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Laurence Landow, MD
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Dear Dr. Landow:

This report is in response to the proposed Phase III trials by the Navy Medical Research Center on biologic agent HBOC-201. I would like to say at the outset that it is somewhat unclear why this proposal is moving forward. The FDA has put this on hold twice, and in the table provided to me (V) summarizing the aggregate events of HBOC-201 vs control (711 v 620), the cardiovascular, CNS, pulmonary, and renal events are such that it would be unsafe to progress further into larger studies of either 50 proposed initial patients or the 928 patients after the initial assessment of the 50 patients. Of the 910 evaluable subjects in years 1-3, 455 would be subject to significant adverse events.

I will now answer the questions proposed by you in your introductory letter. In regards to question number one, "Has the sponsor submitted adequate evidence to support their claim that the benefit to risk profile of HBOC-201 compared to standard of care is reasonable with respect to administering up to 10 units of product at a rate of 10 minutes per unit?" According to the authors, HBOC-201 dose consists of two 250 ml units, each containing 32.5 gms of Hgb. They state, "EMS providers will be advised generally to infuse an entire dose of CTM over approximately 10 minutes, as for standard resuscitative fluids." However, they state that individual subject infusion rates will be determined by the judgment of the EMS providers. They further state that EMS providers will be educated about HBOC-201's vasoactive properties. Of some concern is their statement, "Although rare, hypertensive SAEs occurred in the prior HBOC-201 Phase III Orthopedic trial and in subjects with ACS undergoing a percutaneous coronary intervention. Although this risk is expected to be significantly lower in hypotensive subjects enrolled in RESUS, idiosyncratic severe blood pressure responses are a theoretical possibility." I believe this is based on the hemorrhagic shock models, but this may not be the same in primates or humans. Of even more concern, is that CTM or HBOC-201 will not be discontinued until the pressure reaches >150 mm/Hg. I think resuscitation to 150 mm/Hg puts the patient at increased risk for dislodging clots, and thus aggravating bleeding, particularly if it's in the head, pelvis, abdomen or upper leg. Furthermore, I do not believe that the vasoactive properties of HBOC-201 are "idiosyncratic." It is most likely due to the scavenging effects of nitric oxide, and thus is predictable and is confirmed by the adverse events cataloged in Table V.

The second question states, "Has the sponsor submitted adequate evidence to support the view that the traditional paradigm is valid when a vasoactive HBOC is used?" The answer is, in my opinion, no. If the patient's systemic vascular resistance increases

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because of nitric oxide scavenging, perfusion may not be maintained, and the patient would be in a state of continued “compensated shock.”

Question 1C is complex. Some of the most elegant studies done on shock were done during WWI by Walter B. Cannon. He concluded that in the prehospital setting, a blood pressure of 80 mm/Hg was necessary to maintain blood perfusion to the brain. I think this is a very comfortable number, since autoregulation does not deteriorate until a systolic blood pressure of 60 mm/Hg. He further showed that thirst, cool, pale extremities, and a clammy skin was indicative of poor perfusion to the extremities. Tachypnea and tachycardia did not really occur until perfusion to the torso was diminished. Tachycardia, however, is not a good sign of poor perfusion and occurs regularly, whether the patient has lost volume or is simply frightened because of injuries. A narrow pulse pressure is a very good indicator of poor perfusion, as are changes in mental status, provided no drugs or alcohol have been used by the patient. There are at least four classifications of deterioration in mental status, including those by Plum and Posner, Ransahoff, Becker, and guidelines developed at Grady Hospital in Atlanta. In general, the patient progresses from lethargy, where the eyes are closed, but the patient will open them on command. The next level of consciousness is obtundation, where the patient, when stimulated by pain, will not necessarily open his eyes, but will try to remove the offending cause of pain. Stupor is when the patient will simply grimace as the only response to painful stimuli. Coma is when there is no movement to painful stimuli. These clinical signs of perfusion are not all routinely gathered by paramedics or EMS providers. In the same paragraph, but in the preface for the two questions a reference is made to paradoxical bradycardia. Patients who are well conditioned, such as soldiers, may well not develop a tachycardia, but in an elegant study from Los Angeles County Hospital, USC, several hundred patients were examined, of which approximately 600 or 6% had a BP \leq 90 mm/Hg. Sixty percent had tachycardia, but 40% were bradycardic. Surprisingly, those patients who did have bradycardia (40%), had better outcomes than those with tachycardia. In response to question 1 under C, “Has the sponsor submitted adequate evidence to support their claim that these parameters are valid, sensitive and specific in detecting occult hyperperfusion when a vasoactive solution is administered?” The answer again would be no. In response to the second question under 1C, “Do the RESUS dosing and administration guidelines provide adequate assurance that the benefit to risk profile of HBOC-201 would be reasonable when compared to standard of care?” As noted above, I have concerns regarding the cut-off of 150 mm/Hg when HBOC-201 would be discontinued. In addition, if one refers to the adverse events in Table V provided by the FDA; I do not believe that the benefit to risk profile of HBOC-201 is warranted.

