and red blood cells, and for ease of communication, in yellow the group difference. I will focus just on the group difference.

[Slide] I think this slide is probably the most important, despite its simplicity, of anything that is being presented. What it really says -- the overall AEs are pretty much mainly non-serious. We really believe that with a mortality of almost 60 percent, they don't have an enormous bearing on benefit-risk, as long as they are mitigated. The overall SAEs are another matter. In that trial, there was basically a 7 to 8 percent difference. What I believe this committee is ultimately deciding -- although there are multiple complexities to it, but if you simplify for a minute -- is, is the overwhelming preclinical database reasonable in terms of its prediction of benefit? There are a lot of other aspects, but does it so overwhelmingly predict benefit that it is worth having a potential worst-case scenario, if everything was exactly the same as 115, where there was no real potential for benefit, of a 7 to 8 percent excess of SAEs?

Now to look at these more specifically.

[Slide] In terms of cardiac AEs -- and it's very important to remember that these are not necessarily additive. A patient that had a cardiac AE may have had a stroke AE. Therefore, the real number that is important is

probably the overall SAEs.

Nevertheless, cardiac SAEs were statistically more significant. Of vital importance is that MI AEs were about the same -- 4 out of 350 versus 2 out of 338, not significant. What is apparent is that troponin elevations, nevertheless, were higher, and statistically so. I will come back to that later on.

A second issue is that heart failure and fluid overload was also more frequent. I will come back to that later on also.

[Slide] Cerebral ischemic AEs were also more common. In stroke, there was a 1.7 percent group difference, which was significant. All cerebral ischemic AEs, which includes stroke, TIA, and RINDs, were also statistically significant. But it is worth remembering that the group difference is still relatively small.

[Slide] HBOC-201 does have mild to moderate vasoactivity, as seen in the preclinical studies, and therefore hypertension AEs -- not necessarily serious ones -- were statistically more significant, but hypertension SAEs were not -- 2 out of 350 versus 0 out of 338.

[Slide] Of most importance is that mortality was statistically the same. Even any apparent trend was a group difference of 1 percent.

[Slide] In concluding our analysis of this ITT overall population data -- in a manuscript that we have been working on for who knows how many years -- this is what we have summarized: In a relatively older population undergoing orthopedic surgery, overall clinical outcome is better with red blood cells than HBOC-201, but, remarkably, minimally so, and where safe and expeditious transfusions are available -- i.e., in-hospital setting in developed countries. Thus, HBOC-201 is likely to have significant clinical utility where safe and rapidly available transfusions do not exist -- for example, prehospital, military, disaster stockpiling, and underdeveloped-country settings.

[Slide] With that overview of the ITT -- in a sense, the worst-case scenario -- I would like to look at the younger subpopulations. The reason we looked at those is threefold:

• One, trauma patients are younger, so it makes sense.

• Two, it was apparent to us on reviewing the safety data -- and it’s apparent to anybody -- that the group differences are simply less in younger patients, and one wonders if the safety is better in younger patients.

• Thirdly -- and this was a critique that FDA has stated that I think is very valid -- let’s face it, the

animal studies are not in old pigs with cardiovascular disease. They predict what would happen in younger patients.

[Slide] We stratified the age as follows: over 70, the ITT population, and less than 70 and less than 50. We need to acknowledge that when one decreases the N by stratifying like this, obviously the sensitivity to detect adverse events diminishes. But I should note that even the smaller subgroups are reasonable Ns that are commensurate with, and sometimes even larger than, typical Phase 2 trials, based on which FDA frequently makes regulatory decisions.

[Slide] This might be the second-most important slide in this presentation. It summarizes the key adverse events that I mentioned earlier. These are group differences. Red is over 70, yellow is the all-encompassing ITT, dark green is less than 70, and light green is less than 50. From the back of the room, it becomes apparent that pretty much every key clinical-adverse-event signal either goes away or becomes minimal.

To look at these more specifically, individually, the next series of slides will also look the same. In red is HBOC, in blue is the control fluid, and in white is the group difference. I am going to focus on the white error bars, again to make it easy.

[Slide] In terms of overall SAE risk, which we said earlier was a 7 to 8 percent difference, you can see that the pattern diminishes with diminishing age.

[Slide] Cardiac SAE risk: The same thing.

[Slide] MI AE risk: You can see there was barely a change in overall population. It's certainly concerning in older people. I think there is a question about that. But it goes away in the younger people.

[Slide] Heart failure and fluid overload: The same pattern.

[Slide] Cerebral ischemic AEs: Stroke, on the top, goes away. TIA, the combined ischemic -- in fact, the trend reverses, so that it's starting to look better. Of vital importance also is that the mean age of all cerebral ischemic AEs in those patients who got HBOC was about 76 years old.

[Slide] Cardiac arrest was not statistically different, but whatever trends there were went away. Again, the insignificant mortality trend -- whatever there was went away.

[Slide] So in that same paper, these were our conclusions after looking at subgroups: Our finding of an improved relative safety profile in subpopulations of subjects more closely resembling younger subjects who would be enrolled in acute trauma trials predicts that the

relative safety of HBOC-201 will be improved in such trials.

[Slide] We believe that these data, as required by 21 CFR 50.24, show that risks are reasonable in relation to what is known about the medical condition -- i.e., in the RESUS trial.

[Slide] I would like to pause for a second and switch from all of that background to the specific assumptions that we used to estimate benefit-risk in RESUS, just to remind the audience what the five requirements are in the applicable regulation:

• Human subjects must be facing a life-threatening situation.

• The available treatment must be unsatisfactory.

• The research must hold out the prospect of direct benefit. I think outlining and reiterating the word “prospect” is very important.

• Preclinical studies support potential to provide benefit -- the same idea, “potential” to provide benefit.

• Finally -- and I think this is most important to RESUS -- the risks associated with the intervention are reasonable in relation to what is known about the medical condition.

[Slide] Assumption number one is that predicted

mortality is 58.1 percent in the RESUS target population receiving standard care. This is based on two redundant and, we believe, confirmatory resources. First, most relevant to RESUS is the combined University of Alabama-University of Maryland database. This is a prehospital trauma registry using specific inclusion criteria, as is the case in RESUS. This is akin to doing a Phase 2 trial and then collecting the trauma-registry data and then making predictions. It's not huge, but it is 500 patients, despite those very tight inclusion criteria.

The mortality is 58.1 percent, with a reasonable 95 percent confidence interval. When you look at the larger National Trauma Data Bank, which is considered the *sine qua non* and the standard in terms of queries of trauma registries, one gets a larger N. Again, it's only in the database. It actually has tens of thousands, but when one looks at the specific inclusion criteria, you get almost 5,000 and a similar mortality and a similar confidence interval. One has to acknowledge that it's an in-hospital database. But whatever confounding seems to not be significant, in light of the higher numbers.

We believe that these data show that subjects are facing a life-threatening situation and available treatments are unsatisfactory.

I will come back to the heterogeneity issue later

on.

[Slide] Numbers 2 and 3 assumptions: The preclinical hemorrhagic shock studies with HBOC-201 show improved outcome and predict potential for benefit, including decreased mortality in RESUS patients. Dr. Stern went through this in detail, but I am just going to highlight that there is potential for significant survival benefit based on those studies, and there have been consistent physiologic benefits in multiple studies.

[Slide] Fourth, as efficacy data from both preclinical and *in vitro* studies and clinical trials show that HBOC-201 effectively transports oxygen, it can be predicted that similar effects would happen in RESUS. There are a number of reasons, but I would like to highlight that HBOC-201 consistently increases tissue oxygenation and decreases markers of anaerobic metabolism in preclinical studies. Again, as stated earlier, the fact that 95 percent of patients avoided blood transfusions suggest that surgeons and doctors taking care of those patients were content with the oxygen-content physiologic response provided by the HBOC-201 product.

[Slide] Assumption number five is really a recounting of our acknowledging that red blood cells were better than HBOC-201 in the population studied in 115, basically stating that in the prior Phase 3 trial, the AE

profile of HBOC-201 was certainly inferior to red blood cells in the overall ITT older population.

[Slide] That's not the question. The difficult question -- and I think this is the third-most important slide of all these -- is, how do you extrapolate and try to predict benefit-risk from a study that is so very different, for multiple reasons, from RESUS? I would like to go through that a little bit.

The potential benefit, as I stated earlier, in the prior Phase 3 trial was only, from a practical point of view, transfusion avoidance, as opposed to potential-for-survival benefit in RESUS. The clinical setting was in-hospital, where there are multiple modalities available, and it was elective-surgery patients. In RESUS, it's a prehospital environment, with acute hemorrhagic shock, where the armamentarium is incredibly minimal for paramedics.

The population was mainly elderly patients; in RESUS, it's mainly younger adults. The exposure was days -- prolonged blood-transfusion substitution, as opposed to a brief oxygen bridge in RESUS. The physiologic state was mostly hemodynamically stable. Most of the patients were euvolemic. Some were even hypertensive before they even got clinical test material. In RESUS, they are hemodynamically unstable, and because their blood

pressure is less than 90 -- in fact, it will be much less than 90 in most, because the RTS of 1-to-5 is a very, very tight, severe population -- all the patients will be severely hypovolemic and hypotensive.

The comparator is gold-standard red blood cell transfusions, versus suboptimal asanguinous crystalloid fluids that don't carry oxygen. There is potential for study-design issues.

[Slide] Nevertheless, even if you do believe that extrapolation from the 115 trial predicts a lot in RESUS, we still believe that the safety data in the overall population predict, as required by the regulation, reasonable risk. Why? Because the group differences -- basically, the key number is the overall SAE rate, a difference of 7 to 8 percent -- we believe is relatively low if you consider it in the context of an almost-60 percent mortality population and the potential for survival benefit, as demonstrated in preclinical studies.

[Slide] Secondly, if that is not sufficient, even if one assumes that extrapolation is reasonable, in the younger subjects, the key safety-signal group differences were significantly narrowed.

Also -- and this is where I hope I will answer one of the panel member's questions -- there was improved safety in patients with cardiovascular disease. This is

almost like asking, is water wet? Younger trauma patients, of course, have less comorbid disease. But let me prove it.

Millham recently reported a large query of the National Trauma Data Bank, and he showed that only 7 percent of patients had a history of cardiovascular disease. In the HEM-0115 trial, almost three-quarters of the patients had a history of cardiovascular disease. I submit that just this fact unto itself suggests that there is lower risk of cardiovascular and cerebral ischemic SAEs in the RESUS trial.

[Slide] On top of that there are accumulating (although small and limited) trauma data now in 20 total patients, 10 of which received HBOC-201 in a South Africa ongoing ER trial. This is the trial that has patients which most -- although there are significant differences -- have the most simulation of RESUS conditions. But it was still a very high bar, because the standard of care was the comparator, which, of course, includes red blood cells. In that study -- and I will come back with more detail about it later -- there is equivalent mortality, despite the high-bar comparison, and there are trends already apparent to improved -- not equal, but improved -- safety in HBOC versus the comparator, which includes blood. Actually the AE- and SAE-per-subject rates are lower with HBOC-201, and

there are decreased fluid requirements. The blood-transfusion requirement already has a P value of .08, just having enrolled 20 patients.

Finally, a U.S.-based DSMB has just finished reviewing these interim data and has recommended continuing the trial.

I think this adds additional data to just suggest that risks are probably reasonable in the medical condition in RESUS.

[Slide] I would like to shift and go back a few years to the late 1990s. Diaspirin cross-linked hemoglobin is probably on the forefront of people's thoughts when they think of HBOC-201, the prior Baxter product. DCLHb is 100 percent tetrameric hemoglobin. I am going to come back to this in more detail later. But multiple studies show that HBOC-201 -- strongly suggest that it is less vasoactive than DCLHb.

Also people always remember the Sloan study, which was the in-hospital trial where mortality was increased with HBOC-201 versus comparator -- again, not much potential for benefit there. But the comparator was red blood cells.

There was equivalent mortality, in fact, in a larger trial, which most people don't know about. That was the prehospital European HOST trial published not too long

ago by Kerner. It was stopped mainly as a byproduct of that study in the in-hospital setting.

Finally, physicians learn. This was back in the 1990s. An improved understanding of vasoactivity has prompted incorporation of multiple risk-mitigation strategies related to potential for vasoactivity in RESUS.

[Slide] Our ninth assumption is that preclinical and clinical data support RESUS dosing guidelines. I will come back to this in more detail later. But there are multiple hemorrhagic shock studies, as alluded to by Dr. Stern, with doses and rates of infusion that are equal to or sometimes significantly above those that are proposed in the RESUS trial.

