FOOD AND DRUG ADMINISTRATION

CENTER FOR BIOLOGICS EVALUATION AND RESEARCH

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BLOOD PRODUCTS ADVISORY COMMITTEE

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P R O C E E D I N G S

Agenda Item: Statement of Conflict of Interest, Announcements

MR. JEHN: My name is Donald Jehn. I will be the executive secretary for the 88th meeting of the Blood Products Advisory Committee.

Today's meeting is completely open to the public.

At this time, I would like to go around the table and introduce the committee and consultants that are participating in this meeting.

[Introductions]

Committee members not in attendance today are Drs. DiBesceglie and Kuehnert. Dr. Demetriades was going to be a temporary voting member, but he got ill at the last moment and will not be in attendance today.

Invited guests of the committee are Dr. John Hess and Dr. Jeffrey Scheulen.

We would like to thank all the members and TVMs for joining us today.

I have a statement to read, briefly.

Many have gone on the Web site and noticed that some of the information might be misleading, the way it is presented. CBER's advisory committee staff apologizes if there has been any confusion regarding the titles of materials posted on the FDA Web page. Some materials were

listed by the first few words in the documents rather than by the more appropriate title. Specifically, review number 4 was incorrectly attributed to Dr. Laurence Landow of the FDA. This document was, in fact, written by a special government employee engaged by the FDA as an outside consultant.

We will attempt to correctly name the posted documents after the meeting.

I have the conflict-of-interest statement to read. Bear with me.

The Food and Drug Administration is convening today's meeting of the Blood Products Advisory Committee under the authority of the Federal Advisory Committee Act (FACA) of 1972. With the exception of the industry rep, all members and consultants of the committee are special government employees (SGEs) or regular federal employees from other agencies and are subject to the federal conflict-of-interest laws and regulations. The following information on the status of this advisory committee's compliance with federal ethics and conflict-of-interest laws, including but not limited to 18 USC 208 and 21 USC 355 Section 4, is being provided to participants in today's meeting and to the public.

The FDA has determined that members of this advisory committee and consultants of the committee are in

compliance with the federal ethics and conflict-of-interest laws, including but not limited to 18 USC 208 and 21 USC 355 Section 4. Under 18 USC 208, applicable to all government agencies, and 21 USC 355 Section 4, applicable to certain FDA committees, Congress has authorized FDA to grant waivers to special government employees who have financial conflicts when it is determined that the agency's need for a particular individual's services outweighs his or her potential financial conflict of interest (Section 208) and where participation is necessary to afford essential expertise (Section 355).

Members and consultants of the committee who are special government employees at today's meeting, including special government employees appointed as temporary voting members, have been screened for potential conflicts of interest of their own, as well as those imputed to them, including those of their employer, spouse, or minor child, related to the discussions of preclinical and clinical studies of the hemoglobin-based oxygen carrier bovine polymerized hemoglobin, HBOC-201.

In addition, the committee will discuss an emergency research study of HBOC-201 proposed by the Naval Medical Research Center. These interests may include investments, consulting, expert-witness testimony, contracts, grants, CRADAs, teaching, speaking, writing,

patent and royalties, and primary employment.

Today's agenda also includes an updated summary of the October 11, 2006 public hearing on emergency research. In accordance with 18 USC Section 208, Part III, no waivers were required for today's discussion. With regard to FDA's guest speakers, the agency has determined that the information provided by these speakers is essential. Dr. John Hess is professor of pathology and medicine, and associate medical director, Blood Bank, University of Maryland Medical School. Mr. Jeffrey Scheulen is an EMS training specialist, Emergency Medical Services Education, Washington Hospital Center. As guest speakers, they will not participate in the committee deliberations, nor will they vote.

In addition, there may be regulated industry and other outside organization speakers making presentations. These speakers may have financial interests associated with their employer and with other regulated firms. The FDA asks, in the interest of fairness, that they address any current or previous financial involvement with any firm whose product they may wish to comment upon. These individuals were not screened by the FDA for conflicts of interest. Dr. Louis Katz is serving as industry rep, acting on behalf of all related industry, and is employed by the Mississippi Valley Regional Blood Center. Industry

reps are not special government employees and do not vote.

This conflict-of-interest statement will be available for review at the registration table. We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record. FDA encourages all other participants to advise the committee of any financial relationships that you may have with any sponsor products, direct competitors, and firms that could be affected by the discussions.

At this time, I turn the meeting over to Dr. Siegal, the chair. I believe Dr. Epstein wanted to make a statement at this time.

Agenda Item: Opening Remarks

DR. EPSTEIN: I will just defer to Dr. Siegal, if he would like to offer a word of welcome.

DR. SIEGAL: I just want to thank the FDA for appointing me to this. I hope I can live up to the expectations of the chair.

DR. EPSTEIN: On behalf of FDA, I would like to add my welcome to that of Dr. Siegal and to thank the members of the committee in advance for the important work

that you have each come to do today.

The topic for today's discussion, as stated earlier, is a proposed clinical trial by Naval Medical Research Center of Biopure Corporation's bovine-derived hemoglobin-based oxygen carrier, HBOC-201, in the setting of acute urban trauma with hemorrhagic shock. FDA has placed this trial on hold since 2005, for scientific reasons that will be presented and that you will be asked to discuss. Our action in this matter has been taken against a background of intense interest at the Center for Biologics Evaluation and Research in facilitating the development of hemoglobin-based oxygen-carrying products for a variety of unmet medical needs, including potential improvement in resuscitation of trauma victims with life-threatening hemorrhage. CBER is interested in promoting progress in this area and in this case has sought input from the Center for Drugs, as well as from outside experts.

FDA recognizes that the issues we will be discussing are difficult. We also recognize the importance of such products to public health and to individual patients. Although the decision to permit the proposed clinical trial or any modification to proceed lies with the FDA, the advice of the committee is very important and will be considered both fully and very carefully by the agency.

In this spirit, we welcome your deliberations at

this meeting and we look forward to receiving your expert scientific advice. Thank you.

DR. SIEGAL: Let's start with agenda item 1. Toby Silverman, MD, chief, CRB, DH, OBRR, CBER, will give an overview of CFR 50.24.

Agenda Item: Summary of October 11, 2006 Public Hearing on Emergency Research

DR. SILVERMAN: [Slide] Good morning, everyone. My name is Toby Silverman. I'm the branch chief for the Clinical Review Branch in the Division of Hematology in the Office of Blood Research and Review. It's my group and others in the division which are responsible for the review of IND 12504 from Naval Medical Research Center.

[Slide] 21 CFR 312 is a set of regulations that governs the conduct of investigations with investigational new drugs. It specifies, in general, that research subjects are not exposed to unreasonable risk. Investigations with investigational new drugs are subject also to other regulations to protect the rights and safety of subjects. These are found at 21 CFR Part 56, which governs institutional review boards, and 21 CFR Part 50, which governs informed consent.

[Slide] 21 CFR 50.24 is the set of regulations governing the conduct of clinical trials in emergency situations with exception from the requirements for

informed consent.

[Slide] 21 CFR 50.24(a)(2) specifies that subjects must be in a life-threatening situation for which available treatments are unsatisfactory or unproven; that there is a need to collect valid scientific evidence to determine the safety and effectiveness of particular interventions; that obtaining informed consent is not feasible because the subjects will not be able to give their informed consent as a result of their medical conditions and the intervention under investigation must be administered before consent from the subject's legally authorized representative is feasible; finally, that there is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the clinical investigation.

[Slide] Part (a)(3) states that participation in the research must hold out the prospect of direct benefit to the subjects participating in the study. There must be a potential for direct benefit. So information from appropriate animal and other preclinical studies and related evidence must support the potential of the product to provide a direct benefit to the individual subject. Despite the uncertainty, the investigational intervention is intended to be beneficial and there is conceptual preclinical and possibly clinical evidence that the hoped-

for benefit outweighs the potential risks. This is found in the preamble to the October 2, 1996 rule.

[Slide] Harms must be minimized. To minimize harms, the risks associated with the study are reasonable in relation to all available information about the medical condition of the subjects of the study, the risks and benefits of standard therapy, if any, and the risks and benefits of the proposed intervention or activity.

Thank you.

DR. SIEGAL: Next we will hear from Diane Maloney, JD, associate director for policy, IOD, CBER, FDA, discussing the public hearing on October 11, 2006, on emergency research.

Agenda Item: Summary of October 11, 2006 Public Hearing on Emergency Research

DR. MALONEY: [Slide] Good morning. I am Diane Maloney, the associate director for policy in the Center for Biologics. IOD is the Immediate Office of the Director. You have a lot of acronyms up there, so I just wanted to say where I am in the Center.

You have just heard from Dr. Silverman, who has given you a brief introduction to our emergency research rule. I will give you a brief update on a public meeting that we held in October to seek input on this important topic. I am providing this talk for your information only.

We will not be asking for your input on the specific elements of the rule, but just more for your background and where we are.

[Slide] FDA held a meeting and the scope of the meeting was emergency research conducted without informed consent. The purpose of the meeting was to obtain input from the public on their experiences, challenges that they have seen with the rule, any concerns they had, and any suggestions that they might have for us, and also for us to determine, after we assessed the input that we received, whether any changes were needed.

We were seeking input from all interested parties, including those mentioned on this slide: patient advocacy groups, individuals who had participated in these trials, institutional review boards, sponsors, clinical investigators, medical societies, ethicists, and anyone else who wanted to provide comments to us.

[Slide] The background: We issued the rule to facilitate research and protect subjects. In doing this rule -- this is going back to 10 years ago -- we sought a lot of public input before doing the rule, with a lot of emphasis on what human subject protections would be needed in an area where you would be involving an exception from informed consent. It’s a narrow exception:

- It involves patients who are in life-

threatening conditions that cannot give consent.

• The available treatments are unproven or unsatisfactory.

• The investigational product must hold out the prospect of direct benefit.

• The study cannot practicably be done with consent.

• In addition, we had a number of other protections in the rule for human subject protection.

[Slide] So now we have had 10 years of experience with the rule. We have gotten together numerous times within the agency to talk about our experiences. Over these years, we have received informal input from the public on various aspects of the rule. A number of people have commented that additional guidance is needed on various aspects of the rule. In addition, people have commented on the adequacy of the safeguards. Some have said that the safeguards in the rule are adequate, but additional guidance, spelling out more about what we mean by them, would be helpful. Others have said that what we have in the rule is too burdensome; it's standing in the way of research moving forward. Others have suggested that maybe additional safeguards are needed. In addition, we have heard from people that despite the goal of having more research done that leads to products that really will help

people in situations where there really aren't good products out there, a lot of emergency research to achieve this goal is not occurring, for multiple reasons, some of those reasons being that it's very difficult to design studies in this area and the burden of conducting such research.

So after our experience of 10 years, we decided to seek more formal public input, so we held a public meeting. In addition, we opened a public docket seeking written comments from the comment.

[Slide] We announced the public meeting in the *Federal Register* in August. In the *Federal Register* notice, we described the rule. We gave a lot of background about how we came about doing the rule, what the rule covered, questions that came to our minds that we thought were important to receive input on from the public. In addition, we issued a draft guidance at that time, again trying to provide additional guidance to people who were implementing the rule on some of the things that we thought would be helpful to them. But we issued it as a draft, recognizing that we wanted to seek additional input and then go ahead and issue a final guidance after we received that input.

We requested written comments on the public meeting to be submitted to us by November 27, and the

meeting was held on October 11.

[Slide] This slide just summarizes some of the input that we received. We received approximately 80 written responses. Most of the people that wrote in did voice support for the regulation, recognizing the need to advance getting therapies out there in situations where there really aren't good therapies. Some of those who wrote in did voice the need for additional guidance, especially in the areas of community consultation and public disclosure. There were a number of people who did express opposition to any research that involves a waiver of informed consent.

At the public meeting, we heard from 17 speakers. All of those who spoke did support the need for the rule and the exception for consent, although in addition to supporting the rule, they did make a number of different suggestions. Those suggestions varied quite a bit. The majority of people who presented were researchers. We also heard from representatives of a number of different organizations, as well as from a sponsor and an IRB representative.

