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

Subj: **Docket No. 2004D-0462.** Draft "Guidance for Industry: Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes"

Below are comments concerning the subject draft Guidance. They are limited to a single concern relating to the evaluation of safety of investigational hemoglobin-based oxygen carriers. Aside from this one significant concern, I found the background discussion and recommendations in this document to be to be clear and comprehensive.

In its draft Guidance, CBER correctly notes that "patients may be more vulnerable to adverse effects of [an investigational] product than are normal, well-hydrated, healthy subjects." Before introducing the investigational agent into a physiologically stressed subject (e.g. cardiopulmonary bypass surgery, hypotensive hemorrhagic trauma victim), it is obviously prudent to look for indicators of toxicity in healthy persons whose major organ systems are fully functional with intact self-repair capacity, and therefore more able to recover from a potential toxic insult. By the same reasoning, CBER's recommendation that sponsors "conduct studies initially in controlled settings such as elective surgery before embarking on studies in unstable surgical patients or unstable trauma patients" is very well-considered.

This principle has a logical corollary, whose importance has already been demonstrated in the reported findings of at least two recent Phase III trials of investigational HBOCs: **older clinical testing subjects, with lesser physiologic reserve and higher rates of comorbidities affecting major organ systems, have a higher toxicological risk profile than younger, previously healthy subjects.**

Calls by an expert panel to focus safety assessments on older, more physiologically compromised patients with more frequent and advanced co-morbidities are reflected in a summary statement highlighting a September 1999 Workshop on Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Cell Substitutes co-sponsored by the FDA and the National Institutes of Health.

There were strong statements from panel members that a surgical study should include a wide range of patients, all ages, and that it was important to look at all different risk factors; that patients, many surgical patients--basically, the study

*should not be studying Olympic athletes who are going through surgery, but should include older patients who have coexisting and often undiagnosed diseases--diabetes, chronic obstructive pulmonary disease, cardiac ejection fractions less than 25%, chronic liver disease, etcetera--that these should be included.*¹

In their zeal to present their investigational agents in the most favorable light, certain sponsors and/or their investigators have sometimes described “poster boy” case reports to illustrate the capacity of their product to sustain life. Typically these are relatively young, previously healthy adults, with the ability to tolerate more physiological stress than older individuals, particularly those with preexisting comorbidities. The remarkable resilience of younger severely hemorrhaging adults is well known; a very recent story in the *Los Angeles Times* even brings this remarkable “survivability” of young adults to the attention of the general public.² (attached)

Evidence of an important association between more advanced age and increased risk of adverse events – *above and beyond the event rate in age-matched control subjects* – has been directly documented in the recent aborted Phase III trial of Baxter Healthcare’s “DCLHb” (*HemAssist*). In that trial, the mortality odds ratio in patients ≥ 55 years was about 9.0 favoring saline controls over the DCLHb group, while for age cohorts under 30 years and 30-54 years, the mortality odds ratios were around 4 and 2, respectively.³

Similarly, in the attached summary of a Phase III elective surgery trial of a polymerized human hemoglobin, Biopure’s “HBOC-201” (*Hemopure*),⁴ investigators reported that:

- The majority of patients with serious adverse events in the following body systems had preexisting diseases of the related organ systems: cardiac, pulmonary, renal, hepato-biliary, and vascular.
- Patients older than 75 years may be at an increased risk for adverse events, particularly if they have evidence of underlying disease and multiple co-morbidities.

¹ Blood Products Advisory Committee, March 16, 2000. *Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Cell Substitutes* (P. Aebersold, presenter).

² Leovy J. A Race to Stop the Bleeding. *Los Angeles Times*, November 9, 2004.

³ Sloan EP, Koenigsberg M, Gens D et al. Diaspirin cross-linked hemoglobin (DCLHb) in the treatment of severe traumatic hemorrhagic shock. *JAMA* 1999; 282:1857-64.

⁴ Jahr JS, Stewart LM, MacKenzie C, et al. Pivotal phase III study: safety of polymerized bovine hemoglobin (HBOC-201, Hemopure®) as compared to RBC in patients undergoing orthopedic surgery. Poster presentation: American Society of Anesthesiology, 2002.

In light of these facts, expert opinions and relevant study findings, I encourage CBER to include recommendations of the following nature specifically with respect to clinical evaluation of investigational oxygen therapeutics in the severe hemorrhagic trauma setting:

1. Before exposing the subpopulation of older at-risk patients to significant doses of the investigational oxygen therapeutic in a hemorrhagic trauma setting (where there is substantial confounding heterogeneity and variably extensive physiological stress associated with the traumatic insult), **study the safety of the product in a controlled, high blood loss elective surgery setting in a similar age cohort** (e.g. >55 years of age). Power the elective surgery study to assure that sufficient numbers of subjects are enrolled in that higher-risk age cohort to document reasonable safety of the investigational product in the chosen elective surgery setting.
2. In designing a pivotal clinical trial, ascertain that **sufficient numbers of subjects in a specified older-age risk cohort be enrolled to achieve adequate power** to document reasonable safety of the investigational product in the severe hemorrhagic trauma setting.

I appreciate this opportunity to contribute to your draft Guidance.

Sincerely,

Keith Berman, M.P.H., M.B.A.

Attachments (2)