Secondly, in the 0115 trial, the preponderance of data is in patients receiving a maximum dose similar to RESUS -- i.e., less than or equal to six units. In fact, it’s 81 percent. In that population, there was, overall, we believe, a reasonable risk and, in fact, a better overall profile than the older population, especially when one looks at younger subjects.

Finally, in the 125 interim data in the South Africa trauma trial, you have favorable interim results, again with doses and infusion rates that are very similar to, and sometimes higher than, those proposed for RESUS -- just an added bonus.

[Slide] I would like to end our assumptions section of this talk with trying to convey that there are multiple risk-mitigation strategies. We classify them in four categories. I will go through each one.

[Slide] The target population was selected to maximize benefit and to minimize risk. In particular, by exsanguinating hemorrhage -- these are the FDA words; you need exsanguinating hemorrhage -- we believe that a mortality of 58 percent, assuming it is correct or even close to correct, satisfies that. This is a population that has significant potential for benefit.

In terms of maximizing benefit, we also have an exclusion of short transport times. Again, those are patients who are probably not going to benefit much, because they will get blood soon anyhow.

Additionally, to minimize risk, we exclude the elderly.

Finally, to minimize potential risk in terms of impact, causing hypoperfusion from under-resuscitation by paramedics related to vasoactivity, we have included a tachycardia criterion, as mentioned earlier, beyond simple blood pressure. I will come back to that in more detail.

I just want to make one other point. Standard fluids can be given, no matter what, if the paramedic feels that they are clinically indicated, irrespective of any

RESUS inclusion criteria.

[Slide] Our second category of risk-mitigation strategies is that we have standardized and optimized care as much as we can. We have spent an inordinate amount of time on putting together training modules. Of course, those would have to be executed as well, if the study went forward. We have insisted on standard care. That includes access to standard blood transfusions as soon as they are available -- i.e., even in a prehospital environment. Vanderbilt does actually have blood on some of their air ambulances. That would be an exclusion from participation in RESUS.

[Slide] Finally, there are comprehensive surveillance methods which allow for early detection, so you can do something about them if adverse events do happen. I want to focus on one, which is sort of an aside. In order to minimize the potential risk of idiosyncratic higher blood pressure responses -- there were those two patients in 115, although they were considered unrelated and they were hypertensive before they got HBOC-201. Nevertheless, it obviously shows that there is some minimal risk of a rare hypertensive response. We included an HBOC-201 infusion stopping criterion of 120 mmHg. This doesn’t guarantee that it will never happen. What it does is, it minimizes it.

You might say, where does that come from? In preclinical studies, it is rare. I don't remember in my head the numbers. We will have to look. But I think it's 10, 12, or 15 percent of animals that reached an equivalent number. We looked back at the prehospital DCLHb HOST trial -- again, DCLHb being much more vasoactive than HBOC-201. Ed Sloan has these data, and we would be delighted to elaborate about them more later on in the Q&A. Only about 20 percent of patients ever reached, in a prehospital environment, this kind of blood pressure.

It means it is going to happen and that this mitigation strategy will be incorporated, but not that often.

[Slide] This talk is very dense and there are a lot of issues. I just wanted to take a 10-second breather for everybody and then move on to what the RESUS IND clinical hold issues are and try to address them specifically.

A notation before we get into that: It's really important, in our opinion, that the panel knows that the consultant reports that were included in FDA's BPAC issues statement were all completed prior to incorporation of very significant -- some at the recommendation or consideration of the FDA -- that were included in the RESUS IND and protocol since the summer and the fall of 2006. One did

include updated comments, but the others did not.

DR. HINTZE: Before you begin, how many units of HBOC-201 are in the trial? I read three; someone said six; someone said 10. What is the real number?

DR. FREILICH: The confusion is dose. It's three doses. Each dose is two bags. So it's six units.

[Slide] The first comment: FDA has stated, "There is inadequate information to assess whether risks and benefits are reasonable."

[Slide] We believe that there is much more information than is usual for consideration in an IND. There is a substantial preclinical database, as stated earlier, of 22 hemorrhagic shock studies, with or without traumatic brain injury. There is a substantial clinical database, in over 1,500 patients, about half HBOC. In that Phase 3 trial, actually there were trauma patients, although they were stable trauma and they don't have a lot of relevance to RESUS. But they certainly have a lot more than the older ITT population. As mentioned, there are 20 with traumatic hemorrhagic shock in South Africa.

Additionally, it is rare that one actually has postmarketing experience. This was recently published by Dr. Levien in South Africa.

[Slide] The second concern: "The toxicity profile of HBOC-201 precludes study in field trauma, unless

the target population is projected to have an extremely high mortality risk with exsanguinating hemorrhage or rapid bleeding with prolonged delay to emergency care." I alluded to this earlier.

[Slide] We believe that a mortality of greater than 1-to-2 simply equates with exsanguinating hemorrhage. Secondly, our inclusion of that delay to emergency care -- basically, that you need a minimum amount of time that would be excluded -- we think satisfies the second criterion which was stated in writing by FDA, rapid bleeding with prolonged delay to emergency care.

[Slide] Next, "Entry criteria for RESUS suggest that the patient population is likely to be heterogeneous." I am going to talk about this in the next few slides. Of course it's heterogeneous. You can't do a trauma trial without heterogeneity. The question is whether you have attempted, to the best of your effort, to make it reasonably homogeneous.

[Slide] This is what we have done. Actually, this was at the direct recommendation of FDA back in 2004 or 2005, that we include the Revised Trauma Score. The Revised Trauma Score was alluded to by Dr. Dutton. It is between 1 and, in round numbers, 7.5. With 1, you pretty much all die; with 7.5, pretty much everybody survives. There are stratifications. That is what we did, at the

FDA's request.

When one stratifies the RTS, you find that, no matter how you look at it, the ranges that are in RESUS -- 1 to 2, 2 to 3 -- are reasonable. They are not all equal. Of course they are not. But even in the highest RTS, which is the patient population that has the least mortality -- i.e., the least ill in RESUS -- they still have about a 30 or 40 percent mortality.

What about the N in terms of distribution, coming back to one of the panel member's questions? The same RTS stratifications. You can see that it is relatively reasonably distributed. In fact, it's actually bell-shaped-curved and normalized, such that the highest incidence distribution is right in the middle, around 2 to 3. If we could really reproduce this -- and we are going to reproduce this in RESUS -- this suggests that you have a reasonably homogeneous population, with high mortality in all RTS ranges.

What this does is, it eliminates the classic nemesis of trauma trial, the bimodal U-shaped distribution. You have excluded these on both sides.

[Slide] When you look at the NTDB data, they are not as tight, but they are pretty similar. You can see about 30 percent even in the best group. You don't have a bell-shaped curve, but you have a reasonable distribution

in the patient population to be enrolled in RESUS.

I would like to state that this contrasts with the RTS curve supplied in FDA's issues statement. That RTS curve is the original curve, I think published by Champion, about the RTS data, but is not specifically looking at RTS ranges in the inclusion-criteria population in RESUS, which these two trauma databases used.

[Slide] This comes back to one of the other panel member's question about the colloid/crystalloid studies. FDA has stated -- and I think, intuitively, it's a concern -- "For crystalloid/colloid-controlled surgery studies, the imbalances persisted." Again, intuitively, we are comparing against LR and then blood in RESUS. So you would think, okay, they are somewhat similar.

[Slide] But the studies were very, very, very different. First, let's acknowledge the main adverse event. In those studies, whatever they are, for the sake of simplicity, MI is the main issue to be considered. The FDA's issues statement says seven versus one. We believe it's actually five versus one, based on the actual database. Three of the five were in patients over 70 years old. Of course, the P value is over .05. Nevertheless, it's a potential adverse safety signal, no question.

But there are significant numerous potential confounders of these data with respect to prediction of

benefit-risk in RESUS. First of all, in many of the studies, there was a very high hemoglobin trigger. Patients were being given HBOC-201 because they had hemoglobins of 10 to 12. Obviously, there is no significant benefit, based on recent data by Hebert and other people, about transfusions.

Also in many of these, there was minimal blood loss. In one of the studies, the requirement was 500 mL, which is not terribly different from what you do when you donate blood. Again, there was not much benefit in that study.

Many of these studies were top-load studies. There weren't hypotensive/hypovolemic RESUS-type patients. That obviously increases vasoactivity risk. If you start at this level and you give a mild to moderate vasoactive product, you might get more vasoactive responses.

The last one that I want to actually state is that blood transfusion was an endpoint in many of these studies, so that the comparator actually was not crystalloid/colloid; it was crystalloid/colloid and you could get blood soon, in all these studies. There was prolonged exposure to clinical test material, and therefore prolonged exclusion of standard red blood cell transfusions. Obviously, this is a high bar and, once again, increases risk.

There are other issues that are mathematical, for example. Many of them had two-to-one enrollment. They were heterogeneous.

Basically, these data, we acknowledge, demonstrate potential risk, the second arrow, for MI in some situations with HBOC-201. Biopure at the time, in these trials, set up a situation with no significant potential for benefit, but certainly potential for risk. As a consequence, we think they have no significant effect on the overall prediction of benefit-risk in RESUS.

[Slide] The next statement FDA has stated is, “Preclinical studies do not” -- I repeat, “do not” -- “support even potential to provide direct benefit.”

[Slide] As stated by Dr. Stern earlier, the preclinical studies show reduced mortality in all of the studies. When one includes all models, to be conservative, including ones that were never designed or powered for mortality reduction, you still get a 75 percent mortality reduction, with a highly significant P value. When one looks at severe hemorrhagic shock models, which, of course, are much more RESUS-analogous and were powered adequately to look for reduction in mortality, you get the same mortality-reduction size. It’s dramatic -- with HBOC-201, a mortality of 17 percent and a mortality of 93 percent -- these are just the converse of the survival data that Dr.

Stern gave -- again with a highly significant P value. Of most importance, one can critique that these are combined studies. It's not a true meta-analysis. But when one looks -- and you remember the graph that Sue Stern showed -- all the studies individually had the same mortality reductions, irrespective of whether you combine them.

[Slide] Additionally, as she showed, the preclinical data predict improved hemodynamic stabilization and no unreasonable risk. There is more rapid stabilization of hemodynamics, and there is only mild to moderate vasoactivity and no evidence of increased hemorrhage.

[Slide] The preclinical data comprehensively predict tissue oxygenation benefit, whether one looks at improved direct measures or indirect measures -- i.e., those looking for anaerobic-metabolism classic clinical parameters.

[Slide] The preclinical data, especially in light of the SAE incidence in the cardiac SOC and 115, predict equivalent -- I think I answered this with one of the questions earlier -- or improved myocardial effects with RESUS. There is absolutely no evidence of heart failure, overload, and hemorrhagic shock. We looked at lung and myocardial tissue, as I stated earlier, in

multiple preclinical hemorrhagic shock models. There is no evidence of cardiac injury. In fact, in all the studies, troponin-I was equivalent or improved with HBOC-201, and all the histopathologic myonecrosis or myofibrosis scores, as I said, were equivalent or, in one study, improved.

Also, in acute coronary stenosis models -- for example, as published by George et al., lately -- you had decreased myocardial infarction size.

[Slide] The preclinical data predict equivalent or possibly even improved respiratory effects. Certainly there is no evidence of heart failure or pulmonary edema in any of the studies that we have looked at.

[Slide] The preclinical studies do predict mild adverse events related to the GI and hepatic side effects that we talked about once before.

[Slide] The preclinical data predict mild renal pathology in a minority of studies. There was no cortical or medullary injury. We saw mild papillary injury, again, in the one study where fluids were restricted and were lower than in controls.

[Slide] As Dr. Stern stated, there were multiple classic neurosurgery/neurophysiologic parameters that were significantly improved. Many of these are specific primary aims of resuscitation by neurosurgeons in hemorrhagic shock and TBI. These are summarized for you here. I just want

to focus on improved cerebral perfusion pressure, improved brain oxygenation -- also improved histopathology, as shown by Dr. Manley and Rosenthal at UCSF. Just this slide predicts -- although we haven't proven it, because we haven't looked at functional neurocognitive outcome -- that neurocognitive outcome in survivors should be improved in RESUS.

[Slide] There are improved hematologic effects. They are predicted to be the same in RESUS. Obviously, blood content will be improved if one gives hemoglobin. The studies show decreased transfusion requirements. Incidence and dose of transfusions and delay to the first transfusion were all statistically significant in NMRC studies. There are multiple references which show that these parameters are independent predictors of adverse outcome. If you don't have these outcome parameters, they are in trauma.

There was a question by one of the panel members about immune responses. Dr. Dong in our group published one study, and there are a couple that were submitted recently. We have looked at comprehensive immunophenotype, adhesion markers, plasma cytokines, and apoptosis. Dr. Kerby is doing some of that in mice. We have done that in swine.