[Slide] At the meeting a number of issues were discussed. Not all of the questions that we raised in the *Federal Register* were addressed at the public meeting. I am going to highlight the topics that we did hear at the

meeting. The commenters spoke about the scientific aspects of emergency research, as well as human subject protection. Again, we heard mostly about community consultation and public disclosure.

[Slide] What we heard from people is the need for clarification of some of the criteria in the rule. People spoke about the phrases “the prospect of direct benefit” and “available treatment being unsatisfactory or unproven.” Again, they were seeking clarity there.

The agency is still assessing what we heard, so I really can’t give you a final synopsis of what we heard. But I was on the panel, and one of the things I heard from the people who spoke at the meeting -- with regard to “unsatisfactory,” people said that just because a product is on the market as approved, that does not mean that it would be satisfactory in every situation. I think they were looking, again, for more clarity in that area.

[Slide] On community consultation, we heard from the presenters about the costs of doing community consultation and about the feasibility of doing such consultation. In addition, people asked us questions about the effectiveness of doing community consultation as a human subject protection mechanism. People also spoke to the adequacy of consultation: How many meetings do you have to have? Where do you have to go? How many people

should be consulted before you would be considered to have done adequate community consultation?

[Slide] On public disclosure, people again asked questions about what the purpose is, what we are trying to achieve. The rule requires public disclosure of the study both before the study begins -- that is to alert the community that the study is about to begin -- and after the fact of the study results. That is for numerous purposes, but one is, I think, to help researchers know where we are so you don't repeat studies unnecessarily.

People also discussed what level of detail of information ought to be discussed publicly. In terms of, for instance, the protocols, should the whole protocol be available, parts of it, the investigator's brochure?

[Slide] In addition, we heard from people about whether or not additional review, besides that called for in the rule, is needed, and also whether there was a need for additional public discussion. We heard a lot of comments from people on the notion of a national advisory board. It was quite varied. A number of people talked about consideration of the use of a national IRB, for instance. Others talked about the use of an advisory committee to discuss these kinds of studies.

So that is pretty much a summary of what we heard at the public meeting. We are still assessing the comments

to the docket, the written comments.

[Slide] Our next steps are to review the comments that were submitted to the docket, as well as the comments that have been submitted to the agency on the draft guidance that we issued. In addition, we will be reviewing the presentations that we heard at the public meeting. Then we will take all those into account as we evaluate where to go from here, whether changes are needed.

Thank you.

DR. SIEGAL: Now we will move on to a review of the proposed trial of HBOC-201 in trauma. We will have two background presentations. The first is Abdu Alayash, PhD, chief, OBRR -- he can tell us what these means. After that we will hear from Laurence Landow, MD, medical officer.

Agenda Item: Overview of Hemoglobin-based Oxygen Carriers

DR. ALAYASH: [Slide] Good morning. I'm Abdu Alayash. I'm with the Office of Blood, Division of Hematology.

I am going to try to give you a very brief overview of some of the biochemical/physiological aspects of hemoglobin-based oxygen carrier, commonly known as HBOCs. This is largely based on our research at CBER, the Division of Hematology. The research program was established almost 17 years ago. The main focus of the

research is primarily on HBOCs. The idea here is to contribute to the basic understanding of these very complicated, complex biological products.

[Slide] I am going go start with an outline of some of the products that we deal with and some of the common approaches used by industry to produce these products. We have basically two classes of product: fluorocarbon-based, which are primarily synthetic -- I am not going to deal with them -- and, of course, the hemoglobin-based products. These are products that are derived from outdated blood, be it human blood or bovine blood. Hemoglobin is isolated and extensively purified and chemically modified. The chemical modification can take the form of either cross-linkage to stabilize the natural tetramer of hemoglobin -- cross-linked and the surface of the protein is decorated with some other agents to increase the size -- or the product of the hemoglobin is polymerized and a large polymer, in some cases, is actually encapsulated within the lipid membrane.

The chemical modifications serve two basic purposes: to primarily stabilize the hemoglobin in the tetrameric natural form -- otherwise, hemoglobin will dimerize and will be cleared by the kidney very rapidly, and, of course, it’s going to be very toxic. Some of these agents, secondly, are bifunctional. In other words, they

don’t only stabilize and polymerize the hemoglobin, they can also alter the oxygen affinity and force the hemoglobin to deliver oxygen.

You need to bear in mind that these products aren’t really substitutes for blood. They are designed primarily to provide oxygen and volume replacement.

[Slide] If you were to look at the open literature and review some of the preclinical/clinical side effects associated with these products, these are some of the side effects you can find. Primarily, vasoactivity and hypertension has been seen with almost all HBOCs, in animals and in humans. The primary cause for this, in simple terms, is the fact that hemoglobin outside the red cells can scavenge nitric oxide, which is produced by blood vessels, and that may lead to vasoactivity and hypertension.

The rest of the list is not extensive. But primarily, biochemically, one can safely trace them back to the fact that the hemoglobin is very reactive, and most of these reactions are triggered by the heme of the hemoglobin itself.

[Slide] There are a number of issues that you need to bear in mind. Biochemically, one could focus on these two very basic issues, based primarily on our experience and the experiences of others. Firstly is the

nature of chemical modifications, the choice of reagent that you are going to put in your product, the site of modification. Is it site-specific? Does it go where it is supposed to go, the reagent that you are using? Is it random? If the random modifications of your product produce a random modification that may lead to some collateral damage to both the protein and the heme, of course, that will ultimately lead to the heme loss prematurely. Of course, the heme is extremely toxic, and you want to avoid that. So what you put in your product is clearly very important, in terms of the choice of chemistry.

The other issue, of course, is, whether you really have a well-defined chemistry or not in your product, you still have to deal with the fact that hemoglobin is outside the red cells and, of course, is going to be in immediate contact with the vascular system, and that can trigger some vascular oxidative effects. As I said, it’s because of the primary effects of the removal of nitric oxide that may lead to vasoconstriction and hypertension.

The other fact is that hemoglobin is naturally reactive. It can actually produce its own free radical and damage itself. It can react with a number of oxygen radicals produced by a number of cellular components. The

combination of the two pathways close to the vessel wall could lead to some vascular injury.

[Slide] I am going to use Oxyglobin -- this is one of Biopure's products -- as a case model to illustrate some of the biochemical/physiological issues that come into all products. The reason I have chosen this hemoglobin is simply because it is the only FDA-approved product for use in veterinary medicine, primarily in dogs with anemia. Of course, it's the only commercially available product that we and many researchers have used in the last few years. Of course, I am not really trying to draw any contrasts between 301 and 201, which is the subject of today's discussion.

[Slide] It's a polymer, as I said. It's derived from bovine. The first thing you want to do is to break it down to these components and to see if the chemistry that you put in this product is really what you meant it to be.

The first thing we did was to fractionate the polymer into fractions. As you can see here, it breaks down to four fractions. In terms of size, it is about 85 all the way up to 500 kd -- obviously, a large polymer. This is based on size exclusion. We also used laser scattering to confirm the distribution of these fractions.

We actually took each fraction and ran the gamut in terms of characterization, in terms of the oxygen

affinity of each fraction, its heme stability on oxidation, its ability to react with nitric oxide. More importantly, we determined the site specificity of each fraction.

It looks like, overall, these fractions behave the same, and there is no unusual chemistry that we found in our studies.

[Slide] This is one example of how the fractions behave, as compared to the polymer itself, in terms of oxygen affinity. This is your classic oxygen equilibrium curve. Here it shows you the nice sigmoidal shape of a typical bovine and modified hemoglobin. As you can see, the curve has shifted to the right for the fractions and for the polymer itself. The more you shift it to the right, presumably, the more oxygen will be delivered.

There are very minor changes between the native and the modified. To just point out a couple of minor things, the shape of the curve is now altered a little bit. It’s a little bit insensitive to changes in the natural allosteric modifier that the hemoglobin will face in the real physiology. We don’t really know if this limitation will translate to any significant thing in the real world.

I am now going to, after I finish the chemistry, come back to the physiology, the issues that I talked about a little bit earlier.

[Slide] This is just to, in simple terms, remind

you of the vessel wall and the relationship between red cells and free hemoglobin. As you can see, free hemoglobin, of course, unlike red cells, can actually, because of the small size, reach to the vessel wall. Of course, this is the basis of some of the problems.

[Slide] Here is a cartoon illustration of what we think is actually going on. You are going to hear throughout the day about vasoconstriction and hypertension. I think it's important to keep this particular simple picture in mind when we deal with this issue. As you all know, I am presenting here the blood vessel. This is the wall of the vessel. This is inside the vessel. Of course, you all know that nitric oxide is produced by the endothelial cells lining the blood vessels. The primary function of nitric oxide is, of course, to relax the smooth muscle vis-à-vis a set of enzymes that directly impact it.

But nitric oxide can also travel a considerable distance in its short half-life. The yellow circle here represents the distribution of NO. It can travel over a number of barriers and it can actually reach the red cells. It reaches the red cells, and, of course, the hemoglobin within the red cells will react with NO and that will oxidize it very rapidly. But, remember, we have enzymes inside the red cells that can deal with the mess that that created.

[Slide] If you have a free hemoglobin in a blood substitute, it would not flow with the RBCs. It will actually get very close to the vessel wall in the area which is known as the RBC-free zone. It, of course, is going to react immediately with nitric oxide. The affinity of hemoglobin to nitric oxide is almost 500 times more than the affinity of hemoglobin to its natural partner, the oxygen. So the reaction is very immediate. That would lead to vasoconstriction, presumably.

The other thing is, of course, you are tipping the balance in favor of other harmful oxidants. These oxidants can actually interact with hemoglobin. The combination of these two simple reactions can create an oxidative environment which will ultimately lead to some injury to the tissue.

[Slide] This is a simple experiment that we have done, just to show you the immediate response in terms of blood pressure. These are two small animals, rats. We infuse Oxyglobin, or 301, 50 percent exchange transfusion. As you can see, the blood pressure has immediate elevation. Mean arterial pressure is immediate. It peaks within a few minutes. It will gradually decline and more or less reach the baseline within about three hours.

Another interesting point you need to keep in mind is the species difference between the two animals, in

terms of their response to the infusion of the HBOC. That obviously needs to be kept in mind when you actually deal with the design of animal studies.

[Slide] This is one other simple experiment that we have done, just to mimic what I described about these oxidative reactions being due to nitric oxide or the oxygen. We have worked with Ann Baldwin, who had a very simple system, the mesenteric window. She can pull the mesentery from the rat, put it on the Plexiglas, and observe the microcirculation under the microscope. As you can see, there is a clear network of small venules and arterioles in here. The contents of the blood vessels are flushed out. Then, after she closes this area, obviously, she perfuses this area with the hemoglobin, followed by albumin, labeled albumin, to visualize the effect. As you can see, after you perfuse the hemoglobin, you can see that there is a leakage in the marked capillaries, and you can see distribution.

We used a variety of hemoglobins, actually. She looked at the areas of leakage, the surface area of the leakage, and she plotted them here. We compared HBOC-301 with a number of hemoglobins that we have in our hands. As you can see, both the frequency of the leakage and the area of the leakage are reduced with 301 compared to modified hemoglobin, diaspirin cross-linked hemoglobin, and

polymerized hemoglobin A0.

To test that these reactions that I described to you actually occur in this simple system, we block the diaspirin cross-linked hemoglobin with cyanide. Cyanide blocks the heme, the iron. The hemoglobin would not be able to interact with the radical, the one I described. As you can see, the reaction was produced that clearly showed that these would actually occur here.

When we added nitric oxide to the mix, again, we were able to reverse the reaction here.

[Slide] So based on these simple experiments that I have explained to you and based on a wealth of information in the literature, by us and a number of other people, here is a general summary for you to keep in mind.

Most HBOCs that we dealt with and most HBOCs that are in the open literature are reported to be vasoactive. The thinking here is that this is in large part due to the scavenging of nitric oxide.

Also, importantly, you need to keep in mind that it’s really the proximity of the product to the vessel wall that may actually determine the degree of response.

Importantly, not all HBOCs are created equal. It really depends on the chemistry you put in your HBOC. If that HBOC can come out of that mess in one piece, the NO/oxidative insult, due to the intactness, if you like, of

the protein -- you kept the heme inside -- then that should be okay. Probably hemoglobin will deliver some oxygen. If you have natural reductants in the blood that will also reduce the hemoglobin and rejuvenate the hemoglobin, you may be able to deliver oxygen.

