New responses to the revised protocol are underlined.

Executive Summary

This is a review requested by the Blood Products Advisory Committee (BPAC) of the Food and Drug Administration (FDA) regarding the RESUS Protocol, which is a pivotal, randomized controlled and single-blinded trial of the hemoglobing based oxygen carrier HBOC-201—a bovine polymerized hemoglobin—for prehospital resuscitation of patients with severe hemorrhagic shock. The following are key points leading to the conclusion:

1. HBOC-201 is a molecular hemoglobin-based oxygen carrier that appears to have three distinct effects as a shock resuscitation fluid: plasma volume expansion; carriage of oxygen; and vasoaction (vasoconstriction). These three effects are not unique to HBOC-201, but appear to be common among hemoglobin-based formulations. In particular, the vasoconstriction is thought to be due to scavenging of nitric oxide and oversupply of oxygen to arterioles caused by facilitated diffusion of oxygen. The affected component of the vascular system is capillary flow that can be quantitated as the functional capillary density. (Tsai and Cabrales 2006, *Critical Care Medicine* 34:1566-1567). Infusion of HBOC-201 can lower the functional capillary density as demonstrated in exchange transfusion studies in animals. (Tsai (2001) *Transfusion* 41:1290-1298).

There are no changes to this opinion.

2. The RESUS protocol includes a default transfusion rate of 50 ml/min, which is substantially higher than used in prior human studies. This rate, which is likely to represent a rate of 0.5-1 ml/kg/min (inferred from typical adult human weights of 50-100 kg), appears likely to cause significant vasoactive effects based on studies of similar infusion rates in healthy swine (Johnson et al. (2006) *Critical Care Medicine* 34:1464-1474). There appears to be little prior human experience with infusions at this rate. Moreover, the RESUS protocol calls for additional HBOC-201 infusions to a possible total of 2500 ml if reinfusion triggers are met and the patient is still in transport.

The revised RESUS protocol addresses several concerns that triggered this item in the executive summary. In particular, while the infusion rate remains the same, there are stopping criteria that should limit adverse vasoactive effects. There are also tighter limits on the number of units of the test article to be infused versus the original protocol. The dosing rationale summary (p 117) provides insight into the logic of the choice of infusion rate.

3. The record of adverse events (AEs) in prior clinical trials using HBOC-201 appears to show an excess of significant cardiovascular events that can reasonably be attributed to the vasoactive effects of the HBOC-201 compound in the context of patients of sufficient age and with sufficient

comorbidities to anticipate underlying cardiovascular disease. While causality cannot be determined for the AEs, a causal link can be reasonably inferred.

The age restriction to below 70 years in the revised RESUS protocol appears to increase the safety factor, since patients below the age of 70 are likely to have fewer comorbidities and underlying cardiac disease.

4. The RESUS protocol subject population consists of adults who have passed their 18th birthday. There is no upper age limit. As the fastest growing segment of the USA trauma population is the elderly population, it is reasonable to expect that the enrolled subject population will include a substantial number of older Americans with comorbidities. See the WISQARS database at CDC as a resource about trauma prevalence in the elderly. (http://www.cdc.gov/ncipc/wisqars/default.htm)

The upper age restriction in the revised RESUS protocol mitigates these concerns.

Given the existing knowledge of mechanism of action of HBOCs (basic science); the adverse event profile in the prior clinical trials; and the likelihood that the enrolled population will likely include a substantial number of older Americans with comorbidities, the sponsor has the responsibility to demonstrate that the test (HBOC-201) arm of this trial is at least as safe as the control arm prior to granting any waiver of consent.

Data reanalyzed by the applicant restricting the population to <70 (and <50) years suggests that the AE and SAE risk will be reduced.