From a practical point of view, one is

underwhelmed. There really is very little. A simple trend appears, and it's almost insignificant, but it seems to be consistent in all the studies. IL-10 appears to be a little bit higher -- and, actually, now we are finding out, maybe even IL-4 -- these are both Th2 cytokines -- in HBOC animals. We don't know if it's because they got HBOC or they survived to mount the response and have a higher Th2 response. It's something we want to figure out. But it's slightly different, usually not significant, but seems to be a trend.

As I said earlier, there are equivalent effects on 3-nitrotyrosine, which is a surrogate for oxidative potential.

[Slide] So in summary, our conclusion about the preclinical studies is that they predict significant benefit without unreasonable risk in RESUS. There has been official survival and physiologic effects and only mild adverse events. The strength of these studies, as Dr. Stern said, is that they are numerous. In fact, the heterogeneity of these studies is not a weakness; it's a strength. No matter how you look at it, in multiple various ways and models which simulate trauma patients, you still get a pattern of improved outcome, by multiple institutions, independent investigators -- many independently funded, such as all the Navy studies -- for a

variety of hemorrhagic shock models. There are specific models that we did. Some did not include anesthesia. Some were sedation only, as requested of Biopure by FDA. Some were blinded, as much as you can, until you get HBOC. It turns you red, so the technicians then learn what group you are in. But they are certainly blinded until randomization, in all the Navy studies and many of the others. Manley was very, very compulsive about blinding, and Dr. Stern was, in the study requested by FDA.

Basically, there are redundant and highly significant results in all these studies.

I alluded to the main limitation. That is, if we didn't exclude the elderly, they would predict what might happen in younger patients. There are other potential confounders. We think there are nuances in each individual study, but the overall data are conclusive.

[Slide] Vasoactivity was asked about by one of the panel members. FDA has stated, "... our concerns that when a vasoactive HBOC (DCLHb or HBOC-201) is infused, the two endpoints typically used by EMT providers to estimate whether to give additional product, blood pressure and heart rate, are insensitive surrogates of volume status."

We believe that that question actually has a false assumption. Paramedics don't typically rely on heart rate and blood pressure. They rely on multiple clinical

parameters. It's this classic standard training in PTLS and the national highway and trauma safety training -- and this is standard. But let's address these issues specifically.

[Slide] Vasoactivity I consider to be an intrinsic characteristic of this class of drugs. DCLHb, the first-generation product by Baxter, has 100 percent tetrameric hemoglobin. Tetrameric hemoglobin is probably -- although, again, not entirely -- and Dr. Alayash and Dr. Tsai and Winslow and others -- there are many theories about it -- the preponderant reason is probably tetrameric hemoglobin, and then you are left with other reasons. Tetrameric hemoglobin extravasates beyond smooth muscle in the vasculature, binds nitric oxide, and causes a vasoactive response. In the first-generation product, you had 100 percent tetrameric hemoglobin. HBOC-301, which is what was referenced by most of Dr. Alayash's slides, which is Biopure's veterinary product, is still a first-generation product, with the same amount as Hemolink, which, from a practical point of view, in my opinion, went out of business because it was an old-fashioned product. It simply wasn't pure enough to compete with the newer-generation products.

HBOC-201 is relatively similar to what was reported by Northfield Labs about PolyHeme.

[Slide] We believe that as HBOC-201 elicits mild to moderate blood pressure responses in hemorrhagic shock and other studies, in most patients, in most animals, the risk of adverse effects in prehospital monitoring, in the first place -- even if one stated that blood pressure is going to fool paramedics -- is low. Why do we say that? In the preclinical hemorrhagic shock studies, 94 percent of mean arterial responses were classified as mild to moderate, as recently published by Rice in *Journal of Trauma*. Also the more severe the hypotension, as one would expect, the lower the MAP response.

The clinical trial, 115, showed relatively similar responses, such that most SBP responses coincidentally -- 94 percent -- were classified as mild to moderate. The classification occurred prior to the actual tabulations. There were no severe blood pressure responses that were considered by the investigator to be related to clinical test material. There were those two patients -- and I am going to come back to them -- who were considered unrelated.

Analogous to the finding in the preclinical studies, and confirmatory, is that systolic blood pressure responses were lower in subjects who were hypotensive. That’s not surprising. Also they were lower in younger subjects. This is relevant, of course, to RESUS.

[Slide] With respect to heart rate, because preclinical studies -- and this was also published by Rice recently -- show that RESUS fluid-reinfusion criteria -- to remind you, the fluid-reinfusion criteria are blood pressure and tachycardia -- are sensitive, the risk of adverse effects on prehospital monitoring of fluid status is low. We have backup slides, and I will go into that in detail, if the panel desires, later. But a summary is that hypotension, despite the vasoactivity, actually is still a very sensitive marker, as long as you have one condition. It is severe hemorrhagic shock. In mild hemorrhagic shock, with increasing infusions, you start losing it. But we have a risk mitigation for that in RESUS, and that's tachycardia. It was chosen because in these studies tachycardia remains a sensitive marker throughout. It doesn't matter how many infusions you give and it doesn't matter if you have mild or severe hemorrhagic shock.

Also when one looks at, in a sense, the worst-case scenario, the first-generation DCLHb, in the prehospital HOST trial, heart rate -- and we have a graph and we can show that later on, if desired -- was equivalent whether you get DCLHb or normal saline, suggesting that it should be as sensitive a marker, whatever its sensitivity is, as standard patients get.

[Slide] In summary, with respect just to these

vasoactivity slides, we believe that HBOC-201 is unlikely to significantly adversely affect prehospital monitoring in RESUS, for three reasons:

• As I stated just now, there is low *a priori* risk because the vasoactivity is only mild to moderate.

• Standard EMS training includes use of multiple clinical parameters, to the exclusion of reliance on hypotension alone.

• On top of that, there are multiple risk-mitigation strategies to ensure that it doesn't happen, despite all that.

[Slide] A corollary to the blood pressure is what we talked about earlier. There were a couple of patients in the 115 trial and there were two patients in the COR-0001 trial, which is a percutaneous coronary intervention study in old patients. I will mention those. FDA has stated, as a consequences, that "increases in systolic blood pressure to 220 mmHg have been noted with HBOC-201."

[Slide] To put that in perspective, it happened in 4 patients out of a total of 826 subjects receiving HBOC-201, and, you can see, significantly less than 1 percent of the time. Who were these four patients? The two in 115 -- one was 61 years old, one was younger. But they were both classified by the investigator as being

unrelated. One of them, in fact, was euvolemic and hypertensive before he even got clinical test material. This one happened after 10 doses -- in RESUS, you can only give up to six -- and after five days of exposure. You can only give HBOC-201 in RESUS for minutes or maybe an hour. Of course, it resolved.

The second one was in a euvolemic patient. It only happened 43 days later. It is not logical to think it could be due to HBOC-201.

What about the two in the COR-0001 trial? This is a trial of patients undergoing percutaneous coronary intervention because they already have had an acute coronary syndrome or it has been demonstrated that they have coronary-artery disease and are at risk, obviously. These were the actual titles of the SAE, but it doesn't mean that it's really what happened. Both of these patients were euvolemic and were hypertensive -- one of them was over 150 systolic; one was over 170 -- again, before they ever saw the clinical test material, HBOC-201.

This one was very concerning *a priori* in that there was severe hypertensive response. This patient had a bad outcome initially, where there was electromechanical dissociation and cardiac arrest, complicated by an MI and stroke. But the severe hypertension is what happened first. The patient got some nitrates and it stabilized.

The severe hypertension was related to HBOC-201, but it stabilized with nitrates, and only after injection of contrast material and inflation of the balloon -- right after that was when the EMD occurred. The cardiology consultants, the neurology consultants, the investigator, the DSMB, NMRC -- and we conducted a complete separate survey of all RESUS advisory board members about this -- all believed, yes, the initial hypertension response was due to HBOC-201, but the subsequent complications had nothing to do with HBOC-201 and were highly likely to be secondary to a complication of the PCI intervention. We can talk about that, with the cardiologists, in more detail, if you want, later on.

Basically, we believe that these data show that there is a small risk of idiosyncratic blood pressure responses. Dr. Levien, with a lot of experience in South Africa, will tell you that an occasional patient has a higher blood pressure response, and you just don’t know why. That’s why we call it idiosyncratic. But these rare SAEs, in mainly euvolemic and hypertensive subjects, we don’t believe affect benefit-risk in the uniformly hypovolemic and hypotensive subjects in RESUS.

[Slide] Dosing has been another issue. FDA stated, “There are limited clinical data on dose and rate of administration using HBOC-201 to support the RESUS

dosing guidelines." To some extent, it's a catch-22, because to get truly sufficient data, you need to do the study. But what is available?

[Slide] Just to give you the background, I remind you about the dosing guidelines. As I stated to one of the panel members earlier, two units is the standard dose. When you do the math, over 10 minutes, its 50 mL/min, which is .7 mL/kg/min. You can get up to three doses, which is six units, which is 21 mL/kg.

[Slide] Just to have those numbers in mind, when you look at the most important preclinical studies -- you can look at dose and the comparison with RESUS in yellow. When you look at the infusion rate and the comparison, in yellow, with RESUS, and total dose, you can see that the preclinical database comprehensively has bracketed the doses, where you get similar doses, .7, 1.X to much higher X's -- 6 to 12 to 18, very high numbers. So there is improved outcome in all these studies with similar or higher doses than what is proposed for RESUS for dose, for infusion rate, and for total dose.

[Slide] When one looks at the 115 data, in the less than or equal to six units of HBOC, we predict reasonable risk. First of all, it was the largest group of populations. Again, you know what you are getting, because it's a large database. The key safety signals were

actually decreased in patients who got less than six units. You can see group differences.

We need to acknowledge that there is a limitation of looking at it this way. There is possible confounding by patient condition. There is no question of that. But irrespective of that, the fact of the matter is that whatever you do observe is less concerning in younger subjects. But we do completely acknowledge that there is such a limitation. Either way, the database -- whatever it is -- is in that patient population, predominantly.

[Slide] What about rate? We don't have data in 50 mL/min, so we looked at what we do have. We have intermediately rapid rates. Again, the RESUS default infusion rate is 50 mL/min. We looked at 25, because at least we had a reasonable number of patients to look at. When you look at systolic blood pressure responses, after the first infusion, in fact, it appears a little lower with HBOC-201 at that intermediate transfusion rate than in the overall population. When you look at all infusions, the trend seems to be reversed. But either way, what you are seeing are differences of maybe 10 mmHg, which are probably not terribly significant.

Finally, also key safety signals in this small group -- for what it's worth, but at least we are looking at it -- were similar to the overall population. That is

in your package.

[Slide] What about trauma data? Again, to get good, highly relevant data, we actually need to do the study. But we looked at the 125 data from South Africa, which we think is the most relevant. You can see that the volume, the duration of infusion, and the rate are not terribly different -- certainly in the ballpark -- in comparison to RESUS. You have the results here that I stated earlier. Basically, it trends to a favorable safety profile.

[Slide] What about the worst-case scenario? There are extensive DCLHb data in trauma patients in the prehospital HOST trial, which show that systolic blood pressure, with doses similar to RESUS -- about 1,000 mL; our max is 1,500 -- predict reasonable risk. In this curve you can see that there is no difference in blood pressure between those patients in the prehospital setting who got DCLHb and those who got normal saline.

Just in the interest of time, I am going to skip the summary slide and move to the last two categories, before some conclusions.

[Slide] We believe that non-serious AEs are probably not terribly important to RESUS.

[Slide] These are summarized here -- as long as mitigation strategies are included.

[Slide] They are akin to the consideration of nausea AEs in a chemotherapy trial. They are important and you need to deal with them and minimize them, but survival and SAEs should be key adverse signals in patients in the RESUS trial for prediction of benefit-risk.

[Slide] I just want to give you two quick examples. One is oliguria. You do need to minimize risk of oliguria, because it was higher in HBOC-201 patients than red blood cells, in the Phase 3 trial. But we think that more clinically relevant is that renal failure was really not significantly different.

[Slide] Troponins: Troponin, we believe, was a laboratory abnormality, but didn't have very much significance in terms of prediction of benefit-risk in RESUS. Why do we say that? When you look at the classic receiver-operator curve, the ROC, yes, there were a lot more -- an 11.6 percent group difference -- in HBOC patients. But when you look at MI, there was no difference.

[Slide] The question is, is the troponin elevation an MI? The consensus documents state that it's not. The standard 2000 document says that you need a typical rise and gradual fall of troponin, and you need to have at least one of the following. You can't have just a troponin. You need to have ischemic symptoms and ECG

changes, et cetera.