I think that's all I can actually say in these moments that I have. Thank you.

DR. SIEGAL: We will move on to Dr. Laurence Landow from FDA.

Agenda Item: Introduction

DR. LANDOW: Good morning, everyone.

[Slide] In July 2002, Biopure submitted a biologics licensing application, or BLA, using HBOC-201 for the treatment of anemia in patients undergoing orthopedic surgery. After reviewing data from 14 clinical trials, conducted in over 1,300 subjects undergoing all types of elective surgery, FDA did not approve the product, but issued a Complete Review Letter in 2003. This letter asked for clarification about how the trials had been conducted, as well as questions related to safety and efficacy.

Biopure has since decided not to pursue this indication for licensure of HBOC-201.

In June 2005, NMRC submitted the RESUS trial IND, a Phase 3 study using HBOC-201 in subjects with uncontrolled hemorrhagic shock, to be conducted under

exception from informed consent. This IND was placed on clinical hold because of issues related to safety, an inability to derive a numerical estimate of the treatment benefit from animal data, and heterogeneity of the expected mortality for individuals in the target population.

[Slide] The sponsor proposes to enroll approximately 1,100 trauma subjects in the urban ambulance setting with uncontrolled hemorrhagic shock, one-third of whom are expected to have concomitant non-penetrating traumatic brain injury. Any subject with penetrating head injury will be excluded.

The inclusion criteria of systolic blood pressure less than 90, Revised Trauma Score of 1 to less than 5, and age 18 to less than 70 mean that subjects to be enrolled in RESUS represent less than 1 percent of the admissions at large trauma centers.

[Slide] Clinical trial material, or CTM, will consist of either HBOC-201 or lactated Ringer’s solution. Because urban ambulance transport times are short, the sponsor expects that most RESUS subjects will have time to receive only two units, or 500 milliliters, of HBOC-201 over 10 minutes, with the actual rate to be determined by the EMS provider.

Subjects who continue to have a blood pressure under 90 or a blood pressure between 90 and 99 accompanied

by a heart rate greater than 100 can receive additional CTM, up to a maximum dose of 1,500 milliliters. Finally, infusion of clinical trial material will be permanently halted in any subject who experiences a blood pressure of 120 or greater.

[Slide] In subjects who have received 1,500 milliliters of CTM but still have a blood pressure under 90 or 90 to 99 with a heart rate greater than 100, additional standard-of-care solutions can be administered. Subjects with a blood pressure above 99 but who, in the judgment of EMS personnel, remain fluid-under-resuscitated can receive standard-of-care solutions if two or more classic signs of occult shock, such as thready pulse and decreased capillary refill, are evident.

[Slide] Upon arrival in the emergency room, no new bags of HBOC-201 will be hung. Subjects in both treatment arms are expected to require multiple blood transfusions. The sponsor has powered the trial based on the expectation that infusion of HBOC-201 in the ambulance will translate into a 15 percent relative reduction in 28-day all-cause mortality -- that is, from 58.1 percent to 49.4 percent, with an alpha of 0.045. As mentioned earlier, the sponsor proposes to conduct the RESUS under waiver from the requirement for informed consent.

[Slide] FDA has several safety concerns with the

RESUS trauma trial:

First, an increase in adverse events, including serious adverse events and death, was noted in the HBOC-201 treatment arm of Biopure's elective surgery trials and was apparent whether the control arm received red blood cells or crystalloid/colloid, or whether subjects were younger or older than 70 years of age. This excess in the number of adverse events in the HBOC-201 treatment arm could potentially be even greater in critically ill trauma subjects.

Second, the amount of clinical safety data provided to FDA to support the RESUS default infusion rate of 50 mL/min is extremely limited. For example, in the largest trial to date using HBOC-201, the mean infusion rate was 5 mL/min, and only four subjects received the product at a rate greater than 40 mL/min.

[Slide] Third, FDA has safety concerns over infusing a long-acting vasoactive product such as HBOC-201 in the ambulance setting. Because infusion of CTM will be titrated against systolic blood pressure and because many of the classic signs of occult shock are nonspecific for hypovolemia and have not been validated in hypotensive trauma patients receiving HBOC-201, EMS personnel could be misled into fluid-under-resuscitating HBOC-201 recipients.

In addition, since HBOC-201's vasoactive effects

can last for several hours, simply stopping the infusion may not prevent systolic blood pressure from continuing to rise. Because acute elevations cannot be medically controlled in the ambulance setting, hypertension triggered by the product could exacerbate blood loss in subjects with uncontrolled bleeding.

[Slide] Biopure is currently conducting study HEM-0125, a randomized, controlled Phase 2 trial of HBOC-201 for trauma subjects admitted to the emergency room in South Africa. So far, approximately 10 subjects have received the product plus standard of care and 10 have received only standard of care. While results from this trial should provide insight into the safety of administering HBOC-201 to trauma subjects in the hospital, the information will be somewhat limited for the purposes of RESUS:

• First, the study is small and, in addition, may not tell us what might occur with this vasoactive product when administered to trauma subjects in the field or urban ambulance setting.

• Second, HEM-0125 excludes subject with traumatic brain injury. In this subgroup, expected to comprise one-third of RESUS subjects, prolonged blood pressure elevations could exacerbate intracranial bleeding and lead to a rapidly expanding space-occupying lesion.

[Slide] In addition to safety concerns, FDA is concerned that the sponsor's numerical estimate of clinical benefit is based entirely on animal data. Although studies in experimental animals show the product delivers oxygen, there are inherent limitations in extrapolating survival data from animals to human trauma subjects.

Second, since urban ambulance transit times are relatively short and all RESUS subjects will receive multiple blood transfusions once they reach the hospital, the time available for the product to exert its effect is relatively brief.

Third, the rule mandating permanent termination of CTM in any subject with a blood pressure of 120 or greater raises the possibility that premature termination of HBOC-201 could result in subjects receiving too little product.

In another FDA presentation later this morning, Dr. Silverman will present data from a subgroup of 45 subjects in Biopure's pivotal orthopedic surgery trial who became hypotensive to a blood pressure under 90, which is also one of the entry criteria in RESUS, and were then randomized to receive either HBOC-201 or red blood cells. Nine subjects in the HBOC-201 arm, or 36 percent, experienced a peak blood pressure greater than 130 after infusion of 500 milliliters of product, compared to only

two subjects, or 10 percent, in the red-blood-cell arm.

Since most RESUS subjects are expected to require 500 milliliters of product, blood pressure responses to 120 or more could translate into an actual dose lower than that. This could result in HBOC-201 subjects receiving too little product to demonstrate a putative survival benefit when compared to lactated Ringer's.

Because of these concerns over safety and efficacy, FDA placed the RESUS trauma study on clinical hold.

I will now present FDA's questions to BPAC in preparation for the rest of the meeting.

[Slide] The first question is, please discuss the following safety concerns raised by FDA:

• Safety signals and adverse events in previous clinical studies;

• Demonstrated vasoactivity of the product;

• Limited safety data for higher doses and rates of administration.

[Slide] Question 2: Please discuss whether the available preclinical and clinical data are sufficient to estimate a treatment benefit for all-cause mortality at 28 days in the proposed RESUS trial.

[Slide] Question 3: After considering all available data, do the benefits outweigh the risks for

individual subjects in the RESUS trial?

[Slide] Question 4: Are there additional data that could help inform an assessment of benefit to risk in the RESUS trial?

[Slide] Question 5: Please comment on any modifications to the study design that might improve the benefit-to-risk ratio in the RESUS trial -- for example, a trial targeting a group with higher predicted mortality.

Thank you for your kind attention.

DR. SIEGAL: We are going to move on to the sponsor presentations. We will start with introductory remarks by Dr. Dan Freilich, commander, MC, U.S. Navy.

Agenda Item: Sponsor Presentation: Introductory Remarks

DR. FREILICH: Good morning. I want to thank the committee. In particular, Mr. Chairman, thank you so much for your time today. It is an absolute honor and a pleasure to talk in such a venue.

Dr. Goodman and Dr. Epstein, I would like to thank directly your staff for all the time that you have put into it, and in particular the two reviewers, who have spent an inordinate amount of time over the last few years, Dr. Landow and Dr. Silverman. Again, thank you so much for your time.

I am not going to spend much time here right. I

would like to just give you an idea of the discussion points over the next two hours by NMRC.

[Slide] After my brief introduction, Dr. John Mateczun, rear admiral, who is the deputy surgeon general, will talk about the importance of RESUS to the Navy and Marine Corps. Subsequently, Dr. Kaplan will talk about hemorrhagic shock and open the discussion with an academic setting. Next, Dr. Dutton is going to provide an overview of the RESUS study. Subsequently, Dr. Stern will provide a preclinical HBOC-201 study database summary. Dr. Greenburg will do the same for the clinical database. Then I will speak for about 60 minutes on the RESUS IND issues and the overall benefit-risk prediction issues. Finally, Joseph Acker will talk about the importance of RESUS to the EMS community. Finally, Dr. Kaplan will talk again about the importance to the overall civilian trauma community.

Without further ado, I would like to introduce Admiral Mateczun, the deputy surgeon general of the U.S. Navy.

Agenda Item: Importance of RESUS to the Navy and Marines

DR. MATECZUN: Good morning. I am probably the only speaker who won’t have slides today.

Chairman Siegal, Mr. Jehn, distinguished members of the Blood Products Advisory Committee, ladies and

gentlemen, Dr. Goodman, Dr. Epstein: Thank you for the opportunity to address you today regarding HBOC-201 and the Navy and Marine Corps interest. I'm Admiral John Mateczun, deputy surgeon general of the Navy, here representing the Navy surgeon general, Vice Admiral Don Arthur, who would have been here if he could.

We are here today to be expressive of our full support of efforts to deliberate the benefits and risks of HBOC-201 for prehospital trauma patients. We are fully committed to the development of an oxygen-carrying resuscitative fluid capability. Let me tell you why.

Despite advances that have increased the survival rates of military casualties on the battlefield, hemorrhage has been and continues to be a leading cause of death. Ninety percent of military trauma fatalities occur prior to the casualty reaching hospital-level care. In Operation Iraqi Freedom, as many as 68 percent of those fatalities have suffered severe hemorrhage as part of their injuries. Some of these lives could not have been saved even if a Level 1 trauma facility were immediately available. However, some would not have died if they could have received an oxygen-carrying substitute to sustain them immediately during evacuation and until they could receive blood transfusions.

This is especially important in close-quarter

urban combat and in other situations, such as special operations, where evacuation may be dangerous, delayed, or both. We urgently need an oxygen-carrying capability that does not require refrigeration, is universally compatible, and can be readily administered in a field setting. This is a capability that HBOC-201 could provide.

Today you will weigh questions of safety and efficacy, potential risks and benefits of HBOC-201 administration for prehospital hemorrhagic shock patients. There are risks. There are inherent risks in all of medical practice, and we are ethically obliged to assess those risks in relation to the benefits for our patients. A question for this clinical trial is whether the predicted benefits of HBOC-201 administration in a prehospital scenario outweigh the potential risks.

In terms of benefit, we believe that many lives might be saved in Operation Iraqi Freedom with this capability. It would be worth our collective efforts if it ultimately saved the life of only one of America’s sons and daughters that our country has put into harm’s way.

The Navy has aggressively pursued an oxygen-carrying capability for many years. The investment of Defense Department resources and the countless hours of work by our top physicians and researchers underscore our commitment to achieving an effective product. The Naval

Medical Research Center has diligently forged a broad-based collaboration with the private sector and academia to bring depth of medical and scientific expertise to this urgent problem. An FDA-approved oxygen-carrying resuscitative fluid would serve as an important trauma tool in both military and civilian settings to optimize resuscitation of casualties with hemorrhagic shock.

We welcome your expert medical and scientific review of this product and our proposed research protocol. We look forward to your recommendations and hope to move forward with this important emergency research.

On behalf of all the Navy and other military medical providers who work daily to save the lives of our injured, we greatly appreciate your efforts.

I would now like to introduce Dr. Lewis Kaplan, director of the Surgical Intensive Care Unit and the Surgical Critical Care Fellowship at Yale University School of Medicine.