In Section d, question 1, there is reference to oximetry values may decline during infusion of the product. Under d-i, the question is asked if oximetry values start to decline during infusion of HBOC-201. What is it due to? It should be noted at the outset that saturations are problematic in the prehospital setting and the emergency room setting because the patient may be cold (hypothermic), in shock, or the sensor may not pick up blood flow, etc. If the product does interfere with optical pick up of the saturation, it would be difficult for the paramedics to sort this out from the traditional problems. It is also possible in one of the hypotheticals that there might be increased O₂ extraction, as

noted in animal studies. It is unclear to me why ongoing blood loss would lead to any increased O₂ extraction, whereas, activation of white cells, subsequent release of O₂- and/or NO could clearly count for increased oxygen utilization. In animal and human studies, the macrophage increases its oxygen consumption 40-fold once activated. And the final hypothetical is that hyperfusion due to inadequate volume replacement could cause spurious values for oxygen saturation: this is clearly a possibility.

In regards to d-ii, this is one of my concerns that I've already addressed. I believe that a cut-off of 150 mm/Hg is too high. I think the evidence is fairly conclusive, not only in the studies by Cannon, but also in those by Mattox, that this would be an undesirable end point in the prehospital setting. Cannon and Mattox both concluded that it is far better to maintain blood pressures above 80, but not to become hypertensive because this will aggravate bleeding. Over resuscitation is undesirable until control of a hemorrhage has been achieved in the trauma center.

On page 4 of the introductory letter under 1e, the critical questions are being asked. In answer to the first question, "Do these data support the sponsor's claim that the benefit to risk profile for HBOC-201 compared to standard of care in trauma patients is reasonable?" The answer is no. This is based on the human studies and not necessarily the extensive amount of data supplied by the sponsor regarding swine. If 28% of patients have a systolic blood pressure of 141 – 160, this could clearly cause or restart hemorrhage in the shock patient. The next question in the same section asks, "What are the clinical implications of this statement for hypovolemic trauma subjects receiving a vasoactive HBOC?" It would appear that HBOC-201 has a significant risk for hypertension, and in a sense, acts as a vasopressor because of its binding with nitric oxide. The real question is whether the oxygen carrying capacity of the Hgb solution is of enough benefit to offset the risk of hypertension, myocardial infarct, cerebral vascular accidents and renal complications. Based on previous analysis by the FDA and Table V, I would say the benefit to risk has not been achieved.

Under 1f on page 4, the question is asked, "With respect to tissue perfusion, has the sponsor submitted adequate evidence to show that when EMS personnel in the ambulance titrate HBOC-201 against blood pressure, using a blood pressure cuff, the overall benefit to risk profile of HBOC-201 vs standard of care is reasonable?" As I have stated above, a blood pressure above 90 mm/Hg for a vasoactive substance does not necessarily guarantee perfusion. The advantage of HBOC-201 compared to lactated Ringers is that it may increase the oxygen carrying capacity within the patient, and the half life is considerably longer than LR. The real question is "Is this worth it in a substance that has significant adverse events in humans as tabulated in Table V?"

The next section is the Clinical Safety Profile Section. Under 2a, the question is asked, "Are the imbalances and adverse events against the HBOC-201 arm noted in Biopure's 2/3 in hospital clinical trials relevant for RESUS subjects?" In my opinion, no. The experience of most trauma centers in the United States is that the average trauma patient is getting older, and we are now seeing a bimodal distribution. There is a peak of injuries in the 16-24 age group, and now we see an almost equal peak in those 55 years and older.