In my opinion, the sponsor has not yet met that burden of proof. In order to meet that burden of proof, it would be helpful to have animal data where the test animals mirror the human population with respect to age and comorbidities. It would further be helpful to have data from age- and co-morbidity mirroring human volunteer subjects from whom informed consent can be obtained (without waiver) and who then undergo infusion of HBOC-201 at rates comparable to those proposed in the RESUS protocol.

Elimination of the oldest subjects from the trial makes existing animal data more relevant. The paucity of data in subjects who have received the test article at the infusion rates proposed remains a concern and probably should be discussed at the meeting.

Conclusion: The current iteration of the RESUS protocol contains insufficient information to recommend its approval under waiver of consent as discussed in 21CFR50.24 regarding the exception from informed consent requirements for emergency research.

The revised RESUS protocol appears not only to be a safer approach, but also to balance the risks and benefits between the control arm and the test article. Although I withhold final opinion until the scheduled meeting, there appears to be sufficient information provided to consider approval under waiver of consent.

Responses to questions posed by Lawrence Landow, MD to BPAC Primary Clinical Reviewers (text extracted from 7 April 2006 cover letter) regarding the RESUS protocol

1. Dosing & Administration

a. The default infusion rate of HBOC-201 in RESUS is 50 mL/min.
   i. The sponsor has analyzed all HBOC-201 subjects enrolled in pivotal trial HEM-0115 who experienced rapid blood loss. They report that the mean infusion rate for the first unit of HBOC-201 was 5.5 mL/min. The sponsor also reports there were 4 HBOC-201 subjects (out of a total of 353) in whom the maximum infusion rate of product was 40 mL/min.
      (1) 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 (Protocol, pages 93 and 95)?

      Consultant Opinion: No, the sponsor has not submitted adequate evidence. The data suggest that this dosage rage is highly vasoactive, has the potential to reduce functional capillary density and cause redistribution of blood flow that may adversely affect at least some subjects in the population.

      The new limit on number/volume of units to be transfused (3 units of the test article) increases the safety factor.

b. The traditional paradigm for fluid resuscitation uses systolic BP as a surrogate for tissue perfusion.
   i. Has the sponsor submitted adequate evidence to support the view that the traditional paradigm is valid when a vasoactive HBOC is used?

   Consultant Opinion: While the use of systolic blood pressure may not be optimal, it appears to be reasonable. Moreover, the vasoactive effects of the HBOC-201 will probably limit overaggressive resuscitation prior to arrival for definitive care.

   No change in this opinion.

c. The RESUS Protocol indicates that occult shock may occur in patients despite restoration of stable BP and HR: “For example, if other medical conditions that can also cause shock are ruled out in a patient with SBP restored to 100 mmHg but with persistent tachycardia, tachypnea, narrow pulse pressure, cool pale skin, and/or mental status changes (in absence of TBI), he/she is likely to have persistent HS and further IV fluid administration will be indicated. EMS providers will be reminded about potential for paradoxical bradycardia in hemorrhagic shock patients. Some other signs of occult hypoperfusion include weak and/or thready pulse, decreased oxygen saturation, oximeter failure to obtain reading, and decreased capillary refill” (Protocol, page 94).

(1) Has the sponsor submitted adequate evidence to support their claim that these parameters are valid, sensitive and specific in detecting occult hypoperfusion when a vasoactive solution is administered?

Consultant Opinion: Occult hypoperfusion is probably common both in field and in-hospital trauma resuscitation. The fact that the protocol involves reminding prehospital providers that occult hypoperfusion can occur is an important safety measure. Whether the parameters are valid, sensitive and specific is beside the point, as occult hypoperfusion can exist at any blood pressure, heart rate and so on. The preferred assessments generally include (but may not be limited to) urine output, blood pH and lactate, none of which are in-the-field observables. (Note: HBOCs interfere with lactate determinations. See Jahr JS et al, (2005) *Anesth Analg.* 100:431-6) The fact that the protocol calls for both field providers and hospital personnel to be alert for the possibility of occult hypoperfusion can reasonably be expected to provide additional margins for safety.