Agenda Item: Hemorrhagic Shock: Pathophysiology, Clinical Presentation and Current Treatment

DR. KAPLAN: Thank you, Admiral. Good morning.

[Slide] Allow me to direct your attention to the root cause of the RESUS Trial, hemorrhagic shock. What we will do in the next few minutes is talk about

pathophysiology, how this is identified in the field, some initial goals, and then use those to construct a resuscitation paradigm that is absolutely targeted to improve survival.

[Slide] Hemorrhagic shock results from acute blood loss. There are a wide variety of causes, but chief on this list is trauma. That's why we are here today. But certainly hemorrhagic shock arises from a multitude of events that may occur in and outside of the hospital.

[Slide] Acute blood loss reduces both the red cell mass and the plasma, which is the circulating volume. This leads to impaired oxygen delivery to the tissues and an imbalance between the demand and the available supply.

[Slide] This imbalance leads to anaerobic metabolism. We detect this biochemically as an elevated lactate level. But the cellular result is that of hypoxia. This is compounded by the adaptive and effective central shunting of blood to protect cardiac and cerebral blood flow.

[Slide] Hemorrhagic shock is readily classifiable into four different categories. This is a table that is lifted from the Advanced Trauma Life Support book in 2004. You have Classes I through IV and a variety of descriptors, all of which are readily identifiable and objectively quantifiable, that help one to understand how

much blood has been lost. I will direct your attention specifically to Classes III and IV, which are outlined in green. These are the classes of most accelerated hemorrhage. These are the classes that have a different mechanism and a different manner of therapy. I will direct you right down to the bottom, where fluid therapy is identified as crystalloid for the first two classes. This is the standard of care that is carried on the ambulance and delivered in the emergency department initially. But for these two classes, it's IV fluid, which is crystalloid, plus blood transfusion. These are the target patients for RESUS.

It also provides a therapeutic intervention opportunity.

[Slide] But we have to identify these patients. In fact, these triggers are identifiable and discoverable by all of the EMS providers. It is what is taught to them in their national training curriculum: tachycardia, hypotension, the use of physical examination to detect that central shunting of blood, as well as multiple manifestations, including a diminished mental status. That is the end result of progressive shock. This is readily discoverable by all EMS providers, regardless of skill level.

[Slide] The intervention opportunity here is to

avoid the sequelae of unrelieved, uncontrolled hemorrhagic shock. Remind yourselves that in the field definitive control of hemorrhage is not possible for most injuries. So you are targeting an intervention that can act as a bridge. Survival, as we know, is related to the rapidity of hemorrhage control. There are some timelines and guidelines for how long that can go on without untoward sequelae. There are a number of difficult areas where reaching definitive control is problematic -- the military environment, as we have heard from the admiral, and certainly rural civilian trauma. So how do we keep these patients alive to reach definitive care? That will be the subject of the rest of the trial.

[Slide] But when they get to us, there is some very standard therapy: airway control, breathing, circulation, evaluation for neurologic deficits, and exposure control. These are all laid out in Advanced Trauma Life Support. The provision of supplemental oxygen and resuscitation with standard-of-care crystalloid fluid, plus red blood cells as needed for hemorrhagic shock, goes on in a very standard fashion. There are some laboratory and radiologic investigations, all of which are directed at identifying life-threatening problems.

[Slide] We are able to use a variety of techniques to identify when our therapy has not yet been

successful. These are key: vital signs, physical examination correlates, estimates from a variety of catheters, such as urine output. We can assess acid-base levels and a variety of derived indices that correlate with shock.

But when we don't have the kind of response that we would like, the resolution of shock, we are also able to ask, how well did we do? Do we need invasive monitoring? There are a variety of techniques that are readily brought to bear, sometimes in the trauma bay, but quite often in the operating room or the intensive care unit. These are not available in the field.

[Slide] In the field, we have two things. We have external hemorrhage control and we have resuscitation, including airway control. But our current standard is crystalloid. This does not carry oxygen. This does not provide red blood cells. It does not provide clotting factors. We know that it is immune-activating. Large volumes will dilute clotting factors and your red cell mass. It may, in fact, induce an acidosis at the same time that acidosis is what you are combating.

Not all of it remains in the vascular space -- in fact, only a small proportion. This leads to very large volumes of fluid required for significant resuscitation in these already hypotensive and hypovolemic patients. This

is inconsistent with the concept of small-volume resuscitation, and large volumes may, in fact, accelerate hemorrhage prior to definitive hemorrhage control.

[Slide] There are at least two solutions that are currently available for small-volume resuscitation. One is a 6 percent hydroxyethyl starch in a balanced salt solution. This is currently carried by special-forces operatives and it is used at civilian trauma centers. Hypertonic saline is also available. However, this has some limitations, based on induced electrolyte abnormalities, and has its best role, perhaps, in traumatic brain injury.

But neither addresses the pathophysiology that we have reviewed -- loss of red cell mass and plasma volume.

[Slide] The optimal fluid should be small-volume, repeatedly dosable, should not induce electrolyte abnormalities, and should augment oxygen-carrying capacity. These elements would help reverse and target the pathophysiology of shock. This is the prototypical design for a hemoglobin-based oxygen carrier, and this trial seeks to employ HBOC-201.

[Slide] The reason is very clear. It is demonstrated in this graph. These are data from Abramson, in 1993, looking at the rate at which people clear lactate, a biochemical marker of shock, and how well they survive.

I will call your attention to this group, where 100 percent survived if they cleared their lactate by 24 hours. This is part of the reason we wish to use an oxygen carrier. One cannot clear lactate until one has reversed the anaerobic metabolism. You need oxygen to do that.

But we will recognize that HBOCs have vasoactivity. We must guarantee that there is adequate resuscitation. This trial has taken a huge number of steps to ensure that.

[Slide] This is a schematic of the fluid resuscitation algorithm that is in place for this trial. This is the in-hospital portion. Patients have hemorrhagic shock at the start and they are either continuing to bleed or not. If they are not continuing to bleed, they undergo regular hemodynamic reassessment, just like all of our patients, clinically, do now. Those who are bleeding need ongoing standard-of-care resuscitation. They may need some operative or interventional radiology support. Once they have achieved temperature control, they get reassessed. We look for all of these things. We ask whether we have achieved our goal. If not, there are options for invasive monitoring to answer these questions: Are we volume-depleted, volume-replete, or, in fact, are we overloaded (rather uncommon in this patient population)?

[Slide] The color scheme is consistent. There

are guidelines for what to do with volume depletion, again using standard-of-care solutions, with an acute hemoglobin goal of 8 to 10. If we are replete, we ask, is the cardiac performance adequate? If the answer is no, we go back for more resuscitation. If it is yes, we reevaluate. If we are overloaded, diuretics after load reduction may be appropriate. We have a lower hemoglobin goal in the patient who has achieved his endpoint. The goals here are optimization of cardiac performance. You can see how we intend to assess those.

[Slide] It is not enough to simply prevent people from dying acutely. This is a schematic looking at mortality as a function of time. In yellow you see death from the injury that may occur in the early phase of hospitalization. But we are also looking later, out at 28 days, asking, have we helped patients to survive from abrogating the sequelae of unrelieved shock -- namely, multi-system organ failure? So we are looking at each of those aspects of the trial as well.

[Slide] I will leave you with these conclusions. There is a known pathophysiology. We have reviewed that. This should describe a target intervention. We know from extensive trauma data that survival is enhanced with early hemorrhage control and resuscitation. This is a prehospital intervention, to help us achieve those goals.

It addresses pathophysiology and I believe is a sound approach to improving survival and minimizing morbidity.

I will introduce Rick Dutton, chief of trauma anesthesiology, at the R. Adams Cowley Shock Trauma Center.

Agenda Item: Overview of RESUS Study

DR. DUTTON: Good morning. Welcome to my friends, my colleagues. For those who don't know me, I'm Rick Dutton. I'm the chief of anesthesia at the Trauma Center in Baltimore, the busiest trauma center in the United States-- and for those of you who have to get on the beltway this afternoon, fortunately, one of the best. [Laughter]

I have been interested in resuscitation research my entire career. I came to the Trauma Center 12 years ago specifically to study resuscitation and the care of sick and dying patients.

[Slide] Our objective in this trial is to compare HBOC-201 with the standard of care, lactated Ringer's solution, for prehospital resuscitation of patients with severe hemorrhagic shock -- so resuscitation in an environment where we don't have access to blood products.

[Slide] The trial design -- and you have heard some of this from Dr. Landow, so I will go quickly: A Phase 2b trial, part one, to assess the feasibility of

trial protocols, iron out the bugs, 50 subjects; assuming that is going well and the protocol is working, a Phase 3 trial of 1,100 subjects to demonstrate, hopefully, a prehospital benefit with HBOC-201.

[Slide] Inclusion criteria: Adults 18 to less than 70 years old; injury with suspected bleeding; systolic blood pressure less than 90; a Revised Trauma Score -- and I will talk a little more about this in a second -- 1 to less than 5; planned transport to a study hospital; with IV access.

Dr. Landow mentioned that this is only 1 percent of our trauma patients. He is exactly correct. This is the 1 percent that we are most interested in. I teach my residents when they arrive at the Trauma Center that 95 percent of the people we take care of will survive and do well in any hospital, in almost any environment. Three percent or 4 percent will die no matter what. Some things just kill you. It’s the 1 percent in between that represents that cutting edge of medical practice and the advancement of care. This is the population we are interested in. This was brought home to me Tuesday morning, on my way out the door to go to California to lecture, which I almost didn’t make it back from. My boss was in the operating room with a state police officer who had been shot serving a warrant that morning. Some of you

may have seen this in the news. This is the kind of patient we are trying to take care of.

[Slide] The Revised Trauma Score can be calculated by medics in the field. In Maryland, it's part of the Maryland ambulance information sheet. It's basically calculated as they write the vital signs down on the sheet. It includes blood pressure, respiratory rate, and the Glasgow Coma Scale score for neurologic function.

[Slide] Exclusions for the trial: There are two important ones. The biggie is short transport time. We don't intend this therapy for situations where blood is available. If you are shot serving a warrant in downtown Baltimore, you are in the Trauma Center in five to 10 minutes and have access to blood products immediately. As you can see, the protocol is written so that if the transport time is going to be less than 10 to 15 minutes, the patient is not enrolled, unless, in the medic's judgment, they are critically injured, bleeding very severely, and with very unstable vital signs. We have left that area a little bit gray specifically because we trust the medics' judgment in this respect.

[Slide] Other exclusions: penetrating brain injury; spinal cord injury; known pregnancy; burns; cardiac arrest; allergies; and I should point out, any objection to prehospital research, any expressed objection to this kind

of trial; and, as I said, a short transport time.

[Slide] The prehospital procedures: The medics will screen the patients, basically calculate the RTS, determine if this is a patient who is eligible for trial. This is part of their routine care and happens as they are taking the patient's vital signs. To the extent possible, they will disclose that a clinical trial is under way. Waiver of informed consent is a very complex topic, obviously. I will talk a little more about that as we go along. But the first step is simply notifying patient or family that there is a trial under way and giving them the opportunity to express an objection to it, if they have one, or understand that. Many of the patients we enroll in this trial, as those of you who are familiar with the Revised Trauma Score know, will not be conscious, will not be able to consent, or even communicate, at the time they are enrolled.

Once the patient is included in the trial, they receive trial product infusion, either 500 mL of HBOC-201 or the standard of care, a bolus of Ringer's lactate. You have already heard the requirements for stopping and starting that along the way. Again, we trust the paramedics to follow the patient's vital signs and adjust the therapy in accordance with how the patient is doing. That's no different than they do today.

[Slide] There is a clearly spelled-out algorithm for the medics. I don't expect you to read this. This is here to illustrate that it's there.

[Slide] Once the patient arrives at the hospital, any incomplete trial product is finished and the patient receives routine care. Whichever group they are enrolled in, the standard of care is the standard of care, and they get the best practice from that point forward, including the use of uncrossmatched red cells, damage control surgery, acute resuscitation, critical care, and so on.

The informed consent process continues through this. As we have the opportunity to talk with the patient as he awakes or the family as they arrive, we will continue to present information to them about the study, answer their questions, and move forward on consent.

