

NORTHFIELD
LABORATORIES INC

1560 SHERMAN AVENUE

SUITE 1000

EVANSTON, IL 60201-4800

(847) 864-3500

FAX: (847) 864-0353

www.northfieldlabs.com

e-mail: nfld@northfieldlabs.com

16 5 JUN 20 11 10

VIA FEDERAL EXPRESS

January 25, 2005

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

Re: Docket No. 2004D-0462: Draft Guidance for Industry: Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes [Federal Register: October 28, 2004 (Volume 69, Number 208)]

Dear Sir:

Northfield Laboratories Inc appreciates the opportunity to comment on the draft Guidance for Industry entitled "Criteria for Safety and Efficacy Evaluation of Oxygen Therapeutics as Red Blood Cell Substitutes" dated October 2004. As a developer of a hemoglobin-based oxygen carrier, we have been actively engaged in this therapeutic field for over 18 years and have participated in a number of initiatives including the 1999 workshop jointly sponsored by FDA, NIH and the Armed Services. Having reached Phase III clinical development in the trauma setting, we can provide a unique perspective on certain recommendations with the interest of ensuring an improved understanding of the safety and efficacy of these compounds in humans.

General Comments

We commend the Agency on the comprehensive nature of this Guidance and the clear framework it provides in fostering development of red blood cell substitutes. Given the nature of the disease states and knowledge garnered from products that have been in development, a wealth of "Background" and "Recommendations" is summarized and provided. Notwithstanding, it is important to note that the while acellular hemoglobin products have been "thought" to be associated with a number of toxicities thereby leading to recommendations for their assessment in the clinic, it is important to reiterate that in a number of instances causality has not been established.

2004D-0462

CS

In general, while the Guidance is separated into two main sections, "Background Discussion" (Section III) and "Recommendations" (Section IV), certain information in each may be more appropriately placed in the other section. From the clinical perspective, for example, clinical trial recommendations are found in the "Background" section (Section III.C) and items such as evaluation of both clinical settings, that have labeling implications, are found only in the "Clinical Evaluation" section (Section IV.B) with little information in the "Background" section on the rationale for such recommendations. Similarly, recommendations on clinical trial design and endpoints, some of which currently reside within Section III.C, may be more appropriately relocated to the "Recommendations" section of the Guidance. A suggestion to create a separate "Indications/Claims" section between the "Background" and "Recommendations" sections may help provide further clarity to the document. This newly created section would be populated with information currently in Section III.C and would elaborate on specific language around the different possible indications that can be pursued (see discussion below).

A more detailed discussion of the different Sections of the Guidance follows. Please note that our comments are directed to the portable document formatted Draft Guidance as it appears on the CBER Guidance website (www.fda.gov/cber/gdlms/oxytherbld.htm). We have noted differences between this aforementioned document and the document posted in the Docket.

Background/Efficacy Considerations (Section III.C; page 6)

This Guidance document extensively summarizes the known and suspected safety considerations of the class of oxygen therapeutics as well as efficacy considerations specific to the indication and/or clinical situation. These considerations are used to develop recommendations on evaluations during the development of these compounds.

While the different "uses" of red blood substitutes are designated and discussed, actual indications for these settings are not clearly delineated. A separate "Indications/Claims" section prior to "Recommendations" would be helpful. As a sponsor, having an understanding of the specific framework for the indication is important in determining what indications to pursue as part of a development plan. For example, for elective surgery, would a study in one type of elective surgery be generalizable to all elective surgery and thereby permit a general indication? If not, how many and what types of models of elective surgery would be required to obtain a general elective surgery indication?

Similarly with respect to the trauma setting, a framework for the specific wording around the different indications that can be obtained pursuant to study in the 1) the rural or urban field setting only, 2) in the rural or urban field setting coupled to the hospital setting or

3) solely in the hospital setting and the applicability/transferability to the other settings would be useful. While the Agency suggests in Section IV.B.3, that data from the hospital setting “might be expected to provide an advantage over current asanguinous resuscitation, when definitive care is delayed” it does not categorically explain whether and how this is possible, with or without additional clinical studies. It is our position that in trauma, proof of efficacy and safety when blood is not available should be able to be extrapolated from the urban to rural setting and from the pre-hospital to hospital setting.