No change in this opinion.

(2) Do the RESUS dosing and administration guidelines (Protocol, page 92-94) provide adequate assurance that the benefit to risk profile of HBOC-201 will be reasonable when compared to standard of care?

Consultant Opinion: No. There are, at this time, insufficient data to assure that the high dosing rates in the protocol will be at least as safe as the non-HBOC-201 arm. The limitations on dosing and administration (three units, with a stop for SBP >120) appear to provide assurance that the benefit to risk profile will be comparable to the control arm of a balanced salt solution.

d. Section 5.4 of Biopure's proposed labeling for HBOC-201 warns that pulse oximetry values may decline during infusion of the product. The same observation has been noted in preclinical studies.

i. ***If pulse oximetry values start to decline during infusion of HBOC-201 into a bleeding trauma subject in the ambulance, has the sponsor submitted adequate evidence to guide EMTs as to whether these reductions are due to***

(a) interference by the product (Section 5.4, proposed HBOC-201 labeling:
Interference with laboratory tests),

(b) increased O_2 extraction due to the product (noted in animal studies),

(c) increased O_2 extraction due to ongoing blood loss, and/or

(d) hypoperfusion due to inadequate volume replacement?

Consultant Opinion: This is probably not relevant. In the setting of hypoxemia suggested by declining pulse oximetry values, EMT's will provide supplemental oxygen, continue fluid infusion, reassess for other reversible causes of hypoxemia (e.g. pneumothorax) and expedite transfer to a center

where definitive care can be provided. None of these responses are likely to cause additional harm in the setting of severe shock. No change in opinion.

ii. The RESUS Protocol instructs EMTs to stop all infusion of Clinical Trial Material (HBOC-201 or LR) if SBP reaches 150 mmHg.

(1) Has the sponsor submitted adequate data to guide EMS personnel as to how to safety and effectively manage SBP elevations to 150 mmHg, thereby supporting the view that the benefit to risk profile of HBOC-201 compared to standard of care, is reasonable?

Consultant Opinion: The data appear to be adequate. The question remains whether the educational program—that must be delivered to a substantial number of EMS providers who become *de facto* study personnel—will achieve the necessary educational goals. The new SBP cap is 120 mmHg. The benefit to risk profile appears comparable to standard care.

e. According to the sponsor, 28% of HBOC-201 subjects (vs 5% of control subjects) with a pre-infusion SBP of 90 mmHg in orthopedic study HEM-0115 had a peak systolic BP of 141-160 mmHg during infusion of the first unit of HBOC-201. Additionally, 16% of HBOC-201 subjects (vs 0 control subjects) with a preinfusion SBP of 90 mmHg had a >60 mmHg increase in SBP with infusion of the first unit (Protocol, page 135).

i. 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?

Consultant Opinion: The data neither support nor refute the claim. The data simply demonstrate the vasoactivity of HBOCs. The transient change in blood pressure is, by itself, uninformative with respect to the benefit-to-risk ratio.No change in opinion.

ii. The ATLS Student Course Manual states that, "Vasopressors are contraindicated for the treatment of hemorrhagic shock."

(1) What are the clinical implications of this statement for hypovolemic trauma subjects receiving a vasoactive HBOC.

Consultant Opinion: This is not a significant issue affecting the trial in my opinion. The purpose of the statement in the ATLS manual is to prevent an inexperienced provider who is relatively unfamiliar with trauma care from substituting a vasoactive agent for adequate volume resuscitation. It only becomes significant if receiving hospitals are unaware of the fact that the patient has received an HBOC, and unaware of the vasoactive effects. No change in opinion.

f. Page 93 of the Protocol indicates that after infusion of the first unit (500 mL) of the product, subjects with SBP <90 mmHg will receive HBOC-201, whereas subjects with SBP >90 mmHg and HR<100 bpm and all subjects with SBP 100 mmHg, will not be re-infused with HBOC-201 but will instead, receive standard of care.

i. 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 BP cuff, the overall benefit to risk profile of HBOC-201 vs standard of care is reasonable?