[Slide] We have written guidelines -- and you have them in your appendix -- for fluid resuscitation, for blood composition, for use of pressors and inotropes, and for management of brain injury. All of these are what is in the literature now as the current evidence-based standards for care in these areas.

[Slide] The primary outcome of RESUS is reduced 28-day mortality. It can be nothing less for a waiver-of-consent trial. Obviously, the product has to be safe and

tolerable.

[Slide] In any clinical trial of this magnitude, particularly in as difficult a logistic setting as prehospital care, we are going to capture every variable we can from the patients. We have a long proposed list of secondary endpoints. We are not going to throw away any data we can get on these patients. You can see those here.

[Slide] The consent process I have already mentioned. The study will need to be done with an exception from informed consent. We intend to conduct community consultation and disclosure. We have presented plans for that. We expect to work closely with local IRBs to go through this process in individual communities.

As I have already alluded to, we feel that this kind of consent mechanism needs to be an ongoing process, beginning with notification pre-enrollment and continuing in discussions with the patient and family throughout the patient's care, with the option to withdraw from the study at any time.

[Slide] There will be a Web site. You can see an example of this here. We intend to be as transparent as possible with the public and put the information on the study where they can find it and where their questions can be answered.

[Slide] These are examples of some screens

discussing side effects and potential complications of the therapy.

[Slide] This is what the script looks like that we are going to provide the medic with:

• You appear to have severe bleeding. You're in shock. You need treatment.

• As part of a research study, we are testing a new fluid.

• This research study has been approved by our hospital.

• There are risks, but we wouldn't be doing the trial if we didn't think it was beneficial.

• Unless you object, you will be included in the trial and will get either the trial product or the standard of care.

• If you do not want to be in the trial, we will take care of you the best way we know how.

• Tell us immediately.

As you can imagine, even that amount in the prehospital environment is a lot. That's a lot to do. It's a busy time. There is a lot going on. As one of my predecessors, I guess, Dr. Cowley, said, it's the golden hour for hemorrhagic shock.

[Slide] There will be a DMC to monitor the results of the trial, reviewing both efficacy and safety

endpoints. You can see the planned interim analyses.

[Slide] The stopping criteria for the trial: There is an absolute stopping criterion if we demonstrate a benefit of the product. That is appropriately adjusted for boundary conditions and small numbers of patients. You can look at the statistics in the complete plan.

[Slide] There are stopping criteria for safety endpoints. I will abbreviate this to basically say that if the product is not showing a benefit, but is showing a serious adverse side effect or a worsening of one of the key surrogate measures, then we would stop the trial.

[Slide] In summary, RESUS is a pivotal trial of HBOC-201 for prehospital resuscitation of severe hemorrhagic shock. The comparison is in the prehospital environment with the current standard of care, which is asanguinous fluid infusion. The trial will not alter in any way the care of the patient once they arrive at the hospital. Because of the nature of this trial, it will involve exception from informed consent. The trial, with 1,100 patients, has been powered to demonstrate a 15 percent reduction in the relative risk of death in this very highly lethal condition.

Thank you very much.

I will now introduce Dr. Susan Stern from the University of Michigan, another lifelong resuscitation

researcher, who is going to go through some of the preclinical or basic science studies related to HBOC-201.

Agenda Item: All Preclinical HS/Traumatic Brain Injury Studies

DR. STERN: Thank you. Good morning.

I am going to present the preclinical data today from trauma-related studies of hemorrhagic shock with hemoglobin-based oxygen carrier 201.

[Slide] HBOC-201 has been comprehensively evaluated in 22 trauma-related studies of hemorrhagic shock. These studies were conducted using a very wide variety of very complex models, as shown here, including controlled hemorrhage models, ranging from very mild to very severe, uncontrolled hemorrhage models, in which animals received either a severe liver or arterial injury, and models that combined both traumatic brain injury and hemorrhagic shock.

While no single animal model can replicate the wide range of injuries observed in the clinical setting and the heterogeneity of the trauma population, the breadth of the models used in these studies, we believe, provides a comprehensive evaluation of the effects of HBOC-201, and in models that very closely simulate the pathophysiologic processes observed in trauma patients. These models collectively address the range of physiologic conditions

that are expected in the RESUS trial and demonstrate a very thorough evaluation of HBOC-201 in hemorrhagic shock.

[Slide] The majority of these models used anesthetized pigs. The simulated prehospital phase in these studies ranged from 30 minutes to eight hours, while the simulated hospital phase from hours to days, once again covering a very wide range of physiologic conditions. As just described, this model development is consistent with the RESUS trial. For your reference, in the prehospital phase, animals received only HBOC-201 or the control prehospital fluid, and it was only once they reached the simulated hospital phase that they received transfusion, as well as intensive care unit and surgical intervention, as appropriate.

Both bolus and continuous infusions were studied in these trials. The animals were resuscitated to a target mean arterial pressure.

There were some studies that also utilized heart rate as a trigger for reinfusion of HBOC-201 or the control solution.

Also shown on here is the total dose and infusion rates for HBOC-201 in these studies. As you can see, they are representative of what is proposed for the RESUS trial.

[Slide] I will present data from several very comprehensive and representative studies. Obviously, I

cannot present data from all of the trials. These data will demonstrate HBOC-201's effects on survival, hemodynamics, tissue oxygenation, blood loss, and organ function.

[Slide] First we are going to talk about survival. In the following slides, the HBOC-201-treated animals are represented in red, while the control animals are represented in blue.

[Slide] In a combined analysis of 14 utilizing 229 pigs, in which survival was a primary outcome, survival was significantly greater with HBOC-201 as compared to standard resuscitation fluids.

[Slide] This slide shows the survival data from those 14 individual studies. On this slide the less severe hemorrhage models are presented on the left, while the more severe hemorrhage models are presented on the right. What is striking is the tremendous survival benefit seen with HBOC-201 in these more severe models.

[Slide] Now let's look at hemodynamics. In these next slides, I will present data from five representative studies.

[Slide] Once again, on these graphs, those shown on the left-hand side of the slide represent a moderate severe hemorrhage; those on the right-hand side of the slide represent a severe hemorrhage model. In these

studies, the dashed horizontal line represents baseline for HBOC-201 for the parameter on the slide. The dark vertical line represents the end of the prehospital phase, the beginning of the hospital phase.

Again, once the animals reach the hospital phase, only then can they receive transfusion. Prior to that, they only receive HBOC-201 or the control fluid.

On this slide, what we see is that mean arterial pressure was significantly improved with HBOC-201 as compared with control animals. Also of note and importance is that small-volume infusion of HBOC-201 resulted in restoration of baseline blood pressure, but, in contrast, standard fluid resuscitation failed to restore blood pressure. In the more severe models, again, what you see is that standard fluid resuscitation even failed to restore blood pressure back to levels capable of maintaining vital organ perfusion.

[Slide] In general, mean pulmonary artery pressure was greater in HBOC-201 as compared to control animals. HBOC-201 infusion resulted in an increase of approximately 5 to 10 mmHg above baseline. This has been reported in several other studies. These changes are not likely to be of clinical significance, as there have been no observations of associated hypoxia or pulmonary edema in these studies.

[Slide] There was a relative reduction in cardiac index with HBOC-201 as compared to controls. However, in the five studies shown here, these differences reached statistical significance only in this one study. Even in that study, what you see is that cardiac index actually returned to above baseline in the HBOC-treated animals. While there are other published data showing a lower cardiac index in HBOC-201-treated animals, even in those studies cardiac output returned to baseline values in the HBOC-treated animals.

[Slide] The next several slides will look at tissue oxygenation, markers of tissue perfusion.

[Slide] In general, what we saw was that transcutaneous tissue oxygenation was significantly greater with HBOC-201 as compared to control groups in all studies.

[Slide] Other studies that have invasively measured tissue oxygen tension demonstrate improved brain, deltoid, and intestinal tissue oxygenation. In the one study by Knudsen, liver oxygen tension levels did trend lower in HBOC-201 as compared to controls, but those differences were not statistically significant.

[Slide] Arterial lactate levels were significantly lower with HBOC-201 in the severe hemorrhage models, again on the right. Other studies have also reported correction of the lactic acidosis and reversal of

anaerobic metabolism with HBOC-201.

[Slide] With regard to blood loss:

[Slide] HBOC-201 infusion did not increase hemorrhage volume in the setting of uncontrolled hemorrhage. Therefore, despite the mild to moderate vasoactivity, as demonstrated by slightly higher systemic and pulmonary pressures, preclinical data do not suggest increased hemorrhage with HBOC-201 resuscitation.

[Slide] The next slides will talk about organ function and histopathology.

[Slide] Three papers shown on this slide provide data on the effect of HBOC-201 on organ function and histopathology. Together, these papers looked at heart, lung, kidney, and lung. Histopathologic changes and hepatic enzyme elevations were greater with HBOC-201. This was seen in both studies by Johnson and York. The elevations in LFTs were transient and relatively mild, and they returned to normal by approximately 72 hours.

Johnson also observed slightly greater histopathological changes in the kidney with HBOC-201. This was not seen in the other studies.

The findings by York et al. were inadvertently omitted from your hard-copy slides. I apologize for that.

The next several slides show data from studies of the effects of HBOC-201 in the setting of combined

hemorrhagic shock and traumatic brain injury. This is a very special and important patient population that really might stand to benefit the most from small-volume resuscitation with a hemoglobin-based oxygen carrier. That's because morbidity and mortality from brain injury are significantly enhanced in the setting of hemorrhagic shock. The hemorrhagic hypotension results in a secondary ischemic insult to the injured and vulnerable neurons, essentially potentiating the initial primary insult.

[Slide] Hemoglobin-based oxygen carriers might reduce this process by enhancing oxygen delivery to the brain tissue.

A second potential advantage of initial resuscitation with an HBOC for these patients is that the volume-sparing properties of this approach might avoid the increases in intracranial hypertension that are commonly found to occur with large-volume resuscitation, which is the current standard of care.

[Slide] There are, however, some concerns with the use of hemoglobin-based oxygen carriers in these patients, and those do center around their vasoactive properties. First, any increase in vasoactivity might result in an increase in hemorrhage from as-yet-uncontrolled extracranial injury sites. Second, if significant cerebrovasoconstriction does occur, this might

cause a reduction in oxygen delivery to vulnerable neurons and brain tissue, and therefore worsen outcome.

[Slide] To address these issues, several fairly comprehensive studies of the effects of HBOC-201 in models of combined hemorrhagic shock and traumatic brain injury have been performed. All but one of these studies used swine. The hemorrhage insults ranged from moderate to severe. Three of these studies used a controlled hemorrhage model, while the fourth utilized a combination of uncontrolled hemorrhage and traumatic brain injury.

I am going to focus on the last study, the uncontrolled hemorrhage-brain injury study. This study, in fact, was specifically requested by the FDA.

[Slide] In this study, uncontrolled hemorrhage was inflicted via liver laceration. The brain injury was via a fluid percussion model. There were two arms to this protocol. In the short-delay cohort, prehospital time was 30 minutes, while in the long-delay cohort, prehospital time was 75 minutes. The animals were randomized to receive HBOC-201 or LR during the prehospital period, as shown on this slide.

On the following slides, what you will see is that the short-delay cohort is on the left and the long-delay is on the right.

[Slide] As you can see on this slide, survival

was significantly improved with HBOC-201 for the long-delay cohort. There was on significant difference in survival for the short-delay cohort.

[Slide] We studied several markers of cerebral perfusion, all of which were significantly improved with HBOC-201. As you can see here, with regard to cerebral perfusion pressure, there was a significant and sharp increase in cerebral perfusion pressure immediately following the first dose of HBOC infusion. This increase in cerebral perfusion pressure was maintained throughout the study in the long-delay cohort.

We saw a similar pattern with the sagittal sinus oxygen saturation -- that is, a sharp increase initially.

[Slide] We also measured brain tissue oxygen tension. Again, we found a sharp increase in brain tissue oxygen tension immediately following HBOC infusion. Once again, this difference was maintained throughout the entire protocol in the long-delay cohort.