Recommendations/Preclinical Evaluation (Section IV.A)

• **Product Characterization (Section IV.A.1)**

As part of the recommended product characterization testing, oxygen capacity evaluation in the form of P50 analysis, Bohr effect, effects of binding cooperativity (Hill coefficient) and chloride effects should be determined. The guidance further suggests that it is “most useful to determine the entire curve of bound oxygen...at least over a physiologically relevant range (40-120 mmHg)” (pg. 10). As most oxygen therapeutics in development have a P50 below the physiologically relevant range specified, is it implied that P50 and other oxygen capacity measures noted are irrelevant in determination of potency? The guidance later recommends development of a potency assay “that reflects the biological activity sought in clinical studies” that includes a “measure of the ability of the hemoglobin product to load, carry, and unload oxygen reproducibly” (pg. 11). Taken as a whole, this would suggest that the oxygen binding curve itself over the range of 40-120 mm Hg, rather than P50, etc. should form the basis of a potency assay and be shown to be reproducible.

Additional recommendations include *in vitro* biological assays for generation of oxygen radicals and/or activation of triggered enzyme cell systems. While these studies may show that generation of free radicals is possible, for example, interpretation of these results will be difficult in that there is yet no link between these biochemical observations and clinical effects.

• **Design of Toxicology Studies**

Northfield agrees that it is a general tenet in animal safety testing to design toxicology studies to induce toxic effects in the animal at some dose level (Section IV.A.2, pg. 11). However, the evaluation of oxygen therapeutics as red blood cell substitutes is extremely complex. The lines between traditional toxicology studies and the animal model used to evaluate potential therapeutic safety and efficacy are quite blurred. Due to the high volumes that need to be infused over relatively short times, there are a myriad of physiological stresses independent of some frank toxicological event that is a direct cause of the agent administered. For example, exfusing an animal during the infusion of the oxygen therapeutic could result in complement activation, reduction in clotting factors, the need to administer allogeneic blood, etc. On the other hand, top loading an animal

without fluid removal could result in fluid overload. Obviously the fluid status of the animal is critical and determining whether the findings are due to volume issues or the blood substitute can be problematic. Consequently, Northfield recommends that toxicology studies be designed to induce toxic effects in the animal 'when feasible', taking into account the unique issues surrounding these types of therapeutics.

- Microvascular Circulation

Evaluation of the effects of hemoglobin solutions on microvascular circulation and on endothelium is recommended (Section IV.A.4, pg. 12). Studies of this nature appear highly experimental and conducted in only limited academic institutions with little demonstration of correlation to clinical outcomes. We are unaware of a validated model for these studies. We believe it too early for this to be made a recommendation in the Guidance.

- Reliable Markers of Oxidative Damage

The Guidance recommends that reliable markers of oxidative damage be incorporated into animal studies (Section IV.A.4, pg. 12). Please clarify which markers the Agency would find to be appropriate. Research in animal (and human) models of hemoglobin oxidative kinetics is very limited much less the understanding of such changes to the overall toxicity of this class of compounds. It is unclear what physiologic understanding any biochemical changes could predict to clinical outcomes.

- Cardiac Toxicity

In Section III.B.2, pg. 3 of the Guidance, FDA discusses myocardial lesions being seen most commonly in the rhesus monkey and pig. This finding is well supported by the Burhop et al. paper, 2004 (Burhop, K., Gordon, D., Estep, T. Artificial Cells, Blood Substitutes and Biotechnology, Vol. 32, No. 3, pgs. 353-374, 2004). However, this information is not followed in the "Recommendations" section (Section IV.A.4, pg. 13) where only a primate model is suggested. Northfield ascertains that for consistency and in keeping with the Burhop paper the rhesus and pig should be explicitly stated in the recommendations section or reasons why this is not acceptable should be articulated. Notwithstanding, it is important to note that while lesions, as detected by light microscopy, were seen 24-72 hours after hemoglobin administration; this pathology was not correlated with any elevation in cardiac specific isoenzymes. Additionally, lesions were reversible as they were not seen upon further red blood cell substitute administration, and there is no evidence to suggest that these red blood cell substitutes cause such myocardial lesions in man. The relevance of such histopathologic changes in animals to the clinical setting is questionable at best. Consequently, we believe it is premature to recommend this expansive preclinical study.

