to perform studies in animal models demonstrating open blood-brain barrier for only those clinical indications where there is a risk of the blood brain barrier being breached.

B. Clinical Evaluation

1. General

Paragraph 4, line 3, indicates that "separate safety and efficacy data are therefore generally necessary for each clinical setting where an oxygen therapeutic is needed". The paragraph continues to provide guidance with regard to "outcomes that are direct measures of clinical benefit or validated surrogates" for the indication sought. Given the importance of safety, it would also be beneficial if further guidance was included with regard to powering a study for safety evaluations for the listed indications of elective surgery, trauma and other indications in the guidance document, including whether or not, safety endpoints could be aggregated to form a composite outcome when events are rare.

Paragraph 6, line 8, indicates that "we recommend that you design clinical trials to capture a numerical increase and/or an increase in the intensity of adverse events above the underlying background rate/intensity of such events". As stated in the previous comment, further guidance as to powering a study for safety would be beneficial, as changes from background rates would require very large studies; for example, even for a study of reduced power (0.60 versus a usual power of 0.80 or 0.90), detecting increases in background event rates from 1/1000 to event rates of 5/1000 would require more than 1700 subjects/arm using the usual significance level of 0.05 (one-sided, Fisher's Exact test). FDA should provide further guidance regarding the acceptance of creating a composite endpoint from several individual events/outcomes.

Paragraph 5, line 1, FDA refers to a specific clinical setting of acute anemia including trauma and elective surgery in this section. Since this section is labeled as "General" recommendations and FDA recognizes that there are several possible clinical indications for use of hemoglobin-based oxygen carriers as red cell substitutes outside of the setting of acute anemia (including local effects/regional perfusion), FDA should remove the discussion of trauma and elective surgery settings from the "General Clinical Evaluation" section of the guidance (IV.B.1) since the recommendations do not apply "generally" to clinical indications outside of acute anemia. In addition, FDA should change the sub-heading of IV.B.2 to "Acute Anemia" and include elective surgery and trauma as sub-categories under section IV.B.2. This will serve to assure that the recommendations listed in current Sections IV.B.2 and IV.B.3, Elective Surgery and Trauma, apply only if manufacturers seek an indication in acute anemia. An additional category needs to be included in section IV.B. to provide FDA's current thinking on the requirements for determining efficacy in "other clinical indications".

In this section the agency states, "We recommend a clinical development program that includes safety and efficacy assessments in both trauma and elective surgery..." Historically safety and efficacy information is required for the claimed indication a sponsor has chosen to pursue for marketing approval. As written this guidance places added burdens, unfair requirements and added costs for those sponsors who have no intent or desire to pursue a trauma indication. FDA is strongly encouraged to review this section carefully to bring further balance to this direction.

2. Elective Surgery

Paragraph 2, lines 1 and 8 refer to complete avoidance of allogeneic transfusion and total allogeneic exposure as primary and secondary outcomes, respectively. Hemosol agrees with these choices, although it is recognized that neither red cells nor red cell substitutes are expected to reduce total allogeneic non-RBC blood product exposure. Total allogeneic exposure should only be monitored to ascertain that the need for such non-rbc blood products and components *is not increased* by the use of an oxygen therapeutic. Other secondary endpoints that FDA could consider would include avoidance of allogeneic transfusion at specific time points and/or time to allogeneic transfusion.

Paragraph 2, line 6, states "you are encouraged to use non-linear mixed-effects modeling (NONMEM)". Hemosol notes that guidance here is very specific in terms of the model to be used to determine the maximum tolerable dose, but provides no recommendations as to the variables that would comprise the study design. In this situation, further expansion with rationale for this specific analysis approach and/or peer-review journal reference(s) would be of benefit.

Paragraph 2, line 12, states "a suitable trial design should specify and confirm enrollment of patients requiring two or more units of red blood cells". Hemosol agrees that prandomization identification of the subset of subjects that are most likely to require a specified minimum number of transfusions, using recognized practice guidelines, are a useful means to achieve trial efficiency, and the likelihood of an improved complete rbc transfusion avoidance. Nonetheless, it is also recognized that unanticipated circumstances often result in a requirement for transfusion(s) in patients who do not fulfill the practice guideline criteria. It is also

recognized that the unanticipated need for transfusion may present the greater danger in surgical patients. Thus, absolute restriction of enrollment to only those who meet the anticipated transfusion needs criteria may miss those also likely to benefit from avoidance of unanticipated red cell transfusions.

The requirement above is not consistent with that in Paragraph 1 of this section of the draft, in that it requires that in a Phase III trial the "population enrolled should reflect the characteristics of the population likely to undergo that particular surgery in clinical practice". This would imply that subject enrollment should not be restricted to those who satisfy the preoperative criteria for a specified minimum number of transfusions (e.g. small body size and estimated hemoglobin mass).

Paragraph 4, line 7, indicates "a modest level of uncertainty" with reference to the sample size determination based upon "relative safety". It would be beneficial to provide further details (1) to identify examples of specific safety endpoints, (2) by commenting on the FDA position of determining sample size requirements based on individual versus composite safety endpoints, (3) by defining a requirement to show a minimal clinically important difference versus an equivalence requirement or, for example, ability to detect a doubling in effect size / event rate, (4) to further clarify "modest level of uncertainty", for example, $\beta=0.50$, and (5) to clarify if requirements for safety can be built by including safety data over multiple clinical trials.

3. Trauma

Within the first paragraph although FDA comments that surrogate markers related to mortality endpoints are needed there is no agreement on the validity of any such markers. The requirement for each product developer to develop and validate surrogate end points for mortality and clinical bedside guidelines for the use of individual oxygen therapeutics and red blood cells, in the absence of any current clinical consensus, places a great burden on the developers of these products. This area is the best example of where direction and views from FDA, together with expert consensus, would help advance and level the field of the clinical development of oxygen therapeutics.

Paragraph 2, line 12 states "the clinical trial design must take into account the possibility that the patient population enrolled in the study might not adequately represent the patient population presenting at the hospital in actual clinical practice". This comment relating to Trauma is unlike that relating to Elective Surgery. Further guidance elaborating on this statement to provide a clearer understanding of any restrictions with respect to inference of results on larger populations as a whole would be of benefit.

Sincerely,



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