[Slide] As recently published, there has been widespread misinterpretation of the new definition. Troponin concentrations are frequently assumed to reflect MI, without corroborative evidence from the patient's history or ECG.

We are not saying that they don't predict any risk. We are saying that they just need to be considered in context.

[Slide] When you look at the 18 patients who actually had troponin elevations, it's very interesting. Most of them were low levels. Not all, but most were just above the ROC. There are data akin to PCI troponin leaks, as cardiologists frequently call them. Yes, they do have some effect on clinical outcome, but much less than when you have larger troponin leaks. Also the true group difference, meaning these 18 patients -- many of them are not really real risks. Three of them, in red, actually happened before you even got clinical test material. The ones in yellow were either isolated or just had a minimal detectable level, less than ROC, afterwards. These certainly would not actually meet the criteria.

[Slide] Finally, whatever apparent differences there are went away or at least were minimized a lot in the younger patients.

[Slide] In summary, about troponin, we believe that troponin elevation was an isolated laboratory abnormality -- not that it had no effect, but it had no significant effect on overall prediction of benefit-risk in RESUS. I want to summarize this again, because I think this is really important. There was less *a priori* significance, because many of them obviously didn't meet criteria. They have questionable significance, because only one of them was associated with an MI. In younger subjects, which are more RESUS-relevant, there were lower group differences. There were no such similar group differences when you look at hemorrhagic shock in animal studies. Finally, if that is not sufficient, there are multiple risk-mitigation strategies to minimize this further in RESUS.

[Slide] The final area that I would like to touch before summarizing with conclusions: Until now, we have spoken about a qualitative analysis of benefit-risk, but what we tried to do -- and we have to acknowledge up front that these are early drafts. How do you mathematically, in a sense, try to tell a clinician what the potential benefit-risk is? There are a lot of criticisms. I am only going to show you one. In your package we have three of them, but I think this one is the one that clinicians think like.

[Slide] Before I state that, there are a bunch of quotes here that talk about this, but I just want to read one, because this is really the underlying urge to do this: "Both benefits and risks should be considered. The degree of risk that may be considered acceptable is dependent on the seriousness of the disease being treated." This is obvious, but it really needs to be recalled in our minds for the application of benefit-risk in RESUS.

This is a little complicated, but I think it will be simpler when we go through it.

[Slide] We tried, again, to mathematically quantitate benefit-risk. We used conservative assumptions. For benefit, we assumed -- we had to start somewhere -- that mortality truly is 58 percent, as we have alluded to. We assumed that the effect size is 15 percent. The reason I say that this is conservative is that, for risk, we used the HEM-0115 ITT overall population data. We also looked at the less-than-70-year-olds. But there is no real reason to say that because the 7 to 8 percent risk of SAE was higher in 115, it's going to be the same in RESUS, for multiple reasons. But let's just say it was.

The readout was an excess SAE score, which sounds complicated. But what it is, is as follows: What is the number of excess subjects expected to experience at least one SAE for every life saved? We do this in medicine all

the time. I have amphotericin as an example. Let's say you are in the intensive-care unit and you have a patient who you know has fungemia and will obviously die if you don't give him amphotericin. We give that patient amphotericin all the time. In our minds, we know that we are going to certainly save his or her life, because they are going to die without it. But some percentage of those patients are going to get renal failure, or at least will get renal insufficiency. So we do this calculus in our minds all the time.

For statisticians, this is just a standard reversal of the BRR, which is the benefit-risk ratio, and the numbers are there.

NMRC used very conservative numbers. You can say -- and I think it is a valid criticism -- that these are not validated. If we query this audience, there might be 20 opinions. But what I am going to say is what we did. I think it would be highly unlikely that people would be more conservative than this. What we said was an ESS less than 1. In other words, to save every life, you might have less than one additional patient with an SAE. Most people, clinicians and patients, would say it's highly favorable. At 4, we already said it might be transitioning. We queried 14 of our trauma specialists, and the numbers are much higher than that. The median I don't remember

exactly. I think it's 10, 20, 30 SAEs. There is a range. But certainly nobody said that at one or two additional SAEs, that would be unreasonable.

The results are that when you look at these conservative data, you can expect, if the same thing happens in RESUS, less than one additional SAE for every life saved. In English, for every life saved, .7 to .9 excess patients may have an SAE, as these predictions are. We think this corroborates the qualitative benefit-risk assumptions, that, as required by the regulation, risks are reasonable.

[Slide] The final slide, before the conclusions: What if we are wrong? What if those assumptions are wrong? FDA has made this criticism, and I think that's appropriate. Even if we are quite wrong with our trauma registry queries and mortality is as low as 45 percent or the effect size is only 10 percent, the ESS is still less than 1 or just about 1, despite those assumptions. We have a whole bunch of assumption possibilities in the package.

So even if these are inaccurate, favorable benefit-risk is predicted for RESUS. We think that this adds credence to our belief that risks are reasonable.

[Slide] I would like to transition for a minute. We have five categories of conclusions. Really, this is a summary of the initial outline that I had in the first

slide or two.

• One, I hope that we have been able to show that hemorrhagic shock is the most common preventable cause of death in trauma and that most deaths occur during the prehospital phase.

• Second, because trauma registry queries demonstrate approximately 58 percent mortality in a subset of hypotensive hemorrhagic shock populations with severe hemorrhagic shock to be targeted in RESUS, the current treatment is unsatisfactory in these patients.

[Slide] • Third, the breadth and redundancy of improved outcome in the preclinical hemorrhagic shock studies predict the prospect for benefit in humans in RESUS.

• Fourth, as the preclinical hemorrhagic shock studies demonstrate a mortality-reduction-effect size of 75 percent, we believe that a 15 percent predicted benefit in RESUS is highly conservative, with a fivefold margin of error.

[Slide] • That there was only a mild adverse shift in the safety profile of HBOC-201, despite comparison with gold-standard red blood cells and prolonged exposure in an older overall population in prior surgical trials, predicts reasonable risk in comparison with LR and brief exposure in young patients in RESUS.

• That group differences in the younger patients were narrowed further predicts reasonable risk.

• That the interim data from the South African trauma trial were reasonable and actually favorable so far further predicts reasonable risk.

[Slide] • Basically, this qualitative analysis predicts favorable benefit-risk.

• The semi-quantitative analysis somewhat corroborates it.

• On top of that, again, extensive protocol mitigation strategies further reduce the risk.

[Slide] My final conclusion -- and, Mr. Chairman, I thank you for you allowing me to go over -- is that all requirements of 21 CFR 50.24 related to benefit-risk have been met or exceeded in the RESUS IND, and we believe that the clinical hold should be lifted.

I thank you very much for your time.

DR. SIEGAL: Thank you very much for this presentation. Let’s conclude the sponsor presentations as quickly as we can, first with Joe Aker, EMT, MPH, executive director for the Birmingham Regional EMS; and then Dr. Kaplan.

Agenda Item: Concluding Remarks: Prehospital Need

MR. AKER: Members of the panel, I have three

minutes to do something for you. We are going to move quickly.

I have three goals here. One is to convince you that we need to do this program in emergency medical services. This is a civilian program for us, the way it's proposed to you. Secondly, we can do this in emergency medical services, and we will do this. Thirdly, I'm from the South and I can still speak quickly. We will see whether I meet this or not.

[Slide] I wanted you to see a little bit of our system there. I call your attention to two things. We are a system that does 20,000 responses a month. We do over 4,000 trauma system patients. We are recognized by Mitertek and Harvard with the Homeland Security Innovation Award, because they recognize the issue of trauma and what we have to do to take care of trauma.

[Slide] Why do we need the RESUS study? I have been a paramedic over 30 years. I can do things for airways that I couldn't do 30 years ago. I have the ability to utilize certain drugs. There are certain innovations that we have in airways. I can do as good a job in the field as almost any anesthesiologist can do or any surgeon, because I can do a surgical airway also.

Ventilation: I can do almost anything that a surgeon can do. I can put a needle in the chest. I can

relieve a tension pneumothorax. I have temporizing measures.

But when it comes to circulation, the C in that process, I can't do anything more than I could do 30 years ago. This is all I have to give my patient. All I have is Ringer's lactate to give that patient. That's not going to help that patient who has this spleen that has exploded as a result of a deceleration injury. It's not going to do what we need to do for that patient.

[Slide] So we need our interventions for circulation. You have listened long and hard to the risk-benefit ratio. I can tell you, as an EMS system director, in talking to multiple paramedics across the United States, we believe this will help patient outcomes. It is a civilian EMS study. We can do it in emergency medical services. We can help make the decisions that make this study appropriate for the patients, that make a reasonable risk-benefit ratio. We can look at what needs to be done for these patients. We have to do it if we are going to change trauma patient outcomes in the United States, in the world, and in the military theaters around the world.

We can do it with the current protocol. We can take the information that is needed to either exclude or include the patient and we can make sure that patient meets those criteria.

Just like you see that high-top Cadillac ambulance that we used to use when the funeral homes responded to emergencies, we need to move beyond that period. We are still in that period, with the fluids that we use in prehospital care today.

Having said this, I would like to reintroduce Dr. Kaplan, who will provide, from a trauma surgeon's perspective, how what we do in prehospital care is really going to help him make a difference in patient outcomes.

Agenda Item: Concluding Remarks: Trauma Surgeon Perspective

DR. KAPLAN: Ladies and gentlemen, it is a privilege for me to conclude. I want you to understand that this is not simply the perspective from a trauma surgeon, but this is collaborative from many different services.

[Slide] The trauma surgeons that are in this group and those who provide emergency care will recognize that our paradigm has shifted, and it has shifted significantly over the last few decades. Mr. Aker has told you that the paradigm in emergency medical services truly has not. It is load-and-go care. There is not value to staying at the site of the accident when someone has hemorrhagic shock. But I need a patient to be delivered to me upon whom I can bring my armamentarium to bear -- all of

it. There has been tremendous investment in hospital resources. It will be to no avail if the patient that I receive is not salvageable.

[Slide] Based on the known physiology of hemorrhagic shock, I believe that HBOC-201 addresses those prehospital needs in a setting where blood is absolutely not available. This is the high-risk patient population. It is in this group that those who provide clinical care will see AEs and SAEs as a routine part and parcel of their care. In many instances, there are so many AEs and SAEs that result from hemorrhagic shock and the care that is required that it's possible that the signal from HBOC-201 will be orders of magnitude lower, supporting the potential benefit of this agent in delivering a salvageable patient to the hospital rather than having excess risk.

This trial has been designed for military and civilian arenas, but we have the ability to collect the data to demonstrate its efficacy, or not, within the civilian arena at present.

I will urge you to help us to know whether this agent, in this fashion, in the prehospital arena, where there is no suitable comparator, can do what we need it to do -- save single lives and be applicable to a mass casualty situation.

Thank you so much for the privilege of the floor.

DR. SIEGAL: In the interest of speeding things along -- I know that the committee is going to have some questions, and perhaps we ought to take a few minutes, particularly for Dr. Freilich, possibly also for Joe Aker and Dr. Kaplan as well -- are there any specific clarification questions that any of you have at this point?

DR. GREENBURG: I have an answer to one of the questions that was asked before.

DR. SIEGAL: All right.

DR. GREENBURG: I was so fascinated by Dr. Freilich's talk, which I have heard many times. I'm sorry I didn't bring this back to you in an hour. The question was, what is the race distribution in our total population in HEM-115? The African-American population in HEM-115 was 82 patients, for a percentage of 11.9, and in all studies, of a total of 1,468 patients, there were 166, with a reference of 11.4 percent.

DR. SIEGAL: Is there an estimate of the racial and ethnic and socioeconomic population that we are likely to be dealing with in the new clinical trial, the urban population? It's likely to be very different from the 115.

DR. GREENBURG: I do not have that. Maybe Dr. Freilich does. We got the racial stuff. I'm not sure we have any socioeconomic data, but I can ask the boys to look.

DR. SIEGAL: That's a good question for Dr. Freilich, perhaps.

DR. FREILICH: We don't have socioeconomic data. What I do know -- and we can try to get those data -- is the concern that I think you might be getting to, and that is in terms of the distribution of risk, ethically, towards which population. Obviously, trauma occurs disproportionately more in inner-city, urban situations, and you end up with a potential unfair risk burden that certain populations will undergo.

We have tried to do two things. Number one is to make a big effort to include rural trauma centers and trauma centers in populations that have demographic distributions that have a larger Caucasian and other populations.

That also has an effect on the socioeconomic question that you are asking. There are places like the University of Iowa, the University of Kansas, and other such trauma centers.

The second point is that the exclusion of patients with short urban transport, 10 to 15 minutes, actually excludes a lot of that urban trauma, which is in the higher proportion of black populations.