- Neurotoxicity Testing

A compromised blood brain barrier can lead to central neurons being exposed to blood in a trauma situation. Neuronal death, however in these cases, usually results from the primary injury resulting in an ischemic state as opposed to any possible direct effect of

unbound plasma hemoglobin. Attribution of any one cause to this neurotoxicity is very difficult to ascertain given the complicated systemic environment. It is unlikely that an *in vitro* model of neurotoxicity (see Section III.B.8, pg. 5 and Section IV.A.4, pg. 13) can provide any predictability to an *in vivo* setting, given these extenuating circumstances.

Additionally, determining a clinically relevant dose range to test the product is difficult given that such toxicity is unlikely to be a pharmacologically driven effect.

With regards to *in vivo* tests, the most applicable model for trauma would be a model of blunt or penetrating injury. Performing models of such head injury is not practicable either in an academic or contract setting as labs are reluctant to do so.

- Determination of Residual Red Cell Enzymes

The Guidance suggests that for stroma-reduced hemoglobin products, the effects of residual red cell enzymes on hemoglobin potency and stability should be determined (see Section IV.A.4, pg.13). If all non-hemoglobin proteins are considered to be impurities and consistently removed to very low levels, we would consider that this evaluation would not be necessary. Clearly, if red blood cell enzymes were an intended part of the product composition, such an evaluation would be necessary.

- Interference

It is recommended “to evaluate and resolve interference of hemoglobin solutions with measurements of clinical laboratory parameters for all relevant clinical laboratory instrumentation” (Section IV.A.4, pg. 13). We suggest replacement of ‘resolve’ with ‘describe’, since resolution of the interference may not be possible with even correction factors given possible non-linearity of interferent effects. The word ‘all’ should be replaced with ‘representative’ since it is unreasonable to hold drug manufacturers responsible for testing every instrument. Additionally, the term “relevant” should be further specified to mean those tests required for the care of the patient in the desired clinical setting, e.g. acute care of the patient in the trauma setting.

The final sentence in this section states, “Manufacturers of oxygen therapeutics should anticipate ongoing support of clinical laboratories... on new instruments or methods of analyte determination.” A better descriptor of the relationship between the drug manufacturer and the supplier of clinical laboratory instrumentation is ‘collaboration with’.

Finally, we suggest that this discussion of clinical laboratory interference should be moved from its current place in “Preclinical Evaluation” (Section IV.A) to a separate subheader “Clinical Laboratory Assessments” under “Clinical Evaluation” (Section IV.B) after the “General” subheader.

Recommendations/Clinical Evaluation (Section IV.B; page 14)

In general, this section is detailed in its many recommendations. It may be helpful to the sponsor if this detail were further delineated in additional subheadings (under subsection 1, 2 and 3) namely: A) Clinical Development: Expectations for Phase I, Phase II and Phase III studies, B) Population (minimal inclusion criteria) and C) Study Endpoints and D) Statistical Considerations.

- **Clinical Study Endpoints**

Clinical study endpoints are recommended to support indications for elective surgery and for trauma. While the efficacy endpoints are clear, there is no specific direction on the type of safety endpoints required for any of the specific indications. In Section IV.B.1, pg. 14, a recommendation is made to “capture a numerical increase and/or an increase in the intensity of adverse events above the underlying background rate/intensity of such events”, however this does not define what the expectations are.

To be consistent with the discussion of the elective surgery indication, secondary endpoints such as reduction in allogeneic blood transfusion should be discussed in the context of the trauma setting as well. Blood transfusions are clearly associated with a number of morbidities associated with trauma and should be evaluated in conjunction with mortality for this indication as well. Any information obtained from such analyses, while exploratory in nature until validated as a surrogate, should be beneficial language to include in the Clinical Studies section of the labeling (assuming that the primary endpoint has been achieved).