[Slide] Other studies of combined hemorrhagic shock and traumatic brain injury have been able to reproduce our findings. Data from other studies are shown in this table here. You can see that Rosenthal and Patel both showed increased cerebral perfusion pressure and brain tissue oxygen tension. Dr. Rosenthal and Dr. Kerby’s studies also looked at neuronal cellular degeneration and

contusion volume, respectively, both of which were decreased, suggesting that there is further evidence for a reduction in the secondary ischemic injury in the HBOC-treated animals.

In other words, there is no evidence that the mild vasoactive effect of HBOC-201 compromised cerebrovascular perfusion. These data actually suggest that HBOC-201 may be protective in the setting of combined hemorrhagic shock and traumatic brain injury.

[Slide] In summary, despite the fact that there were occasionally mild adverse effects observed with HBOC-201 in some of these studies, the preclinical data demonstrate an overall marked improvement in multiple outcome parameters, including survival, a more rapid stabilization of hemodynamic parameters, improved tissue oxygenation, and decreased anaerobic metabolism. This was true across a wide range of hemorrhagic shock models and in the setting of traumatic brain injury. In these studies, the mild vasoactive effects of HBOC-201 did not result in significant morbidity, and HBOC-201 consistently demonstrated significant and marked beneficial effects, including greatly improved survival.

Thank you for your time. I would like to now introduce Dr. Gerson Greenburg, vice president, medical affairs, from Biopure.

Agenda Item: HBOC-201 Clinical Studies Analysis

DR. GREENBURG: Good morning, ladies and gentlemen.

Only recently, about seven months ago, after 35 years in academic surgery, I retired, but had an opportunity to join Biopure, for the simple reason that, having worked in the development of blood substitutes, hemoglobin-based substitutes, et cetera, I had an opportunity to help bring to active application an oxygen therapeutic that, over my 35 years of clinical experience in trauma critical care, et cetera, would have helped some of the patients that I had seen whom I couldn't help -- patients I saw who needed extra oxygen delivery in order to get them through a problem.

My retirement was indeed short-lived.

[Slide] I am going to give you an overview of the clinical trials of HBOC-201. There have been 22 trials, including over 1,500 patients. These trials fell into the usual Phases 1/2, 1 and 2, 2 and 3. Phase 3 had a pivotal trial in orthopedic surgery, which I will tell you a great deal about. The Phase 1 trials were basically safety trials. The Phase 2 trials were in a variety of surgical settings that we will talk about. This slide also includes the patients in a percutaneous cardiac intervention trial that was completed, just for

completeness. This slide does not contain the data from the 125 study that you heard about a little earlier.

[Slide] Looking at these trials in another way, we can see that some of them were uncontrolled Phase 1 trials. There were colloid-controlled trials, there were crystalloid-controlled trials, and there were some red cell-controlled trials. It's important to observe that the three uncontrolled trials -- five studies were colloid. All of these studies ended up, for the most part, in the Phase 1, 1 and 2, and 2, getting blood at some point off of the protocol. There are many differences in these groups, dealing with different dosing, different blinding schema, different randomization schema. Some were uncontrolled. They make sort of a complex of trying to understand all of these data.

[Slide] With reference to RESUS, it's important to note that in the overall view of all these trials, 87 percent of the patients received six or fewer units. That is the top dose proposed in RESUS. In the 115 trial that I am going to talk about, approximately 81 percent of the patients received six or fewer units. So it makes it a comparable group. It's an important distinction because RESUS is using the six or fewer units.

[Slide] It's very important, obviously, to do a quantitative analysis, a quantitative assessment, for

detection of safety signals. It is our belief that to fully understand the emergence of safety signals, it's necessary to approach this quantitatively and to minimize the subjectivity. The conditional tables in the briefing document represent raw data from which signals can be extracted. Because RESUS is designed to effect an improvement in mortality as opposed to an avoidance of a blood transfusion, we have chosen to concentrate our analysis of the significant adverse events and the profiles of these according to the MedDRA and system organ classification documentation. Because of a higher-risk tolerance in trauma situations for products, procedures to be introduced, all of the adverse events in a mortality trial are appropriate to consider.

We are going to, for a variety of reasons, concentrate mostly on the 115 trial, because this is the most homogeneous and sufficiently powered trial -- 44 percent of all the subjects in our experience -- that will give an accurate and quantitative assessment of risk. We believe this is the safest approach to use.

[Slide] Phase 3 orthopedic trial HEM-0115 is the largest trial, 688 patients, 350 of whom received HBOC. It was powered to detect a 1 to 2 percent difference in AEs between treatment groups. Safety was evaluated by the signals, as well as significant differences. Any safety

signal seen in all of the studies put together were also seen in HEM-0115. That is a very, very important point to make.

I should indicate that efficacy in this trial was transfusion avoidance. I will make reference to some of that in a moment.

[Slide] The overall pattern of serious and non-serious events, as detected in HEM-0115, is shown here. On your right is a column that represents the percentage, the rate, of these events in the overall database, and on your left, the column represents the rate or incidence of these events overall in the HEM-0115 trial. It's important to note that they are statistically significantly different. But what is really important is that the HEM-0115 represents very clearly the same population as the overall database. However, while the rates may be the same, the distribution of events within the two groups may indeed be different.

[Slide] This is a cartoon of the HEM-0115 trial. We have to spend a little time on this, because it's important. Patients who were randomized to the HBOC arm of the trial achieved a 60 percent transfusion avoidance at 42 days, well in excess of the actual predicted amount of transfusion avoidance. Of note, relative to resuscitation, 95 percent of the patients in this arm of the trial avoided

a blood transfusion in 24 hours. RESUS is looking for treatment within an hour.

On average, 40 percent of the patients in the HBOC arm at four days became treatment failures and thus received two treatments, falling into this group, where they received both HBOC and red cells. It is this group of patients where most of the adverse events -- and significant adverse events -- of the 115 trial are indeed concentrated. This becomes an important difference, because factors which differentiate this group from the rest of the group form an interesting subset that needs to be explored. We will show you some of the reasons for this difference in a moment.

This group got both treatments. An average received red cells four days -- an average for the group -- four days after they were randomized to the HBOC arm of the trial, demonstrating that at that time they needed an increase in oxygen-carrying capacity and received both forms of therapy. The red blood cell and HBOC group represents a bridging concept. That is, from the time the initial decision to treat the patient to the time they received red cells represented bridging, and this average of over 100 hours is roughly 100 times greater than that expected within the RESUS trial.

[Slide] There are factors that differentiate

this group that received both treatments from the HBOC-only group: total fluid crystalloid administration; total red blood cells administered; a higher estimated blood loss; longer anesthesia time -- you can read these. A simple statistical comparison identified these differences in a variety of these parameters, as well as some that we will show in a moment. These are some of the examples.

[Slide] Here are other examples of these variables and parameters in which there were differences.

I would like to point out that there were differences in this group between total adverse events, total SAEs, and SAEs per patient -- another way of looking at this issue.

[Slide] Why were these differences there? These are some of the contributors that led to the imbalance seen between these two groups: under-resuscitation/under-treatment; delay of adequate treatment; volume overload; trying to chase transfusion avoidance -- if that's the objective of the exercise, that may be what you want to do -- and where needs possibly exceeded the limitations of the protocol, and possibly the limitations of the product.

What is important is that these are unlikely to be seen in RESUS because of the shorter time for bridging -- an hour or less. Moreover, recognizing these basic issues permits a better design of mitigation

strategies, which my colleague Dr. Freilich will talk about in a few minutes.

[Slide] I would like to move on to some specific data, particularly age data. Age-dependent events are very important. Here we have patients greater than 70 and patients less than 70. We look at the SAEs in cardiac, nervous, and death. There is statistical significance at the cardiac level. We should point out that this exists only in the patients over 70 and that the RESUS trial deals with this by eliminating that group of patients.

[Slide] This series of slides represents, on the top line, the MedRA system organ classification and the areas underneath are the preferred terms. I will go through these quickly and draw the conclusion that at the system organ class, there are differences between the groups in all subjects. However, when you look at patients less than 70, the target population of RESUS, these results are not maintained.

[Slide] This is another set of serious cardiac events. The top line is the same. These are other variables shown in there -- again, no difference when you break it by age.

[Slide] Renal serious events. There are no differences when broken by age. There are no differences in the organ class level.

[Slide] The same is true when we look at CNS. There is a slight difference in the all-subjects group, but it disappears when we break this trial on the basis of patients less than 70.

[Slide] Respiratory system has a potential area of interest in respiratory failure. This may be treatment failure or overdoing with a fluid resuscitation.

[Slide] Hepatobiliary system: There are no differences.

[Slide] Changes in systolic blood pressure have been talked about. We believe these will occur. They are all manageable and have been manageable in all of the trials. Changes in the systolic blood pressure are there. In our experience and the experience of our investigators, this has all been relatively easily managed. The incidence of true malignant hypertension has been minimal.

[Slide] Let’s look at liver function activity over a period -- another question. Anyone familiar with the history of intravenous hyperalimentation from the 1960s and 1970s will note that this is pretty much what happens to liver function when you give the body a load of protein. The liver knows how to handle this and simply manages it by raising the level of its enzymes and, over time, decreasing them.

[Slide] Lipase activity: One patient had some

evidence of pancreatitis. Most of the patients did not. This is an unexplained event. One patient in the entire series had what might be considered clinical pancreatitis.

[Slide] Looking at the renal function, another area of concern, there are no changes over time in the 115 trial in the BUN and creatinine, when we compare the red cells to the HBOC.

[Slide] Conclusions: In 22 trials, 826 patients have received HBOC. Eighty-seven percent of the clinical experience is with six units or less of the proposed infusion dosing for RESUS. In HEM-0115, the clinical trial, there was a reduced allogenic blood cell use, close to 60 percent at day 42 and 95 percent at 24 hours, relevant to RESUS. There was a greater incidence of AEs and SAEs. We noted that. There was a greater incidence of cardiac and CNS AEs. We noted that. But we also noted that that was pretty much age-dependent, based on a variety of factors, which could be expounded on. The age-dependency reduction of SAEs for all of these things is appropriate and has been mitigated by the design of the RESUS trial.

A recommendation for continued monitoring is clearly part of the development of mitigation strategies.

[Slide] Finally, if I can leave my role at Biopure and give a personal note, given that there is a

reasonable risk associated with the use of HBOC -- no one denies it -- and the potential benefits to patients in hemorrhagic shock are really quite apparent, there are compelling reasons to lift the clinical hold and permit this trial to go forward.

My colleagues and I will be happy to answer questions. Thank you very much.

DR. SIEGAL: Thank you.

I think we will take a break for 10 minutes. Try to be back by 10:00 to reconvene.

[Brief recess]

DR. SIEGAL: We have a little bit of time for questions of clarification from the committee to the presenters so far. After the sponsor presentations are concluded, we will take a little bit of a break for that also.

DR. FLEMING: Dr. Siegal, while people are reconvening, I was just looking at this schedule, too. I have probably eight to 10 questions, myself, that I have accumulated here.

DR. SIEGAL: These are just clarification questions?

DR. FLEMING: No, not always. Sometimes yes, sometimes no.

DR. SIEGAL: Because some of the questions we

should probably reserve for the deliberations.

DR. FLEMING: Essentially, that was my question to you. Are we going to have a good opportunity to interact with and query both the sponsor and FDA presenters about what they are presenting, in addition to the general discussion? Generally, do you want a lot of that to be done at 2:30 to 6:00 today?

DR. SIEGAL: Yes, that will mostly be in the committee discussion, if I understand the format.

DR. KLEIN: But will the presenters be here so that we can -- I have some questions that I really would like to ask the people that just showed us the data.

MR. JEHN: Are all the speakers planning to be here all afternoon?

["Yeses"]

DR. SIEGAL: So we will have ample opportunity to ask those questions as well.

DR. FINNEGAN: A clarification question for Dr. Greenburg. Can you tell us, given the concern about vasoactivity, how many African-Americans were involved in any of the studies?

DR. SIEGAL: While we are waiting, perhaps someone else has a question.

DR. PICKERING: Is Diane Maloney here? You said the rule about exception from informed consent has been in

place for about 10 years. Could you give us some idea as to what the experience has been? Have there been clinical trials where this has been used? Have there been any medicolegal or other problems with this process?