So we have made a significant attempt to try to include a more fair and equitable distribution of risk.

DR. SIEGAL: Are there any other questions?

DR. PICKERING: I think Dr. Landow, earlier this morning, referred to a possible high proportion of patients who had brain injury, if I heard him right, and yet penetrating head injury is an exclusion criterion. Could you clarify that?

DR. FREILICH: We expect, based on the trauma registry analyses, that about a third of our patients will have TBI. The problem is, we have no penetrating TBI preclinical data. My own opinion is that maybe it should be relaxed, once the protocol gets going, if penetrating TBI data become available. But right now all four HBOC-201 studies and the one HBOC-301 study that have been completed are in blunt TBI.

DR. KATZ: I was going to say that there's an elephant in the room, but there's not; there's a pig in the room, a big pig. If pigs were people, Iowa and North Carolina would control the House of Representatives and the Senate would look substantially more rational. [Laughter]

When I got the briefing material, I tried to go to the literature and find out why we think pigs are valid trauma surrogates for humans. I didn't find a lot of stuff. What I found was pretty reassuring. But I think that should be addressed in the transcript. You should talk a little bit about why we like pigs. Most of your

data are in pigs.

DR. FREILICH: Pigs are considered the standard for cardiovascular hemodynamic trauma studies. They were recommended -- I think in 2002, there was a preclinical large gathering of specialists, and swine were considered the appropriate animal. Why? I don't know that it is so much more cardiovascularly predictive than canine models, for example, which are used in cardiology studies more. The overwhelming data, no matter how you look at them, in the literature and that are accepted by reviewers are in pigs. But I can't personally say that pigs are better than sheep or better than rats or mice.

The large-animal model is important, because it allows you to comprehensively assess ICU-type data. A critique of that might be, "You have swans, and you have this and that, and all these pigs. You are not going to have that in the EMS scenario in RESUS." But none of the intensive assessments were used to change anything. They were just for collection of data.

I don't know if that answers your question completely. I don't honestly know if it's a better model than others. It's considered the standard of care.

DR. MANNO: I have two questions. The first is, what would happen upon reexposure to HBOC-201? My second is, referring to slide 179, as a hematologist, I'm

interested to understand the AE you described as jaundice.

DR. FREILICH: I'm going to do number two first, if that's okay. Jaundice is, in my mind, an intrinsic side effect of all HBOCs. You see it in all patients. Whether they, in fact, are jaundiced or they just turn yellow -- because HBOC turns everything yellow. When you open the belly of the pigs who have gotten HBOC, the omentum, the omental fluid -- everything is yellow. It's just everywhere. Jaundice would include, obviously, an elevated bilirubin to prove that it truly is jaundice. That happens. It's the same transient liver function test abnormalities that you saw earlier in both animals and humans.

In the histology studies, as I mentioned, you do see mild consistent hepatobiliary changes, very low-scale severity. I think this is a mild adverse side effect of HBOCs.

DR. MANNO: But no concern about a hemolytic anemia as a result of infusion of the HBOC?

DR. FREILICH: No data to suggest that.

The first question was -- I'm sorry, I forgot.

DR. MANNO: What happens upon reexposure to the product?

DR. FREILICH: Are you asking about antibody formation?

DR. MANNO: Yes.

DR. FREILICH: In RESUS, obviously, that's not important, because you are not going to form antibodies in minutes to hours. Dr. Rentko, who is a veterinarian at Biopure, has some data over prolonged exposures.

Do you want to come up and provide some data, please? Do we need to come back to that?

DR. SIEGAL: In the meantime, Tom Quinn has a question.

DR. QUINN: I'm on the learning curve here. With HBOC-201, a well-known mechanism of action is vasoconstriction, which might occur despite hypovolemia, thereby causing this false impression of normal volemia. That is especially true when you are giving multiple doses. It has a longer half-life. So upon arrival into the emergency department, obviously, the key is going to be, what is the actual, true volume load in that individual at that point? I didn't hear you particularly address that. The side effects we are hearing about, the adverse events -- the decreased urine output, the cardiac load, and so forth -- may be a reflection of that hypovolemia, despite normal blood pressures and other types of issues.

I think that was one of the concerns that FDA raised in their presentation. But I didn't hear you quite address that particular issue.

DR. FREILICH: I would like to take a stab at responding to that and then ask some of the critical-care trauma surgeons, Dr. Kaplan and Dr. Dutton, to maybe come up and make comments as to what will happen in the trauma bay.

The preclinical data do suggest, as you state, the potential for lower urine production, as well as lower cardiac output. But it's very important to understand what the pattern is. You don't see that in severe hemorrhagic shock. You see it in mild hemorrhagic shock, because -- not entirely, and there might be some after-load effects -- mainly they are an artifact of the models, because the models only allow you to resuscitate either to pure pressure-controlled models or ours always included heart rate, too. But that doesn't happen in the clinic. You use a thousand parameters. So the only time that you end up with consistent findings of relative oliguria, as you are alluding to, and lower incidence of cardiac output is in the lower-severity models. Obviously, the blood pressure goes up a little bit. Someone wrote a protocol that says, if the MAP hits 60, stop giving HBOC, and that's what you see.

So it's actually back to the Starling curve, that you have not repleted intravascularly adequately. We feel that there are going to be multiple parameters, and I hope

the clinicians can back that up.

DR. KAPLAN: This is really a model-artifact question, as Dan has said. The only thing that happens in the trauma bay is more resuscitation. The standard is two large-bore IVs. You get 2 liters of crystalloid. You get this almost as your entry ticket -- “hi, you came into the ED with hemorrhagic shock. Here you go.” The decision of when to stop is one that we make, not whether we should continue.

This is a unique patient population. They have injuries, as well as vital signs, as well as physical examination characteristics that say, “I’m hypovolemic, and I have consequences.” They may be actively bleeding. You may watch their abdomen distend. They may be draining from their chest tube. You have tremendous indicators that tell you, “You need more.” The concept of stopping in the trauma bay and even considering allowing them to not get more would be most unusual.

Is that how that works at Shock Trauma as well?

DR. DUTTON: Yes. What you are referring to is the phenomenon of hypoperfusion -- that is, a normal blood pressure, but inadequate actual tissue perfusion, due to vasoconstriction. This is something that all trauma patients do, to a large degree, anyway. The young healthy urban warrior gets shot and vasoconstricts, often

extremely, and may come in with a normal-looking blood pressure while still being two quarts down. We recognize this. A lot of what we have learned about taking care of these patients in the trauma resuscitation and the OR, in the early going, has to do with getting beyond blood pressure and heart rate and getting to actual indicators of perfusion.

Lew mentioned some of them -- just visible blood loss, diagnostic tests that demonstrate blood loss or ongoing bleeding, and the laboratory tests. These are all patients who get a blood gas as they come in the door. We can look at their lactate. We can look at their base deficit. We can draw conclusions about tissue perfusion, rather than blood pressure, and react accordingly. That's one advantage we have in the hospital that they don't have prehospital.

DR. SIEGAL: Dr. Finnegan, and then Dr. Fleming.

DR. FINNEGAN: You have stated on several occasions that the reason for looking for this is both military and mass casualty, so there is either not blood available or not sufficient blood available. Most of those are going to be blast injuries. Blast injuries, we know, have a distance effect on vascularity, and probably also an effect on hemostasis. Yet there is no blast model in your preclinicals. Is there a reason for that?

DR. FREILICH: Blast has become a huge issue with the military. The Navy, with the Marine Corps, has a significant research program. They simply haven't been matched yet. We don't have those data. So I can't say in blast injuries. None of the models with HBOC-201 simulated those.

The liver injuries, just to be specific, so you know what they are, are a combination of penetrating and blunt. They are laceration and concomitant crush.

DR. FLEMING: Dr. Siegal, I guess I am looking for some guidance here. I think Dr. Freilich's presentation was very informative. I guess my concern is, we are almost to noon, and much of the day has been spent in sponsor presentation. There are a number of issues that I know I have with Dr. Freilich's presentation, in terms of different interpretations that I would really like to have clarification about, different interpretations about the convincingness of your data that when you go to a younger age, you will have fewer safety risks and that your animal results are truly providing some interpretable relevant insights, and the interpretation that you gave to the South Africa data and the excess SAE scores, where I am coming out with different results.

Just pursuing these with Dr. Freilich will take at least 15 to 20 minutes. I presume this isn't the best

time. Is that right?

DR. SIEGAL: I think probably we had better wait on that.

DR. FLEMING: This isn't unique on advisory committees. I have often stated the concern that we spend an awful lot of time hearing the sponsor's presentation, which we have already read, where I am really most interested in hearing my colleagues' interpretations and getting issues out. I really hope we are building in a lot of time for discussion, because there are a lot of insights that I need to gain from my colleagues and a lot of issues that I would like to raise about the data as they are being presented, relative to my understanding of the data.

DR. SIEGAL: Just to reassure you, we have essentially the entire afternoon to discuss this openly, in open session.

DR. FLEMING: I note that we are an hour behind.

DR. SIEGAL: We are, I know.

DR. HAUSER: A simple, one-word question: Are you using in your formulation racemic or L-lactate?

DR. FREILICH: This went back and forth with the FDA. The current formulation of HBOC-201 is racemic. Therefore, we don't stipulate whatever the standard is locally.

DR. SIEGAL: Any other questions?

DR. KLEIN: I have a lot of questions as well. I think maybe I will hold them for this afternoon.

DR. HINTZE: I think there are increasing data to suggest that oxygen radical production goes up with age, and older people have enzymes -- for instance, NADPH oxidase and xanthine oxidase -- that are not there, because they also scavenge nitric oxide or there is a concomitant down-regulation of nitric oxide synthase with age. I think both of those facts suggest that the aged population, even the non-exercising population, will be very different from a young, healthy group. So I think your NO bioactivity, the vasoconstriction that you show, simply is pointing out that NO is vulnerable in these circumstances. I think with age it's much more vulnerable. I think that's almost dogma now.

So I am not surprised that older patients have a different response to HBOC-201 than do younger patients, who are young and healthy and exercise and have a big eNOS.

DR. FREILICH: I agree. I must say that I'm not positive that the fact that blood pressure responses are higher in older patients and the fact that you have a higher potential for oxidative damage necessarily connect. But they might.

DR. SIEGAL: Hopefully, that's all the questions we have for now. There is one more?

DR. SZYMANSKI: Yes. Dr. Freilich, you showed a very interesting slide, titled “Vasoactivity Is Characteristics of All HBOCs.” Then you showed that the HBOC-201 has the lowest vasoconstrictive activity. Is that really the true meaning of this slide? Why would that be?

DR. FREILICH: I didn’t say that it was lowest. What I said is it’s lower than DCLHb. We have a bunch of backup slides that I would be delighted to put up whenever you want.

After FDA made the comment that DCLHb and HBOC-201 are vasoactive products, it prompted NMRC to complete a comprehensive animal study looking specifically at tetrameric hemoglobin. We took Oxyglobin, we then took HBOC-201 -- so now 32 percent and 3 percent -- and then we actually manufactured the same HBOC-201 with only .4 percent tetrameric hemoglobin. There was a clear difference. The 1 to 3, which is HBOC-201, and the .4 had statistically significantly fewer vasoactive responses, if you will accept that blood pressure responses are probably vasoactive, in comparison to the 30-something percent.

We didn’t do 100 percent at the same time, but Dr. Yu [phonetic] recently published that 100 percent is more than 30 and 70. The accumulating data are very clear that there is a consistent pattern, that elimination of tetrameric hemoglobin minimizes vasoactivity. But there

might be a threshold where you can keep cutting it out and it doesn't matter anymore.

DR. SZYMANSKI: What about the extravasation of this hemoglobin, HBOC-201?

DR. FREILICH: It's the same thing. The t½ increases when you polymerize it. HBOC-201 has a 19-hour half-life. I honestly don't know the number for DCLHb. My conjecture is that it's shorter.

DR. SZYMANSKI: The size of the molecule apparently interferes with extravasation. Is this a large size?

DR. FREILICH: Yes. The mean is approximately 256 kd. It is theorized that that is the reason for less vasoactivity, in that the large size precludes extravasation to nitric oxide and guanyl cyclase and that whole mechanism.

DR. SZYMANSKI: Thanks.

DR. SIEGAL: I think at this point --

DR. FREILICH: We may have an answer to one of your questions.

DR. SIEGAL: All right, I guess we could take that now and then adjourn for lunch.

DR. RENTKO: [Slide] Regarding repeat administration of Hemopure, I will call your attention to the three multiple-dose studies, two preclinical and then

in a volunteer patient study. You will see that there are three different products that are listed. They are all based on the same bovine hemoglobin, so we consider the immunogenicity similar amongst all three of these products. The 301 is the veterinary product and the H-1S is an earlier formulation.