Older people are more active, and thus involved in more accidents. Their mortality is 3.5 times greater in ICUs, and their return to independent lifestyle is less.

In response to 2b. "What is the clinical relevance of any of this finding for RESUS patients?" The answer is again against HBOC-201. The odds ratio for CVA, TIAs, cerebral ischemia infarct was 3.10, three times greater than the controls. This becomes even more problematic when one considers the entry criteria. In the study plan, they state, "Subjects with obvious or suspected TBI will not be enrolled." The inclusion criteria state that the GCS >4 for all patients and >9 if suspected blunt traumatic brain injury. In the absence of CT scanning, it is very difficult to determine what the cause of a depressed level of consciousness is. With a vasoactive substance such as HBOC-201, hypertension could certainly aggravate epidural hematoma formation, subdural hematoma formation, and intracerebral bleeding. It could also aggravate subarachnoid hemorrhage.

The question under 2c. Clinical Safety Profile, really cuts to the heart of this proposal. It is true that the adverse events noted in BLA Clinical Trials are almost nonexistent in the porcine studies. The clinical importance of this difference for RESUS subjects is significant. One would have to accept the BLA Clinical Trials with far more weight than any of the porcine studies. It is interesting that HBOC-201 in monkeys behaves as it does in the BLA Clinical Trials, emphasizing the difference between a primate and the swine model.

Summarily, in question 2d, the infusion of HBOC-201 with small dosages (<1 unit), 3 patients developed significant adverse events characterized as hypertension. Based on probabilities, if given to the trauma patient, the same thing would probably occur.

In 2e, the FDA refers to a statement in the current proposal, "There are no data that suggest that cardiovascular events will be higher in patients with hemorrhagic shock that receive HBOC-201." These adverse events were very significant $p = 0.0004$, and the question asked in e-1 would be: the acute events probably will be no different in the hemorrhagic shock study group. The unanswered question is the benefit from the Hgb solution such that it would outweigh risks of significant adverse events. I would have to answer with the data provided to me, no.

The first question under number 3 is, "Are there additional limitations in the National Trauma Data Bank?" There are questions about any registry in regards to interrater reliability of the information being fed into the data bank. This has been examined in regards to various registries for trauma, and the interrater reliability is acceptable. The point that it does not represent all trauma patients is valid. In a study in California, 44% of trauma patients reached a Level I or Level II center, but not even all of these patients were entered into the National Trauma Data Bank.

The second question asked is, "Can the information from the National Trauma Data Bank be used to estimate the control mortality rate given the RESUS trial enrollment criteria?" The answer is yes, with some limitations. It is valid for the 28 Level I trauma centers, and from a theoretical standpoint, this would be at least 25% less than non-Level I trauma

centers. based on the recent New England Journal of Medicine article by McKenzie and Jurkovich. The hospital mortality was approximately 10% at the non-trauma center designated hospitals vs 8% in the designated Level I trauma center. Similar results have been published from Florida in their statewide trauma system. The second part of the question is. "If so, what is that estimate?" The most recent data from the 2005 NTDB shows with Injury Severity Score >24, the mortality is 33%; for an ISS of 16-24, the mortality is 7%; for ISS 10-15, it is 3%; and for ISS 1-9, it is 2%. It should be noted that this is hospital mortality and not prehospital mortality.

Regarding question 3c, based on the information provided and using other data, including those provided by the authors, I believe the 25% reduction in mortality from 34% to 25.5% is somewhat inflated. The study previously conducted by Baxter is more realistic, with a control mortality rate of 17%. This leads into the next question under 2C regarding, "Does this comport with exception from informed consent, which states that "participate in research holds out the prospect of direct benefit to the subjects..." Based on my assessment of Table V and the possible benefits from HBOC-201, I would say no. Clearly, there are a number of benefits that could be achieved by having a hemoglobin solution that could carry oxygen and have a shelf life of 6 months. This would be a great advantage to prehospital care, but in this particular case, I think the risks outweigh the benefits.

Section 4 – Exception from informed consent

In the question, "Overall, does the RESUS protocol contain adequate evidence to meet the clinical requirements for exception from informed consent?" The answer is yes. I believe surrogate decision making in a prehospital study is clearly warranted, and community consent would be a surrogate.

Please do not hesitate to contact me if you desire more information.

Sincerely,

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