DR. MALONEY: There have been a number of studies conducted under the rule. I apologize, I don't have the numbers. But I think we have received about 50 or so submissions. Quite a number of them have not proceeded, for a variety of reasons -- some of those reasons being because of the IND regulation's grounds for clinical hold for safety reasons, not because of the 50.24. Several studies, though, have begun. Most of them, I don't believe, have been completed. I believe there has been one study, a device study, for which there has been an approval involving this.

In terms of your question about -- you asked about legal --

DR. PICKERING: Have there been any medicolegal issues with regard to the fact that a lot of these patients die, and there is a question afterwards, from family or somebody, about the consent procedure?

DR. MALONEY: Those issues generally wouldn't come to FDA. But I do know that at the public meeting people have raised questions about, for instance, liability in terms of people enrolled without informed consent. As I

think everyone knows, these are very difficult trials. That's why we have tried to build in as many additional protections for the human subjects as we can.

DR. SIEGAL: Dr. Greenburg?

DR. GREENBURG: I understand I had a question. I apologize for not being here to take it directly. The question dealt with --

DR. FINNEGAN: Actually, it turns out that my question is the same as what Dr. Edwards asked you in private: How many African-Americans were enrolled in all of the studies?

DR. GREENBURG: I can't give you that off the top of my head. However, my colleagues are here with the entire database. I hope to have the answer for your within an hour. I will be more than happy to share it with you.

MS. BAKER: Have there been any studies of HBOC-201 in the non-civilian population?

DR. GREENBURG: I don't believe so.

DR. SZYMANSKI: You are talking about a delayed time when the ambulance will arrive at the injured person. You estimate that to be very short. But how long ago did the actual accident happen? That has to be taken into account, too. That might be more than 30 minutes, before the ambulance will get there where the person is.

DR. FREILICH: Thanks for the question. It's

important to remember that the timing that you saw in those preclinical studies -- i.e., the 30- or 75-minute delay -- is from time of injury. Frequently when one talks about transportation times, there is a miscommunication, because you are talking about from the time of EMS arrival. When you look at the databases -- in particular, we looked at the University of Maryland -- in round numbers, what you can expect -- and many of these will be excluded from RESUS -- is that there will be a small number which actually arrive very rapidly, as was alluded to by Dr. Dutton, in less than 8, 10, or 15 minutes. That would be 10 or 15 percent or so. There will be another, larger group which will be between 15 and 30 or 40 minutes. That would probably be about half. The remainder would be even larger. In Maryland, as an example, it's because MEMS brings people in from all over the state to the Level 1 Trauma Center. So it gives you an idea.

What it means is that the biggest group in terms of prehospital trauma time is very commensurate -- in between, more or less, the numbers of the 30- and the 75-minute delay that Dr. Stern talked about.

I hope that helps.

DR. SZYMANSKI: Yes, thank you.

DR. FINNEGAN: May I ask you one more question? Why was heart rate not included in the -- it doesn't appear

to be in the trauma 1 to 5, and it's also not in your group. Why is heart rate not part of the assessment?

DR. FREILICH: It is. It is not an inclusion criterion. It is used as a risk-mitigation strategy in terms of reinfusion, if there is potential for higher mean arterial pressure responses to, in theory, fool paramedics, because the patient might look better if they didn't look at other clinical parameters. We have looked and we have shown that heart rate still remains, in pre-clinical studies, a very sensitive marker. In fact, in the DCLHb study, in the prehospital host trial, it was highly sensitive -- in fact, just as sensitive as with normal saline.

DR. FINNEGAN: My question had to do with the class 3 and class 4 for ATLS shock, where heart rates are very specific and blood pressure is relatively subjective. I am wondering why heart rate wasn't included in your assessment of severe shock.

DR. FREILICH: The answer is based on Victorino's data, and others, that heart rate has a large variability. It is relatively specific, but its sensitivity is not that high. For reinfusion, as a second criterion, what Victorino has clearly stated is that the combination of hypotension and tachycardia do predict very ill patients that are going to do poorly. Individually, heart rate is

not a very sensitive marker.

DR. HAUSER: I would like to ask about the patient age and the underlying diagnoses in the orthopedic studies. Were these predominantly older persons getting total hips and spine surgery? Was there preexisting cardiac morbidity, which might be expected, to make hypertension more of a problem with these people than it would be, potentially, with young trauma patients in whom, let's say, if they had a head injury, hypertension might be a therapy for these patients?

DR. FREILICH: Mr. Chairman, I can answer this directly. I am just asking that the chairman consider that many of these questions will automatically be answered in the presentation which is ensuing. I can answer it directly or if you would like to go directly to the presentation, we may want to hold on these questions and summarize them subsequently.

DR. SIEGAL: Would you be satisfied to wait?

DR. HAUSER: No problem.

DR. SIEGAL: That would be fine.

Informational questions?

DR. KATZ: It's kind of a follow-up to a question I don't think I heard the answer to. We are all very sensitive to what is going on in Iraq right now. It seems like there is a very substantial population of nearly-ideal

candidates who could be consented up front to accomplish a trial of this nature. I didn't hear the answer as to why a trial is not ongoing in the theater.

DR. FREILICH: That's a great question. The answer is as follows. One can, in theory, conduct a clinical trial even in a combat zone. But it is very, very difficult, for reasons that are probably obvious without me summarizing them. Therefore, for a Phase 3 pivotal trial, when one requires completely comprehensive and accurate data collection to submit a biological license application, the Navy made a determination that it cannot guarantee it would be able to do that. Now, that doesn't mean that supplementary, adjacent, so to speak, Phase 2 trials can't be done, but we believe that in the combat setting, there are bullets flying -- you just can't -- especially when it's a prehospital setting, where the paramedic, in fact, is a corpsman whose number-one job and what he is told first is to shoot back and to resuscitate the patient second.

DR. KLEIN: You can tell me if some of these questions will be answered later.

The first one, which I really want to direct to Dr. Kaplan -- but anyone can answer it -- is, are there any data on the number of civilian patients, trauma patients, who die because of lack of oxygen delivery capacity? We

know they bleed a lot and they become hypotensive and they are given volume. But what would we expect to find?

DR. FREILICH: I think that is, somewhat, going to be answered in the talk. The question is, how do you know, when someone has an injury, if they literally died of the reasons that you asked? If you have an injury that is not a guarantee of being life-threatening in the first place -- for example, a vascular groin injury or a pelvic fracture injury with hemorrhage -- the odds are that they died because of severe exsanguinating hemorrhage and the consequences of decompensated shock. When you look at that, my assessment is that a reasonable summary in the civilian community is about 30 percent. Some of that is from the Arizona data, in Pima County, and others. But they come up with about those kinds of numbers -- 20, 30, 35, 40, depending on the study.

DR. KLEIN: From the hemorrhage itself not delivering sufficient oxygen.

DR. FREILICH: It’s an assumption. It’s from severe hemorrhage. That is the assumption of the pathophysiologic mechanism.

DR. KLEIN: The second question I have deals with the histology, where we saw about the liver lesions and renal lesions. I didn’t see anything about cardiac histology. I presume that was done.

DR. FREILICH: It was. We actually did five organs. Most of this work was done at NMRC. It was done in three separate studies -- 40 and 55 percent controlled hemorrhage and a severe liver uncontrolled hemorrhage model. We looked at five organs: myocardium, lungs, jejunum, kidney, and liver.

About the hepatic injury, there was absolutely no increase in hepatic parenchymal injury. What was apparent -- and it was consistent in all three models -- is very mild -- on a severity score of 0 to 5, about 1 or less than 1 -- hepatobiliary injury. That was consistent with the liver function tests.

With respect to the myocardium, we looked at myonecrosis scores and we also looked at fibrosis scores, both in terms of incidence and scores. In two studies, they were absolutely equivalent and in one it was statistically improved with HBOC-201 in comparison to control fluid, for myonecrosis and, I think, for fibrosis -- certainly for myonecrosis.

DR. KLEIN: Your animal studies showed that the animals that had the most severe hemorrhage really benefited the most, I gather, from the HBOC infusion. I don’t quite understand why the elderly patients in the HEM-0115 trial did the worst. You would think they might do the best.

DR. FREILICH: I hope that the talk in the subsequent hour will answer that. I think it has to do with benefit and risk. In the pig studies, these animals had an enormous potential for benefit. In fact, my technicians hate when we have an HBOC-201 day, because they know they are going to be there late, because the animal is going to survive and, after anesthesia, is going to be recovered and they are going to be in the simulated ICU all night.

In the 115 trial, from a practical point of view, there was no benefit, other than blood-transfusion avoidance, which certainly has some theoretical benefits, but is pretty minuscule in comparison to the potential for risk.

DR. KLEIN: In the elevation of the LFTs in that study, Dr. Greenburg mentioned it was related, possibly, to the large volume of infused protein. But we don’t see that with albumin, do we?

DR. FREILICH: I don’t know the mechanism for it. There are some recent basic-science data that try to purport that it may actually be related to vasoactivity. That has just been published in the last year or so -- i.e., that the effects of vasoactivity on the microvasculature, not with HBOC-201, but with HBOCs in general, causes nitric oxide and carbon monoxide effects in

the microvasculature. It is possible that you have microvascular small aberrances in the liver.

I honestly don't know if that is really the reason. What I do know is that you get standard liver function test abnormalities as an intrinsic side effect of HBOCs that just don't appear to be clinically significant, although I will admit that in a patient who happens to have end-stage liver disease, who then got a lot of HBOC -- we don't have data to predict one way or the other.

DR. SIEGAL: Are there any more clarification questions? We are getting behind and we need to move on.

DR. CRYER: Just one. Do any of your data address the issue of ischemia reperfusion injury and whether the HBOC influences that, negatively or positively?

DR. FREILICH: Yes, sir. Actually, we published that in *Critical Care*, first author Johnson et al., from NMRC. In fact, that was a specific request from the FDA, to look at 3-nitrotyrosine staining in the five organs that I enumerated earlier. In all five organs, in all three models that I mentioned, there were absolutely no differences.

For the audience, 3-nitrotyrosine is a surrogate marker for peroxynitrate production, which is thought to be a main contributor for oxidative damage.

Of course, that's a functional thing. That's all

very nice, that there is no apparent increase in peroxynitrate. But what about histology? The histology, as I mentioned earlier, was all similar as well, with the exception of that liver.

I should add that in the kidney -- and I think that was mentioned by Dr. Stern -- in all those studies we mentioned, there were equivalent effects on the kidney, but there was very mild -- again, on a severity score of 1 to 5 -- papillary necrosis only in one model, the mild hemorrhage model, where fluids were restricted.

DR. KULKARNI: I have a question about the effect of this product on coagulation, because some of your patients might be hemophiliacs who may be having acute bleeding.

The second question I have is about immunogenicity of this product. If you are going to address it in your talk, that will be fine.

DR. FREILICH: Ma'am, we have a bullet on each of them, but I would be delighted to just make one comment. We also at NMRC published two studies evaluating hemostasis, again in all the NMRC models. A good summary of the data is that, in general, there is nothing clinically significant. More specifically, what did we look at? We looked at standard coagulation parameters, such as PT, PTT, thrombin time, et cetera. We looked at

thromboelastography in all these studies and we looked at PFA-100 and we looked at bleeding time.

In all of these studies, what one ends up with, to make the simple summary, is that in the simulated prehospital time, whatever coagulopathic effects you were seeing are a little less with HBOC. It's just logical. It's because you have less hemodilution.

What one ends up with in the simulated hospital scenario is a slight reversal, where whatever you are seeing, which is minuscule in the first place, is a little bit more coagulopathy in the HBOC animals. Why? Because they didn't get any blood. The other animals got blood. In the real clinical setting, that wouldn't happen, at least in our opinion.

DR. FLEMING: I am trying to understand what would be the most relevant Phase 1/2 clinical data to the setting that we have here in urban trauma and HS. Dr. Greenburg's slide 72 mentioned that there were 10 crystalloid control trials, but went on to really focus on the 0115. In essence, is that because that gives us 600 patients and these other 10 only have 300, or 30 per? Is it essentially the sponsor's view that if we really want to drill down on what is known from Phase 1/2 clinical data relevant to the setting of RESUS, the 0115 trial is probably the best source of that information?