Basically, repeat-dose studies, in both patients and animal studies, showed that antibodies do develop, IgG antibodies. They are not neutralizing. It appears that an immune-tolerance type of phenomenon occurs. We hypothesize that that's related to the fact that we are giving gram quantities of a protein via an intravenous route, which is not a good immunogenic route. No serum sickness occurred and no immune complex deposition occurred, at least in the preclinical studies in which we evaluated the histopathology.

DR. SIEGAL: Thank you very much.

At this time, FDA has requested that we adjourn for lunch, so that we can start fresh with their view of this, before the open session. Please try to be back in an hour.

(Thereupon, at 12:10 p.m., the meeting was adjourned, to reconvene at 1:05 p.m., the same day.)

AFTERNOON SESSION

DR. SIEGAL: There are a couple of things that we are going to come up with in our consideration of the questions. Question 3 is going to be restated for the committee at some point. There are also a couple of written statements that we will read prior to the FDA open public hearing.

Right now we are going to go back to the FDA considerations, starting with studies in animal models of hemorrhagic shock. The first speaker will be John Hess, the second Thomas Hintze, and the third Carl Hauser.

Agenda Item: Studies of HBOC-201 in Animal Models of Hemorrhagic Shock

DR. HESS: Thank you.

I am Rick Dutton's blood banker. In a previous existence, I ran the U.S. Army's blood product development program. I point out that the Army spent about $100 million to develop the field of hemoglobin-based blood substitutes, investing mostly in chemistry, in industrial development, and in toxicology. When the field had been well-sown with commercial and private money, we left the activity.

During the same time, the U.S. Army spent another $100 million to develop the swine as a model in biomedical research. It was a congressional rule that basically said

that we could only use dogs, companion animals, when there weren't reasonable alternatives, and a series of investigators, largely successfully, completed that activity. The dog is now only rarely used. We developed resuscitation fluids, such as hypertonic saline, dextran, really pioneered the field of hypotensive resuscitation, worked out issues in hemoglobin toxicity and hemorrhage-control drugs and devices.

During that process, we learned several important facts about pigs. Two of them really play a role in understanding these studies. Pigs are relatively anemic. They start with a hematocrit of about 30. They die when their hematocrit gets down to 9, which means you can only exchange one blood volume in them, a 70 percent reduction, and they die.

In the Navy's pig hemorrhage and brain-injury study, they gave the animals a fluid percussion injury, resected 50 percent of the liver lobe. They treated some of the animals with Ringer's lactate at 20 mL every 15 minutes for an hour. The HBOC group was treated at 10 mL every 15 minutes for an hour. In the group that was delayed for 30 minutes, there were no significant differences. In the 75-minute delay group, there was a marked mortality at about 75 minutes in the Ringer's lactate-treated group.

This occurs because the hematocrit falls rather promptly under those circumstances to 9 and the animals die of hemodilution. Here are the actual amounts of volume that were given in the study. You can see that, as the blood pressure is maintained as a pharmacologic effect of the hemoglobin, they are getting successively less amounts of hemoglobin, but they get the full 80 mL of Ringer's lactate and are diluted.

A model like this relay doesn't reflect current thinking on volume administration in the brain-injured. The model really doesn't test the efficacy of the hemoglobin against equivalent volumes of the fluid it comes in. It really sets up conditions that kill the animal in the control group. So there is this marked falloff at 60 minutes. But the real question the study raises is, why do the hemoglobin-resuscitated animals, in fact, die 15 minutes after they get to the hospital? Do they, in fact, suffer from this hypoperfusion syndrome and it is actually caused by the drug? The study doesn't critically evaluate that.

A second study by King, Steve Cohn, and Keith Proctor, another traumatic brain injury model, again used blood pressure as a trigger for whether resuscitation should be given. Because the dilution leads to low blood pressure and pigs naturally drop their blood pressure, the

pigs continued to get fluid throughout the study, ultimately getting the equivalent of 20 quarts of water in a 70-kilogram person. This is associated with swelling in the injured brain and bad outcomes. Here are the brain pressures that result from giving 20 liters equivalent of fluid.

Again, these models simply don't reflect current thinking on volume administration to the brain-injured. It doesn't test the efficacy of the drug against equivalent volumes of fluid. We have now come to have very fine guidelines in the Brain Trauma Foundation about what should be done with brain-injured people. The models just don't reflect that.

Just in summary, a large series of 16 studies tended not to address physiologically important questions about known toxicities of HBOCs. We discovered and published a whole series of known toxicities of hemoglobin-based blood substitutes in the early 1990s. Baxter went on and conducted a large number of animal studies, all of which showed that their alpha-alpha cross-linked hemoglobin would perform very well, by setting up studies very much like this, where they compared the drug and used the pressure to drive physiologic differences that would ultimately lead to good or bad outcomes in groups that really had nothing to do with oxygen transport.

With that point, I will stop.

DR. SIEGAL: Are there any questions for Dr. Hess?

DR. SWENSON: I'm not totally clear on what you are getting at. Is this an issue of volumes of distribution of lactated Ringer's versus the HBOCs, and that's not what is being controlled for?

DR. HESS: The added volume will drive additional hemorrhage, and the volume will go in, cause brain swelling. But very small volumes of the hemoglobin cause an increase in blood pressure. If you design a model where you are treating hypotension, you can set up a situation where the treated animals get a relatively small volume and the control animals get a very large volume, and the large volume itself is what drives the failure of the model.

DR. SWENSON: Could you tell us, then, how you would design the experiment, to get at the points you think should have been attended to?

DR. HESS: We have now come to realize that no resuscitation is bad and a lot of resuscitation is bad. One seeks for some intermediate point. An obvious one is the same volume as the carrier for the hemoglobin. Is the hemoglobin any better than the water it is in?

DR. SIEGAL: Anyone else?

[No response]

Dr. Hintze is a professor in the Department of Physiology at New York Medical College.

DR. PROCTOR: Sir, may I be permitted to comment? It was my study that was reviewed up there and I just wanted to correct a few factual --

DR. SIEGAL: Could you please identify yourself?

DR. PROCTOR: My name is Ken Proctor. I'm from the University of Miami.

That was HBOC-301, not 201. There were actually two control groups. One group got Ringer's only, because that was the control, but the other group got mannitol, pressors, and a blood transfusion. Basically, what the data showed was that HBOC-301 was equivalent to the group that got standard of care, which included mannitol, pressors, and a blood transfusion.

We also did a three-day survival study and showed that the animals that got the blood substitute survived in the same manner as the animals that got transfused.

But that was HBOC-301.

DR. SIEGAL: Thank you.

DR. HINTZE: I was asked by the FDA to review the large-animal studies. I didn't participate in the studies that I am going to review, but I started out looking at them from a technical point, looking for generalities, and then going back and having to reevaluate that.

[Slide] My first love is nitric oxide biology. I tried to view what HBOCs do in terms of scavenging nitric oxide. We have heard a lot today about NO affecting vascular smooth muscle. It causes vasodilation; when it's absent, it causes vasoconstriction. Within the studies that I reviewed, there were also studies designed to look at white cell adhesion and platelet aggregation. NO inhibits both of these. Therefore, when NO is absent, you tend to get thrombus formation and tend to get white cell adhesion.

In addition, nitric oxide affects cytochrome oxidase in mitochondria, to reduce oxygen consumption. So when NO is absent, oxygen consumption and extraction increase. If hemoglobin were to bind NO, then this effect on the mitochondria would increase tissue oxygenation by causing a bigger gradient for oxygen diffusion.

[Slide] Finally, nitric oxide controls, at least in the heart, glucose, fatty acid, and lactate uptake, by phosphorylating a number of enzymes in intermediary metabolism.

So although we have been talking about NO as a vasodilator, it has a number of other effects that have to be considered.

I also looked at the data I was given in terms of Guyton curves. These are curves from Guyton's *Textbook of*

Physiology, showing what happens when you alter blood volume or when you alter vascular resistance. Normally, we are on this black curve -- where the cardiac output extrapolated from animals to humans, by the way, of about 5.5 or 6 liters a minute. If you reduce blood volume, you shift the venous return curves downwards to the left, resulting in a decrease in cardiac output and a decrease in cardiac preload. Therefore, the heart gets smaller and moves down the front end of a Frank-Starling curve. If you replenish the blood volume, then you move back towards normal, reestablishing the normal venous return and cardiac output.

Because HBOCs are vasoconstrictors, you also have an effect of vasoconstriction, which is shown in this curve. We move from normal -- if you increase vascular resistance, cardiac output goes down again, but this time because resistance is high, not because blood volume is reduced.

So the way I looked at these data was that they are evidence that cardiac output was reduced because of this, and then the vasoconstrictor properties of hemoglobin again causing cardiac output to be down, as you have an increase in vascular resistance.

The way I looked at the data in a scientific sense was in terms of nitric oxide bioavailability, and

secondly, in terms of Guydon's curves regulating resistance in blood volume.

[Slide] I did some studies previously with the Biopure HBOC-301. Maria Gawryl was the person at Biopure at the time. We looked at the effects of bovine polymerized hemoglobin in chronically instrumented conscious dogs. In one of the studies, we matched the hypertension to HBOC with angiotensin and then looked at cardiac oxygen consumption and substrate use, et cetera. If you do this, what you can see is that MVO_2 is higher in the presence of a hemoglobin. Oxygen consumption per unit work is also higher. This is because hemoglobin binds NO that no longer regulates cytochrome oxidase.

The fact that oxygen consumption is higher simply means that oxygen extraction is bigger, so that hemoglobin is promoting oxygen extraction by affecting mitochondria inside various cell types.

We looked at fatty acid, glucose, and lactate uptake in the heart. Fatty acid uptake goes down; lactate uptake and glucose uptake increase. This is very typical. If you give an NO synthase inhibitor, the heart switches from fatty acids to glucose. This is another effect that we should think about. The jury is still out as to whether switching the heart from fatty acids to glucose is a good or bad thing. Be that as it may, all of our dogs survived

these protocols and were healthy, as far as I could tell.

[Slide] To look at the data that I was given, the 20 papers or so that I analyzed, I did it based on a couple of assumptions:

- Transit time to the hospital is short.
- This seems silly, but survival for long periods includes survival for short periods.
- Preclinical RESUS will not be technically sophisticated.
- Neutral HBOC-201 is not bad.
- Based on Demetriades, who is not here, most of the mortality occurs early.
- With blunt trauma, about 30 percent die in the first hour, another 18 percent die in one to six hours. So to do something quickly is probably important.

[Slide] These are the Demetriades data, just showing where mortality occurs. This is the sort of analysis that I did. I took a large number of studies and I started looking at trying to make generalizations.

[Slide] Things that you haven’t heard today: All of the pig studies were done in anesthetized pigs, with isoflurane anesthesia. Some of the pigs were paralyzed. Some of them were ventilated. Some of them got lots of oxygen. Some of them got atropine. Now, atropine is going to be problematic, because it’s going to make heart rate

high, it’s going to make the heart smaller, and it’s going to prevent any bradycardias that might be seen as part of the compensatory -- or used to evaluate hemoglobin’s pressor effects.

Some of the animals were female. Some of them had a laparotomy on top of other things. Some of them had the spleen removed. Because the spleen is an organ that can expel blood during hemorrhage, that actually became a consideration.

Some of the animals got lidocaine. One group had *Ascaris* and was still used.

[Slide] I went back to look at baseline data for these studies to try to see if the variability that I was reading was determined by the baseline. If you look at cardiac output, they vary from 7 to 9 L/min in some of these animals, down to 3.8. When you normalize to cardiac index to get in surface area, there is still a good variability. Mean arterial pressures, before you did anything to the animals, ranged from 75 to 100 or 120. Heart rates varied from 80 to 60 to 140 in the presence of atropine, to 120 to 160 in the presence of atropine. 115 or 126 seems to be just naturally high.

[Slide] If you look at the remaining studies, heart rate is generally high and arterial pressure is generally low. So you are already starting at a fairly low

cardiac output, low arterial pressure, high heart rate or variable heart rate in many of the studies.

[Slide] I started looking at the compound and simply looking at survival. The upshot of this is that the animals who got hemoglobin survived better, in my opinion, than the ones who did not. This is a listing of all the studies. For instance, over here, seven of eight survived for four hours, seven of eight survived 72, and only one of eight with Hex survived. So the generalization I would make is that the animals survive better, despite the fact that they were anesthetized and had various regimens associated with that.

[Slide] The conclusions that I would make:

• All or many of the studies in pigs use anesthesia, ventilation, paralysis, splenectomy, laparotomy, ventilation with oxygen, and especially used atropine, which I think is probably to prevent tracheal secretions, but it has many other effects.