- **Clinical Development Plan in Both Elective Surgery and Trauma**

The Guidance initially sets up the three distinct “uses”/indications (Section III.C) that can be sought but then suggests in a number of places that a sponsor develop a “clinical development plan that includes safety and efficacy assessments in both trauma and elective surgical settings” (Section IV.B.1, pg. 14). The interpretation is that documentation of the safety and efficacy of a red blood cell substitute for emergency use in the setting of acute blood loss accompanying trauma would not suffice to assure safety and efficacy in elective surgical settings. It is important to note that patients undergoing elective surgery would be hemodynamically stable and specifically selected not to have comorbid conditions that would put them at increased risk for operative complications. In contrast, patients enrolled in a trauma trial would of necessity be unstable in order to meet standard clinical indications for transfusion of an oxygen carrier, typically blood. Therefore, extrapolation of results obtained in an elective surgical setting to support use in the setting of acute hemorrhage accompanying trauma is not supported, for the reasons also outlined in the Guidance. Given that elective surgical patients would be less subject to adverse effects of the red cell substitute being tested and to clinically relevant hypoxemia, success in clinical trials involving trauma patients in hemorrhagic shock would represent a higher standard. Therefore, we would recommend that it is not

necessary to assess either safety or efficacy in the elective surgical setting if demonstrated in the setting of acute hemorrhagic shock.

- Dosing Guidelines (Section IV.B.2, pg. 15)

Red blood cell substitute products should be used to treat patients who are at immediate risk of or those patients who are actively demonstrating a symptomatic deficiency in oxygen carrying capacity, in settings where red blood cell transfusions are either not available or would predispose the recipient to additional risk. It is our view that these products would have little value in treating chronic nutritional or renal-mediated anemias that could be corrected by administering B₁₂, folate, iron, or erythropoietin. Likewise, such products are not appropriate to treat non-symptomatic blood loss where routine restoration of lost volume with asanguinous solutions would be sufficient. The decision to infuse a patient with a red blood cell substitute is a very complicated process that considers available laboratory and physiologic data, the treatment setting (e.g., field or hospital, trauma or elective, sea-level or at elevation, etc.) and available assessment parameters therein, resuscitation and surgical options, the duration of the anemia, and the effectiveness of the compensatory mechanisms or the interaction of preexisting medical conditions on those mechanism. We would expect that, at minimum, the recommendations proffered by expert panels, such as the National Institutes of Health Consensus Conference in 1988, the 1996 Anesthesiology Task Force, the American College of Surgeons Committee on Trauma in their ATLS guidelines, and others using physiologic data and total hemoglobin levels to indicate transfusion thresholds would help shape these decisions. Notwithstanding, we further recognize there is not absolute consensus regarding this decision.

From a technical perspective, however, we agree with the Agency that the sponsor must provide physicians with detailed instructions that explain how these products, once administered, may be clinically measured, both *in vivo* and *in vitro* (e.g., using total hemoglobin concentrations rather than hematocrits to measure circulating acellular hemoglobin solutions) and how one would gauge their effectiveness. These data should generally be garnered from clinical trials with the product and should be integrated into established practices for blood transfusions.

The guidance states that oncologically active red blood cell substitutes preclude “the use of routine measures such as total hemoglobin as a reflection of the need for additional transfusion/infusion”. It is unclear why total hemoglobin would not be a valid measure of the oxygen carrying status of the patient and therefore indicate the need for additional transfusion/infusion? Current resuscitation also involves frequent alterations in blood volume, and yet hemoglobin or hematocrit is still used. As stated above, the transfusion decision is a composite of many different assessments.

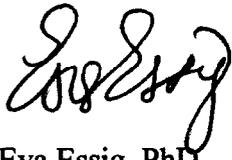
- Statistical Considerations

A data analysis section entitled "Statistical Considerations" of the Guidance explaining FDA expectations for clinical data analysis including imputation of missing data would be helpful.

Northfield appreciates the opportunity to comment on this important draft document and respectfully requests that FDA give consideration to these recommendations. If further clarification is needed, please contact the undersigned.

We look forward to the issuance of the final Guidance.

Sincerely,



Eva Essig, PhD
Vice President of Regulatory Affairs and Quality