Consultant Opinion: I do not think this is an especially significant issue. Generally, EMS personnel are not titrating fluid rates to blood pressure with any great precision, especially in the busy urban environments proposed for this study. No change in opinion.

2. Clinical safety profile

a. The sponsor states that unlike patients undergoing orthopedic surgery, trauma subjects are younger and thus, at lower risk for the adverse events observed than patients in HEM-0115.
   i. ***Are the imbalances in adverse events against the HBOC-201 arm noted in Biopure's Phase 2/3 in-hospital clinical trials (Enclosure #5: tables 2-5,Medical Officer Safety Review: Pivotal Trial HEM-0115) relevant for RESUS subjects?***

Consultant Opinion: I believe that they are relevant. The basic science data and the cardiovascular disease endemic among older Americans suggest a causal link between administration of HBOC-201 and the excess adverse events. Given the aging of the trauma population and the inclusion criteria allowing anyone who has reached their 18th birthday into the trial, at least some portion of the subject population in the trial will have a risk of excess adverse events. The age specific AE/SAE data (p137) support a reasonable safety profile in patients <70 years old.

b. In their BLA, Biopure reported that the incidence of CVA, TIA, cerebral ischemia/infarction was 14 vs 4 (odds ratio 3.10, p=0.05). ***What is the clinical relevance, if any, of this finding for RESUS subjects?***

Consultant Opinion: I believe they are relevant. Changes in hemodynamics can precipitate cerebrovasuclar events as well as cardiovascular events. See the immediately preceding opinion regarding the age of the trauma population. See above.

c. Adverse Events noted in the BLA clinical trials are virtually absent from the porcine studies of hemorrhagic shock. ***What is the clinical importance of this difference for RESUS subjects?***

Consultant Opinion: I think the relevance here is that the swine model may well not reflect the age and comorbidity constellation of the civilian trauma population. It better reflects the age and comorbidity constellation of active duty warfighters who are predominantly young and healthy and who have negligible underlying cardiovascular and cerebrovascular disease. No change.

d. In December 2004, Biopure reported 2 hypertension SAEs after infusion of #1 unit of HBOC-201 in their European PCI trial (N=45). ***What is the clinical importance, if any, of this finding for RESUS subjects?***

Consultant Opinion: This merely verifies what is already known concerning the vasoactivity of the HBOCs. No change.

e. The Protocol notes that even though 319 HBOC-201 subjects (vs 246 control subjects) in orthopedic surgery study HEM-0115 were reported to have cardiac AEs (p=0.0004 according to FDA; Protocol, page 137), "There are no data to suggest that cardiovascular events will be higher in patients in hemorrhagic shock who receive HBOC-201."

   i. With respect to RESUS, are there adequate data to indicate that the benefit to risk profile of HBOC-201 compared to standard of care, is reasonable in terms of cardiac AEs as well as AEs in other organ systems?

   Consultant Opinion: The answer to this turns on the interpretation of "reasonable" and the particular population under study. Given that older Americans will be included in the study population with the protocol as written, and given the potential for significant cardiac AEs, I do not think that the existing data justify the sponsor's statement. Again, with the new age restriction to <70 years, the risk profile appears to be reasonable compared to standard of care.

3. Sample size estimate

a. The National Trauma Data Bank (NTDB) is a voluntary data repository managed by the American College of Surgeons that contains all trauma admissions to 28 Level I Trauma Centers in 36 states.

   i. The NTDB website (http://www.facs.org/trauma/ntdb.html) states that, "...the NTDB is not population-based, nor is it necessarily representative of all trauma care in the nation. Statistics derived from the NTDB represent patient information contained in the NTDB, and cannot be generalized to represent all trauma patients."

   Are there additional limitations of the NTDB?