• Hemorrhage was almost always sterile.

• The fluid was often warmed and the pig was warmed.

• Measurements of cardiac output and heart rate were variable prior to hemorrhage due to the anesthesia, et cetera, even when normalized to cardiac index.

• It is obvious that all hemoglobin solutions are

not the same. The diaspirin hemoglobin and polyhemoglobin are obviously different, and I think to the point where HBOC-201 and 301 should be considered separately.

• The nature of the invasive measurements during the preclinical phase confounds the conclusion to some degree and will not be used in RESUS.

• The removal of blood from the abdomen in experimental studies to measure total hemorrhage volume is unlike RESUS and may prevent pressure from building up in the abdomen, to help with clotting.

• In many instances, HBOC is administered to a fixed volume and certainly not to a high systolic pressure. Dr. Freilich mentioned this as well.

[Slide] So my conclusions would be:

• In general, the use of HBOC-201 increased survival to simulated hospital arrival and longer periods.

• The results are fairly uniform across models.

• The results are applicable to varying times of treatment and to hospital arrival.

• Generally, the use of HBOC to support pressure to various levels -- 50, 60, 70; in RESUS, it will be not higher than 120 -- is beneficial.

• Generally, less fluid is needed for resuscitation when giving HBOC.

• Generally, there appears to be

vasoconstriction. Either pressure rises more or calculated resistance rises more.

• There may be some utility in measuring lactate, but it depends on how long it will take to get to the hospital.

• The histology from the papers that I read seems to indicate minimal damage in most organ systems, and what damage there was, was not carefully organized.

What I tried to do was look at these studies with a critical eye. I don't mean that the use of anesthesia, et cetera, is a large criticism. It obviously has to be done for experimental purposes, but it also has to be considered when we think about the implications of the studies that we heard about today.

DR. SIEGAL: Thank you. Any questions for Dr. Hintze?

DR. KLEIN: The issue of anesthesia is one, I think, that is extraordinarily important. We heard a lot this morning about vasoconstriction. I, for one, am less concerned about the systolic blood pressure, especially when the rises are small, or the pulmonary artery pressure than I am about vasoconstriction in the microcirculation and what might happen in areas that become quite hypoxic that ordinarily might not.

I am wondering whether you have any way of

telling us whether the use of anesthesia in these models might change the microcirculation so that the potential adverse effect might be mitigated in this particular model.

DR. HINTZE: I'm really a basic scientist. You are going to have to get an anesthesiologist to tell you what isoflurane did. But certainly if there is a large sympathetic effect associated with that or it releases circulating catecholamines to cause peripheral vasoconstriction, it would be a problem. But I can't evaluate that technically.

DR. PICKERING: A question about the blood pressures. I think in the animal models they are referring to mean arterial pressure. Is that right?

DR. HINTZE: Correct.

DR. PICKERING: Whereas in the human studies, it's systolic pressure. So if you had a mean pressure of 80 millimeters in a pig, what would the systolic pressure be?

DR. HINTZE: I don't know the answer to that. I would think 110 or so. I can't tell you specifically.

DR. FINNEGAN: Can you give us some idea of whether isoflurane has an effect on nitrous oxide?

DR. HINTZE: I don't think so. I don't know the answer to that. I have not heard that.

DR. SWENSON: There is quite a bit of literature

to show that many of these fluorinated anesthetic gases have important effects on antioxidant and radical injury, and even an emerging literature that they may be quite protective in ischemia reperfusion injuries.

DR. HINTZE: The comment that I made this morning to Dr. Freilich -- the amount of superoxide around from any source, in the young versus old, versus various sorts of anesthetics or drugs that might be used, is critically important in terms of NO bioactivity. So, yes, it would be important.

DR. KAPLAN: One of the issues with anesthesia is that for this patient population, especially those that have hemorrhagic shock that arrive at the emergency department, they may end up with an anesthetic truly within minutes, as part of their care plan.

DR. HINTZE: The problem is, RESUS is prehospital. Most of what I evaluated was from the time they got the hemorrhage to the time they got to the place where they could get red blood cells. I think my comments are directly related to that initial phase that RESUS is important for.

DR. CRYER: If I could just comment on Dr. Klein’s question, most general anesthetics would perform on a sympathectomy, essentially, so they would vasodilate everything. Then you would be working from there. I guess

the potential downside of that is, if you vasoconstricted more during -- of course, anybody coming in with bad hypovolemia is also going to be maximally vasoconstricted. So adding a vasoconstrictor shouldn't do too much. But whether there is a confounding effect when you release that vasoconstriction with a general anesthetic remains to be -- it is a potential confounder.

DR. SIEGAL: Carl Hauser.

DR. HAUSER: I'm Carl Hauser. Don Jehn gave me the unenviable task, after considerable discussion, of trying to translate some of the preclinical data from the animal stuff to human studies.

I am a trauma surgeon, for those of you who don't know me. I also do basic science. I have been interested in hemoglobin resuscitation since I was in Will Shoemaker's lab in about 1977-78. So this is old, familiar territory to me, including the hypertension and all that stuff.

In any case, our job here is to assess, from our point of view, for the panel, as I see it, the efficacy of HBOCs as a resuscitation fluid. They fill two roles, and they are separate. One is a volume expander, and they are colloid volume expanders. The other is that they are oxygen carriers. The other is to assess for potential harmful effects in animal models, in the ways that we have discussed before.

In order to model outcome predictions, we have to say, “What are the potential benefits to humans of these effects? What are the potential harms to humans,” and try to predict some of the AEs that may occur in the RESUS trial and then determine whether waiver of consent was really warranted and, to a certain extent, to use this meeting as an opportunity to improve the translational process with respect to acute care studies.

I think the last thing we really need to discuss is which populations should be tested. That’s for going forward as much as anything else. Those are the populations with the most benefit and least risk.

I must say that I wrote these slides before some of these other issues were addressed by the study group, in the interim between the last time we were supposed to do this and this time.

In terms of the modeling parameters that I looked at, I looked at whether they were controlled or uncontrolled hemorrhage. I looked at the depth and duration of the shock -- and I looked at all of the papers -- the inclusion or exclusion of associated tissue trauma, which will be extremely important in terms of the animals’ immune response, and to what extent the clinical resuscitation protocols may reproduce what will be done in the field, and also to look at the undesirable effects. I

think we have to recognize that undesirable effects with this, like with any drug, are inevitable. The question is, does the punishment fit the crime?

Lastly, I think we have to say how humans should be tested. I think it's fair enough to say that the clinical studies should reflect the animal data, to the extent that they point us in the right direction, and they should not reflect marketing concerns or client concerns, such as carry weight for paramedics in the field. That's not the way that we should be doing science. That's the way we should be doing, in my estimation, late-phase studies, 3Bs.

We have to answer here, what are the populations that we should be looking at going forward? What are the applications we should be looking at? Are they urban? Are they rural? Are they far-forward use? What are the appropriate comparators, and are they appropriate in the study? What are the appropriate endpoints that we should be looking at? We should be looking at nitric oxide vasoconstriction side effects. I won't call these adverse effects; I will call them side effects. They are expected. The question is, are they going to be a net win-win or are they going to be a net lose? That's what we have to focus on.

In terms of the physiology -- just my overview,

going over all of these studies -- what I found -- and this is my impression, looking at I don't know how many papers. I can't count that high. Being a surgeon, I don't have that many fingers.

The HBOCs clearly produced higher blood pressures than either lactated Ringer's or Hextend. But the cardiac index and oxygen delivery were often lower. Unfortunately, the SVR was often unreported in these trials, and should have been reported. I had to back-calculate them in my head. I can back-calculate them. They were uniformly higher than SVRs. This did appear to have an effect on hepatic bleeding. However, in terms of volume resuscitation, there was uniformly better volume resuscitation in the trials. That is, of course, an expected effect, because at two-to-one versus four-to-one, which would be appropriate for a colloid versus a crystalloid, that is basically written into the protocol. So you can't really say that there is any indication of benefit from that respect.

In terms of mortality, my impression, like Dr. Hintze, was that there was a mortality difference. In my general appreciation, it was mostly in the severe shock preps that that was concentrated.

However, mortality does depend on hemoglobin. As was pointed out, these pigs die as they become anemic. In

that sense, one model really stands out, and that was the Carolina model, in reading through all the papers, which was a constant-blood-loss/constant-fluid-replacement protocol. That really, to me, does most closely replicate long-distance, which is either rural or delayed urban or military, scenarios. In those cases, the HBOC clearly allowed for survival, as the hematocrit gets to very low numbers. It therefore indicated to me that it may be of crucial benefit in long-distance transports.

In terms of the immunology and pathology data, I didn't really see much difference. Lung pathology wasn't much different, except in the severe, uncontrolled hemorrhage. But it was unclear to me whether that was a statistical aberration, because there was earlier death in the comparator groups. That has to be looked at very carefully, because in the human group you would be using ventilator-free days rather than the presence of pathology as your endpoint. So that needs to be looked at differently going forward.

In terms of hepatic pathology, there was a clear transaminasemia and some cholestasis. It probably was related to decreased visceral perfusion. But so what? In clinical reality, hepatic dysfunction almost never determines outcome in trauma patients.

In terms of significant differences in post-

injury inflammatory events and ICU stays, I think it's unlikely to have an effect.

The next thing that I thought was important was to look at coagulation and hemostasis. As other people have said before, the PFA-100s, which are really the state of the art in this -- and these were good studies -- do show a clear HBOC effect. So there is some coagulopathy associated with this drug. This will affect control, eventually, of the primary injury. However, if you look in the studies, they look equivalent. Why? Their comparators are always Hextend. Hextend also creates a known thrombopathy. So this is a straw man and should not have been used.

However, although it might be a significant issue in clinical use, the reality is, corpses don't bleed. So if the patient arrives at the medical center alive because of HBOC allowing them to maintain a blood pressure and a cardiac output, so be it; I will deal with the bleeding.

The next issue that I looked at in comparison was tissue oxygenation. These were actually rather sophisticated and complex studies. I think it's clear that HBOCs do improve tissue PO2. There are regional differences, to be sure. Hepatic oxygenation appeared worse. Brain appeared better. Injured brain appeared better still. But there was no obvious increase of lactic

acidosis or increase in base deficit, the way these trials were done.

I could quibble a little about the way they were matched and the fluids, but I don't think it was a big deal. It clearly does suggest that there may be a possible advantage to using these drugs in the trauma transport arena, especially in patients with significant traumatic brain injury.

The next thing I looked at was the nitric oxide metabolism -- again, some rather sophisticated studies done. I think it's clear, as Tom Hintze pointed out, that these drugs clearly do sump nitric oxide. There are some differences between the different studies, based upon the assays and whether you assay nitrates and nitrites or S-nitrosylation. However, in my judgment, looking at this versus the others, I think it's fairly clear that the vasoconstriction does seem to be less than prior hemoglobins, but there is no way to figure this out except to look at it clinically and see how it plays out. We are not going to be able to predict this.

In terms of predicted benefits, my judgment is, reading all these papers, that it will be potentially useful, especially in extreme anemia and prolonged transports. Secondly, the volume expansion benefits and blood pressure effects may be useful, especially in

traumatic brain injury. I did not see a clear excessive nitric oxide sump effect. I think these drugs are likely to cause coagulopathy, but so are all the other fluids that we use, especially with dilution.

So my impression is, on those bases, that exemption from consent appears to me to be warranted.

In terms of concern for AEs, there are no obvious excess AEs in the animal trials. I think we will have to watch for acidosis in human trials. I think what we will have to watch for very carefully is that the distribution of MOF events postoperatively may change. They may change away from lung injury towards splanchnic-hepatic injuries. But in survivors, this will be an expected and welcomed disease of survivorship. I'm happy to take care of live patients in the ICU who have MOF if they would have died otherwise.

I think we should avoid the preclinical resuscitation bias. We should recognize that these are colloids; they are not crystalloids. The EMTs, as in the trials here have pointed out, have to titrate in the field to effect. I think the two-to-one or four-to-one should not be used as a basis. It should be pure titration to effect.

As a last comment -- this is from me -- I think it's unfortunate that the sponsors have to play to their

clients and that the FDA is a client for them, and so is the DOD, obviously. We should be looking at science here and not at, particularly, getting the drug through the FDA.

I really appreciate the opportunity to interpret these data with a group of true experts. I think that is a real benefit of having a meeting like this. I think the FDA would be well-advised, in my humble (or not so humble) opinion, to reward unspun data rather than the spun data which tend to come from the sponsor, from their animal trials, and that the outsourcing, both of scientific expertise and ethical expertise, such as is done here, will tend to insulate the FDA, I hope, from political fallout.