DR. FREILICH: I think a lot of what you said is true. There are other reasons. That is an intrinsic part of my talk. There are some reasons why those colloid/crystalloid, so to speak, studies really were not colloid/crystalloid studies. They are multiple and they are heterogeneous, and they really have very little relation to the RESUS prediction of benefit-risk, in our opportunity. I will elaborate about that. If you need more, we can give you more afterwards.

DR. SWENSON: Central to all of this possible toxicity of the HBOCs is this nitric oxide avidity. It has been suggested, but I haven't seen any data -- maybe they are to come -- what are the data to suggest that this product may be superior with that facet, either *in vitro* studies to show the point or *in vivo* studies?

DR. FREILICH: There is a plethora of preclinical studies. I will elaborate on some of the key ones later on. There are not many *in vitro* data. They used to do the aortic ring stuff in the 1980s and 1990s, and I really haven't seen any of that. But they are going to be animal data, which I will provide later, if that's okay.

DR. SZYMANSKI: Have you measured the methemoglobin levels during this resuscitation? I am asking this because Dr. Olsen, who is studying cell-free hemoglobin products, maintains that during NO

disappearance, the reaction is that methemoglobin and NO3 are formed.

DR. FREILICH: I think it's a great question. I think that mild methemoglobinemia is another classic characteristic of all HBOCs. An HBOC is in a plasma solution, where it has no glutathione and other reductive mechanisms, unless it has some sort of reducing agent included. Dr. Chang at McGill, as you probably know, is spending a lot of time trying to crosslink SOD and catalase to it. What Biopure has done is to incorporate N-acetylcysteine, which, to some extent, keeps the product reduced.

From a clinical point of view, in all these preclinical studies that we have looked at, one does see, classically and consistently, mild methemoglobinemia with levels of, usually, 2, 3, 4, at the most 5 percent. We don't think these are going to be clinically significant. In most patients, people say 10 or so percent. But we will admit that patients who are intravascularly depleted -- who knows? They are very ill. There is a comprehensive training of trauma center personnel about methemoglobinemia and how to treat it and how to detect it. It is followed very, very serially in the trial, just as a final risk-mitigation strategy.

DR. SIEGAL: Two more questions, Dr. Edwards and

then Dr. Ballow.

DR. EDWARDS: In your discussion -- and I am looking forward to hearing the full presentation -- you mentioned in your slides that there is a target population, and there is 58 percent mortality and reasonable homogeneity. Could you please explain that?

DR. FREILICH: If it's okay, I think the figures -- this is a significant aspect of the talk. If it's okay, I would like to defer that.

DR. BALLOW: In the orthopedic 115 study, I thought I heard that the subgroup that received blood transfusion subsequent to the trial product had more adverse events. Are we going to hear more about that subgroup?

DR. FREILICH: Not a lot. What you are going to hear is that -- when you look at that subgroup, there are two ways to look at it. You could actually say the glass is half-empty, in that these patients did really poorly. They were sick. They got HBOC and then red blood cells. In a sense, this sounds like RESUS, where you get HBOC and then you get red blood cells, most of the time. But they have nothing to do with each other. In RESUS, you get HBOC for a few minutes. Maybe there will be an occasional long extrication and there will be a patient who will get it for 30 or 40 minutes. In that subgroup, the mean time before

they got blood -- in other words, it was withholding what we well know is standard of care -- was 100 hours. So the potential for risk was just very, very high in that study. Again, the potential for benefit was only blood-transfusion avoidance.

We look at it as a certain signal that there is the potential for significant risk. The only question is, is there unreasonable risk as it pertains to the RESUS population?

I hope that helps. If you want more, specifically, about the matching groups, I think Biopure can answer more questions about it.

DR. BALLOW: I only ask that question because maybe we can learn something about what we can expect from the RESUS, from that subgroup. I assume that a lot of the patients in the RESUS -- well, they are going to get additional blood transfusions when they come in.

DR. FREILICH: Yes, sir.

DR. BALLOW: Even though the timing may be different, maybe we can learn something from that subgroup.

DR. FREILICH: I think a lot of that will be answered in the talk. If not, we can come back to it and actually focus specifically on that matching group, if that’s okay, after this talk.

DR. SIEGAL: Dr. Freilich is going to continue

now with the sponsor presentation.

Agenda Item: Overview of the HBOC-201 RESUS IND and Discussion of Benefit: Risk

DR. FREILICH: This is kind of a complex talk, because there have been complex deliberations for a long time. I just want to summarize the three questions that FDA posed.

I know we got a copy this morning and they have been modified somewhat, but I don't think very significantly. If it's okay, just to set the stage of the talk, I would like to remind you what they are.

[Slide] First, it revolves around safety. The safety concerns relate to AEs seen in previous clinical studies. And, secondly, is there adequate information for the product dosing and the potential for patient-monitoring limitations, specifically in the EMS scenario?

Secondly, heterogeneity in the expected mortality population is a potential question. I think that comes back to one of the questions that was asked by one of the panel members.

Thirdly, is there a sufficient basis for estimating the mortality-reduction-effect size in RESUS, which currently is at 15 percent?

[Slide] With that in mind, just to give you an idea of what I plan to do over the next hour or so. There

are basically 11 conclusions that we would like to transmit to you that, we hope you will agree, will answer indirectly the questions that have been posed.

[Slide] First, traumatic hemorrhagic shock is a significant public health problem, and if mortality is truly greater than 50 percent in severe hemorrhagic shock, as we predict, one would think the treatment is unsatisfactory.

Second, the RESUS program has evolved over five years, again, as I stated a moment ago, with comprehensive deliberations with multiple specialists, from many world-renowned and nationally renowned institutions in the U.S. and overseas. It has a potential -- and it is rare in medicine to have this -- for transformational impact on trauma care.

Third, we believe that the target population has a very high mortality -- almost 60 percent -- and reasonable homogeneity. We will come back to that later.

We believe that the preclinical database, as summarized previously by Dr. Stern, reveals a certain prospect for benefit. We don’t know that there is definite benefit until we do the trial. Hence, the regulation says “prospect for benefit.” The fact that there is an overall 75 percent mortality reduction supports that contention.

We believe, therefore, that a mortality-

reduction-effect size (despite the difficulty, potentially, of extrapolating animal to human data) of 15 percent is very conservatively estimated.

[Slide] Sixth, we believe that the clinical database reveals benefit -- i.e., blood-transfusion avoidance -- and reasonable safety when it is considered in the overall population, and especially in younger subjects. This will be a large part of the talk over the next hour.

We believe that there is extensive preclinical and clinical rationale to support the dosing guidelines.

We believe that non-serious AEs, although they need to be considered, have an insignificant effect overall on the benefit-risk prediction.

We believe that there are insignificant monitoring limitations in the prehospital setting, because HBOC-201 has mild to moderate vasoactivity, the inclusion criteria mitigate this risk, and very significant training modules help to further mitigate that risk.

Our tenth statement that we would like to convey is that there are multiple risk-mitigation strategies that further increase benefit-risk.

Finally, all these qualitative analyses and also an attempt at a mathematical, semi-quantitative analysis, which I will mention at the end, robustly predict highly favorable benefit-risk in RESUS.

[Slide] Just a little bit of background.

[Slide] Trauma is the leading cause of death -- and this is obvious to most people on this panel -- in young adults, both in the United States and overseas, of which hemorrhagic shock, as I stated earlier, accounts for about 30 percent. More importantly, hemorrhagic shock is the most common cause of potentially salvageable deaths in trauma. If they are going to die anyhow, it's really not much of an issue.

In Operation Iraqi Freedom, of the about 3,000 service members who have died, it is possible, with the predictions from our trauma registries, that 1,300 to 2,000 of them likely were due to severe hemorrhage.

Of very significant importance in terms of relevance to RESUS is that the majority of patients with traumatic hemorrhagic shock die before you arrive at the hospital -- 80 to 90 percent in the civilian rural and military environments and about 50 percent in civilian urban environments.

[Slide] HBOC-201 has the potential to equilibrate prehospital and in-hospital capabilities. As we know, in the prehospital setting, resuscitation with standard care relies on crystalloid/colloid fluids, which do restore intravascular volume, but, of course, have no oxygen-carrying potential. In-hospital, we would never do

that. Yes, we do give crystalloid/colloid fluids, but, of course, we give blood, which restores oxygen content as well.

Very intuitively, HBOC-201, because it's available in a prehospital setting, has the opportunity to restore both intravascular volume and oxygen content.

[Slide] After 9/11, there have been multiple and comprehensive reasons and approaches to try to diminish morbidity and mortality in trauma in the war on terrorism, and it was not known exactly what it would be. There were force-protection approaches, which include improved body armor, and improved field resuscitation for those who already have been injured -- i.e., newer or improved, or studying new or improved, hemostatic agents and resuscitative fluids. NMRC looked at Hemolink, Hemopure, and PolyHeme, because they were all in advanced tech development and they were all potential candidates for Phase 3 trials. The reason HBOC-201 was down-selected will be mentioned in the next two slides.

[Slide] HBOC-201, just to give you some of the basic specs, is modified bovine hemoglobin. It comes in a bag of 250 mL of modified lactated Ringer's solution. It comes from a U.S. source -- cows -- hence the risk of potential for BSE is negligible. It is highly purified and highly polymerized, such that only 3 percent is tetrameric

hemoglobin, which I will come back to later on in terms of vasoactivity. (I think that was asked.) It is the main, although not the entire, culprit in terms of vasoactivity etiology.

It is universally compatible, which means that it requires no blood banking. Any paramedic, any nurse without any blood-transfusion training could hang it up. It is stable without refrigeration for three years.

[Slide] There were multiple objective criteria, as alluded to a moment ago, that we used to down-select HBOC-201, but I just want to highlight two of them. First of all, there was a substantial preclinical and clinical database. At least you know what you are getting. Secondly, the Navy insisted on an independent Navy-sponsored and directed and funded trial. This is not a drug trial, in quotes.

Some of the specific requirements were that a comprehensive community disclosure process occur, where all potential risks were stated. Secondly, we insisted on the absence of any withholding of standard of care throughout the protocol.

[Slide] This slide is just trying to convey that this has been going on for a long time. It was conceived in 2001, after 9/11. A pre-IND meeting occurred with OBRR in 2004. The IND was submitted later on in the summer of

2005, after completing the Stern hemorrhagic shock TBI study requested by FDA. Of course, we are here now, in December.

[Slide] Finally, in terms of this overall background, RESUS can potentially have a transformational effect on trauma care, as I said, if the 15 percent mortality reduction is realized. Just the RESUS inclusion criterion, which is pure efficacy -- a very, very conservative approach -- with just the trial itself, you would save 48 individuals. In the U.S. and worldwide, using those very tight criteria, you can see that thousands, potentially, could be saved. Usually, drugs are extended, and one analyzes or assesses and predicts effectiveness. In Iraq, we predict that 200 or 300 additional service members may not have died. As you can see, thousands, potentially, could be saved overseas.

[Slide] With that background, I would like to switch specifically to the Phase 3 trial that was elaborated on by Dr. Greenburg earlier.

[Slide] The trial design, I think, was summarized, but I want to highlight a couple of important points in terms of benefit-risk for RESUS. The mean age of the trial was over 60 years old, as opposed to RESUS, where the mean expected age is in the mid-30s. The maximum dose was 10 units, as opposed to RESUS, where the maximum is six

units. The intervention occurred over about six days -- high-risk, lots of exposure -- as opposed to, as I stated earlier, in RESUS, just minutes, maybe an hour or so.

[Slide] The 115 trial showed high blood-transfusion avoidance. In the first 24 hours, which is the time when physiologic benefit would be expected because the half-life of the product is 19 hours, 95 percent of patients avoided blood transfusions; over the entire 42-day follow-up, 59 percent, which is still pretty high. Just this fact unto itself at least predicts transfusion avoidance in RESUS, which simply does already predict some prospect for direct benefit. We are not saying it’s a lot, but just the idea is prospect for benefit.

Of course, the converse has to be looked at. The prolonged clinical test material exposure and the transufion-avoidance, although it looks good when you look at it that way, also increased AEs. It was a very high bar in that study.

[Slide] There were a lot of AEs. I think many of them were summarized by Dr. Greenburg. But in terms of relevance to RESUS, we think that these are the ones that should be focused on, because they are potentially more significant and potentially life-threatening.

The next slides will all look about the same. I will just walk you through them. The table will show HBOC