   Consultant opinion: While the limitations of the NTDB cannot be gainsaid, it is far and away the best source of trauma performance and outcome data available. The addition of the UAB/UMD outcome data enhances attractiveness of the study.

   ii. Can information from the NTDB be used to estimate the control mortality rate, given the RESUS trial enrollment criteria? If so, what is that estimate?

   Consultant opinion: Yes, the database can be interrogated to estimate a control mortality rate. The final estimate depends ultimately on the profile of subjects that are ultimately enrolled. The comparator group extracted from the NTDB should be matched for age, comorbidities, extent and complexity of the injuries themselves and so on. A secondary estimate of the control rate could be obtained from registries maintained by each of the collaborating trauma centers using a similar matching process. (see above)

b. The sponsor has submitted reprints of clinical trauma studies in support of their control mortality rate estimate (see Section 9, below).

i. Do the RESUS trial and these studies share the same, or nearly the same, enrollment criteria?

(1) For studies meeting this criterion, is it possible to estimate the predicted control mortality rate in the RESUS trial ? If so, what is that estimate?

Consultant opinion: It is of course possible to make an estimate. Whether it would be meaningful is another matter. A better strategy, as suggested above, is to interrogate the trauma registries of the participating centers over the past 3-5 years for survival/mortality data according to the inclusion/exclusion criteria.

c. The sponsor proposes a relative 25% reduction in mortality (34% to 25.5%) in the HBOC-201 arm of RESUS.

i. Has the sponsor submitted adequate evidence to support this effect size?

Consultant opinion: The effect size of 25% appears to be a reasonable estimate. Sponsor has reduced the effect size. This enhances attractiveness of the study

ii. A previous field trauma study using another hemoglobin-based oxygen carrier (DCLHb) was conducted by Baxter in 1997 (Sloan EP et al. *JAMA* 1999;282:1857-1864). Their sample size calculation was based on a predicted control mortality rate of 40%, a figure derived from "prior experience and trauma registry data of the participating investigators". In fact, the control mortality rate was only 17% when the trial was prematurely terminated in 1998 due to excess deaths in the test group. Even if the sponsor's estimate (34%) is correct, 66% of the remaining subjects would be expected to survive without HBOC-201, yet those receiving the test product would be exposed to its risks.

(1) Does this comport with exception from informed consent (see 21CFR50.24(a)(3), below) which states that "Participation in the research holds out the prospect of direct benefit to the subjects..."

Consultant Opinion: This is an inherently unfair question. Trauma care continues to evolve, yet carriage of oxygen in the emergency situation remains a challenge. Whether the control mortality rate is 34% or 17% is important only with respect to the power calculations. The key is that the test agent—HBOC-201 –must be at least as safe as the existing best practice if there is to be an exception to informed consent, something that the sponsor has yet to demonstrate. My impression is that with the age and volume restrictions, the test article is now nearly as safe as receiving standard care and moreover, with the additional scrutiny of patients associated with the study, patients in both arms—standard care and test article—may have direct benefit to patients. I reserve final opinion until the meeting.

4. Exception from informed consent

a. Overall, does the RESUS Protocol contain adequate evidence to meet the clinical requirements for exception from informed consent(as detailed in
21CFR50.24)?

Consultant opinion: Not at this time. The available treatments are neither unproven nor unsatisfactory, but rather represent current best practice in the management of severe hemorrhagic shock.. Nevertheless, the test article HBOC-201 represents a potentially significant advance in care whose efficacy cannot be tested any other way. As a consequence, the burden is on the sponsor to persuade reviewers that the safety-effectiveness balance of the test-article is at least comparable to the existing treatment in the context of the population to be studied. Given the likelihood of enrolling older trauma victims with significant co-morbidities who appear to be at additional risk for adverse events, I do not think that the sponsor has yet met that burden. The restriction on age and on the volume of the test article suggests that the clinical requirements for exception from informed consent are much closer to being met than in the original protocol.