My own personal opinion -- and I hope that the impression of the people here going forward will be that waiver of consent must be more readily available, where the preclinical data warrant, or else acute-care research in the USA will die.

Thank you.

DR. SIEGAL: Thank you, Dr. Hauser. Are there any questions for Dr. Hauser?

DR. KLEIN: Dr. Hauser, why do you think we saw no severe adverse events in the animal data, and yet we seem to have seen them in the human data that we were shown?

DR. HAUSER: If I were to guess, it’s because

what constitutes an adverse event in the human is much more poorly drawn and much more nebulous. I think a lot of things have to get reported as adverse events which may not be. You have, essentially, complex patients with multiple problems, rather than healthy swine.

Is hypertension an adverse effect? I would say, no, it's not if you have a head injury and if you have increased intracranial pressure. Is it if you have underlying cardiac disease and have three-vessel disease and you need offloading of your ventricle to allow subendocardial perfusion? Yes, it is.

In the clinical realm, we are forced to have a big tent and assume all those things are adverse events, and then have somebody who is non-biased, such as a group like this, presumably, sort them out.

DR. SIEGAL: No further questions?

[No response]

Thank you very much.

Now we are going to hear the FDA assessment from Toby Silverman, MD, from whom we heard earlier.

Agenda Item: FDA Assessment

DR. SILVERMAN: I'm going to try to give just such an unbiased opinion.

Again, I'm Toby Silverman. I'm the head of the Clinical Review Branch that has responsibility, in the

Office of Blood, for reviewing this IND.

At the outset, I want to thank Dr. Landow, who is an intensivist and anesthesiologist, for his work in preparing a portion of the discussion about risk-mitigation strategies for RESUS, and for his work in analyzing the safety signals for this product.

[Slide] FDA recognizes the important role that oxygen therapeutic agents might play in improving outcomes in traumatic hemorrhagic shock and supports the development of safe and effective agents for use in resuscitation. FDA further recognizes that there is a critical unmet need for improved outcomes in both civilian and military trauma.

[Slide] The RESUS protocol proposes a comparison between HBOC-201 and lactated Ringer's for the treatment of life-threatening post-traumatic hemorrhage, with or without blunt traumatic brain injury, in the urban ambulance setting. The product will be administered in the prehospital setting exclusively. Unused product will be finished, but no new bags of product will be started after arrival at the emergency department. The study is to be run under the provisions, as you have heard, of 21 CFR 50.24, waiver from informed consent.

The primary efficacy endpoint is a 15 percent reduction in all-cause mortality at 28 days, from an estimated 58.1 percent to 49.4 percent, with an alpha of

0.045. The proposed sample size is approximately 1,130 subjects.

Finally, the RESUS protocol includes a Phase 2 50-subject randomized study of HBOC-201 versus control (lactated Ringer's) to assess the logistics and feasibility of the study and the ability of the study to answer efficacy and safety outcome questions. It is also planned that this feasibility study will be used to assess the appropriateness of the entry criteria to target the desired subject population.

[Slide] Given the commitment of FDA to developing a safe and effective oxygen therapeutic for use in trauma, we have to discuss the reasons for the clinical hold imposed on the RESUS protocol. You have heard a summary of this earlier today.

First, RESUS was placed on clinical hold because of safety signals arising out of previous Phase 2 and Phase 3 studies performed by Biopure Corporation using HBOC-201. These safety concerns also inform FDA's understanding of issues surrounding dosing and administration of the product. There is, as you will see, an excess of clinically significant adverse events in all analyses performed by FDA for the clinical data roster of HBOC-201.

There is a paucity of studies, and therefore data both from preclinical studies and clinical studies, to

support the proposed dosing and administration in RESUS.

The mortality estimate, based on the RESUS entry criteria, has a wide variability in projected risk of mortality for individual subjects to be enrolled in the RESUS trial.

The magnitude of the treatment effect cannot be derived from animal studies.

[Slide] The significant and serious adverse events observed in previous trials, the uncertainty of the treatment effect, and the wide variability in expected mortality for individual subjects to be enrolled into the RESUS trial all serve to make a determination of a positive benefit-to-risk ratio very difficult and may even preclude such a determination.

Finally, it is the opinion of FDA that the risk-mitigation strategies proposed by NMRC do not fully mitigate the risks of the product, for reasons that we will discuss -- namely, that the monitoring and therapeutic interventions may not suffice to offset the risks associated with the use of the product.

[Slide] FDA has expressed concerns about restricting RESUS by age and excluding subjects older than 69 years of age. These concerns go to the generalizability of the data from RESUS to the overall trauma population, which includes an increasing number and percent of older

subjects. FDA also expressed concerns about the generalizability of RESUS to day-to-day trauma care. These concerns are highlighted by the extraordinary precautions in training of EMS providers and hospital personnel in the hopefully safe use of HBOC-201 in severe trauma. The needs for a Phase 2 feasibility study to evaluate whether the entry criteria select the appropriate and intended subject population and to evaluate logistical considerations for the study all serve to emphasize this point. The ability to obtain the requisite information from which to calculate an RTS score real-time is also of concern.

Despite the uncertainties that underlie the need for a feasibility of this type, NMRC plans to conduct the study under the provisions of 21 CFR 50.24, waiver from informed consent. If it is found that the logistical and feasibility concerns do not materialize, then data from the Phase 2 study will be combined with data from the Phase 3 study. If, however, questions or issues arise out of the Phase 2 study, then modifications, as needed, will be made before starting the Phase 3 trial.

FDA and NMRC will have to discuss whether this Phase 2 feasibility study comports with the requirements of 21 CFR 50.24, that the study hold out the prospect of direct benefit to the subjects enrolled in the particular study.

[Slide] Before we discuss safety, it is necessary to discuss certain issues related to data collection. In its Complete Review letter of July 30, 2003, FDA documented numerous deficiencies in the conduct of the pivotal trial, HEM-0115. These deficiencies are noted on this slide and are related to good clinical practice, data quality, data completeness, and difficulties in assessing and verifying the seriousness and frequency of adverse events. There were critical issues related to the laboratory database because of commingling of central-laboratory and individual-site information. Biopure has undertaken an extensive effort with regard to the clinical laboratory data to separate central from site laboratory data.

[Slide] Because of the limitations of the databases that were analyzed, the dataset provided to you, to be discussed today, represents a minimum estimate of the adverse-event information. For purposes of discussion at this advisory committee meeting, FDA will be presenting information on adverse events and serious adverse events derived from a consensus safety database developed together with Biopure. FDA and Biopure differ on the adjudication of a few cases, which will be highlighted in the FDA tables.

[Slide] First, it was assumed *a priori* that a

rigorous statistical assessment of differences between HBOC-201 and control for a particular adverse event would not be possible because of small sample sizes, even for HEM-0115.

Second, adverse events and serious adverse events were expected to occur with low frequency, as the subjects of these clinical trials were either normal volunteers or were undergoing elective procedures from which they expected to emerge intact.

Adverse events were expected to occur with low frequency in any one particular study, and it was the stated intent of the company to conduct studies of sufficiently similar design to permit the pooling of safety data. Data were pooled to achieve a larger sample size from which to estimate the frequency of low-incidence events.

[Slide] It should be noted that subjects in previous studies, including HEM-0115, were stable, medically cleared to undergo the various procedures, judged not to be at excess cardiovascular risk, and were monitored and treated according to standard care. The study designs were generally similar, in that HBOC-201 or control was administered to subjects at a target hemoglobin below a predefined threshold level, with or without other signs of symptoms of anemia, or after a fixed volume of blood loss.

In all surgery studies, red blood cells were available as needed in both treatment groups. Crystalloid and colloid were available as needed in both groups. The studies all included an evaluation of safety and tolerability in comparison to control. In fact, for many of the crystalloid/colloid-controlled studies, safety was the primary endpoint of the study.

Some of the studies -- in fact, most of the studies -- also included as a secondary endpoint effect on allogeneic red blood cell usage.

[Slide] Trends seen in the pooled database had been seen at lower numbers in the individual studies. In addition, these same trends were seen across studies that differed in the types of control solutions used. So the pooled analysis showed safety signals already noted in the various individual Phase 2 studies leading up to the pivotal HEM-0115 study and identified new concerns, such as myocardial infarction, renal failure requiring dialysis, and CVA, for further analysis.

[Slide] This is a rather complex slide, but what I want to show you here is that the groupings I will be showing you were devised by FDA to categorize individual coded categories into medically related and similar events. For example, cardiac arrest, cardiopulmonary arrest, and ventricular fibrillation, which are separate MedDRA codes,

were combined into a category called “Cardiac Arrest” to enhance detection of safety signals.

This slide shows how cases of hypertension were grouped. These are the categories, the MedDRA codings, for hypertension: hypertension, blood pressure increase, hypertensive crisis, systolic hypertension, SVR increase, malignant hypertension, systolic blood pressure increase, postop hypertension, and hypertension aggravated. As you can see on the top line, in the crystalloid/colloid-controlled studies, it’s 54, or 30.6 percent, versus 15, 11.5 percent. In the red blood cell-controlled studies, it’s 64, of 12.1 percent, versus 32, for an overall of 118 versus 47.

Overall, there is an imbalance against HBOC-201 for hypertension in both crystalloid/colloid-controlled studies and red blood cell-controlled studies. FDA conducted similar analyses for all organ systems. The results of these analyses are summarized on the next few slides.

[Slide] This slide tabulates clinically important adverse events that occurred in the overall roster for HBOC-201. There are various control agents against which HBOC-201 was compared, including crystalloid/colloid and red cells. The studies evaluated low doses and ranged up to 300 grams, or 10 units,

depending on the particular study. There were normal-volunteer studies, as well as non-surgical studies. However, the bulk of the data are derived from surgical studies, and study HEM-0115 represented approximately 48 percent of the subjects described in this particular table.

Brain, heart, lung, and kidney are represented on this slide. There was also an imbalance against HBOC-201 for other organ systems that are not on this slide. The issue summary provided to the advisory committee members contains a more extensive comparison of HBOC-201 and control. There is a consistent imbalance against HBOC-201 in all major organ systems, including those listed here.

I have highlighted the imbalances in the number and percent of deaths for the overall database. These deaths occurred among subjects who preoperatively were medically stable and expected to emerge intact from whatever procedure they were undergoing. So the imbalance against HBOC-201 is notable.

If we look at the types of severe and serious adverse events that can lead to death, we see again consistent imbalances against HBOC-201. I would like to walk you through that: myocardial infarction; pneumonia; ARDS; stroke; oliguria; most important, renal failure necessitating dialysis.

[Slide] The first question that FDA asked was

whether the imbalances observed in the overall database could be explained by one study -- for example, HEM-0115 -- that contributed the majority of the data to the database. The answer to this question, as seen on this slide, was no. When the surgery studies were stratified by type of control, the imbalances against HBOC-201 are still evident, as, for example, with the lactated Ringer's/Hespan-controlled surgeries. Thus, there was still an approximately 1 to 1.5 percent difference in the percent of deaths.

[Slide] The next question that FDA asked was whether the adverse-event imbalance was age-dependent. As this slide shows, the imbalance against HBOC-201 is apparent for subjects older and younger than 70 years of age, the proposed RESUS cutoff. Although the absolute percents are higher for older individuals, as would be expected, the imbalances are still present in younger subjects. This is true whether one is looking at death or cardiac disease or pneumonia, and so forth down this slide.

[Slide] I noted earlier that I would discuss unpooled data. The foundation for the RESUS clinical hold is based in large part on FDA's review of the BLS, especially pivotal trial HEM-0115. HEM-0115 was a multicenter, randomized, single-blind, red blood cell-controlled, parallel-group clinical trial conducted in 693

subjects, five of whom dropped out, undergoing elective orthopedic surgery, who were randomized to receive either HBOC-201 or red blood cells at the first transfusion decision.

[Slide] This slide, which again is rather complex, highlights the safety findings for HEM-0115. Just as there is a consistent imbalance against HBOC-201 when compared to all controls, so, too, is there a consistent imbalance against HBOC-201 when analyzed in the context of HEM-0115. The same trends emerge, whether one is looking at the overall roster or stratifying by age or presence or absence of antecedent trauma. It must be remembered that the so-called trauma subjects were actually subjects who were undergoing semi-elective fracture repair 24 to 48 hours after the trauma event and that these subjects were stable and euvolemic.

[Slide] The first suggestion by Biopure that many adverse events occurred because clinicians administered large volumes of product in an attempt to raise the total hemoglobin concentration may be valid. Inaccurate dosing guidelines and unrealistic expectations led clinicians to increase infusion of product in an attempt to increase the total hemoglobin. However, not all of the adverse events are explained by this occurrence, as not all clinicians made this attempt.