one situation, we found that our CT surgery fast-track protocols were able to be employed a little more frequently, from about 10 percent before institution of this to about 30 percent afterwards.

[Slide.]

In addition, our admissions in our ICU for spine surgery tended to decrease from about 9 percent to about 3 percent. And, in addition, our average length of stay in our ICU actually decreased from about seven days down to five. Once again, in essence, we found no real change in terms of our perioperative outcomes for any clinical marker that we could look at.

[Slide.]

So I think, in summary, it is becoming increasingly apparent that Hextend is at least probably clinically equivalent to albumin, at least in terms of in vivo coagulation studies, transfusion requirements as well as in cardiac-surgery clinical outcomes.

I would like to thank the committee for its time and answer any questions.

DR. NELSON: Thank you very much, Dr. Shaughnessy.

We have a number of people that wanted to present for Abbott Labs. One of the concerns I have is that, if we have four more presentations, we won't be able to get to a discussion. I wonder if there are data that are different than what has already been presented that is relevant to the committee's charge.

How many people have to leave at 1:30? I don't want to cut your--this is a public forum. You are certainly welcome to testify. But if it is too long, we may preclude looking at the issue.

DR. WANGLIN: Mr. Chairman, we have two remaining presentations. I believe we can hit the high points, and they do present additional data.

DR. NELSON: Okay. The first one is James Wanglin.

DR. WANGLIN: I am James Wanglin. Actually, Abbott Laboratories is being represented by Dr. Lew Kaplan and by Dr. Moskowitz.

DR. KAPLAN: Thank you for the opportunity to present. I am a trauma surgeon. I am an intensivist. I am different from the anesthesiologists that you have heard present already and I am going to talk to you about trauma surgery but I am going to give you a different

background.

This is about cardiac surgery. I actually had cardiac last July. The only fluid that I got for my bypass surgery was Hextend. My blood loss was about 600 out of my chest tubes and I did just fine. There is anecdote for you.

DR. NELSON: Obviously.

DR. KAPLAN: But I only had a 2 kilo weight gain. They are terribly uncomfortable when they come out, let me tell you.

Part of what you are going to hear today is the physiologic background for identifying that Hespan and Hextend are very different fluids. They are markedly different in their characteristics and that is part of what I want you to embrace. If I can actually get the slides to come up. We are threatening to have them come up.

I am at MCP Hahnemann University in Philadelphia but if you need me later, you will have to track me down at Yale because I am changing my job.

How are we doing with the slides? Let me start and we can go through a couple of these things quickly. One of the things that is missing from a lot of these studies is acid-base balance

and how you control acid-base balance has got to be one of the most dry and boring topics, but it is absolutely essential to evaluating the differences between these two products.

When you look at what controls the pH of pure water, you find that that pH is markedly different depending on the temperature at which you measure it. That process is essential to acid-base balance, the process of water dissociation. That is where all of your protons come from. That is what controls the ultimate pH of your body.

All of your enzyme systems, including your coagulation system which is a series of serine proteases have a maximum rate at which they work and they are pH-dependent. So how we control pH and how we perturb it is just as important as which fluid we use because it is related to the fluid.

You should remember that CO2 combines with water and makes carbonic acid. Carbonic acid dissociates into a proton and bicarbonate. The bicarb is handled by your kidney and your liver. You also have a set of buffers in your blood stream that are related to the proteins which are weak acids. They exist either with or without a proton attached to them.

They are principally negatively charged most of which comes from albumin. The histidine residues on albumin are what contributes this negative charge. Lesser amounts come from phosphate and a smaller amount from sulfate. This negative charge is balanced by a positive charge from things called strong ions. Strong ions dissociate from their partners.

There are strong cations like sodium, potassium, calcium and magnesium and there are negative ones like phosphate and lactate and sulfate. The net negative on the proteins is balanced by the net positive from the strong ions. The relative difference in these two charges determines whether you dissociate water to generate a proton or not.

The fluids that we use change the strong ion difference component of your plasma.

Keep on going with the slides. We will get up to where we are.

DR. NELSON: One of the issues, I think, is that what the committee is asked to look at is the label change with regard with to the coagulation and bleeding issue. I realize--

DR. KAPLAN: This will be essential

understanding that because there is data--

DR. NELSON: If you could do it as quickly as possible and particularly focus on what the committee is--

DR. KAPLAN: It's coming. Keep on going. One more.

[Slide.]

What we do with fluids is we frequently give fluids that are rich in chloride. The body does have a compensatory mechanism which reduces phosphate and albumin and raises protons in order to restore balance.

[Slide.]

Hyperchloremia is bad for you and there are a lot of studies that show it. If you use chloride-rich fluids in surgery, you can predictably increase your chloride and induce an acidosis. So what? Big deal.

[Slide.]

There has to be clinical relevance to it. Here it is. I am going to take your blood and put it in a test tube and I am going to deliberately change the chloride concentration, raise it by 4 all the way up to 20 milliequivalants per liter. I am going to do it with 3 percent saline so I don't

use a lot and dilute the clotting factors or normal saline.

Because the 3 percent saline functions like a colloid, I am going to give starch and saline, starch in a balanced salt solution. Watch what happens to pH. Predictably, decreases in the 3 percent group. Same thing for the normal saline group. Plateaus in these two groups. It is not a starch effect. It is a chloride effect.

[Slide.]

If we look at the strong ions, the arbiters of change in pH, we can see that the strong-ion difference decreases predictably in the high-chloride groups, is relatively flat in the two starch groups but something else unanticipated happens here. You got unmeasured ions. These are part of what is called the strong-ion gap which is well beyond this talk, but the induction of a strong-ion gap has been associated with increased mortality in liver patients and in trauma patients.

[Slide.]

That is bizarre. All the fonts got changed. This is looking at PT and PTT, gross arbiters, because I don't have a TEG. In the 3 percent group and the normal saline group, when I

raised the chloride up to 20 milliequivalents above where it started, predictable increases in prothrombin time and partial thromboplastin time. No change in the starches because they are given in small quantities.

[Slide.]

This allowed me to ask some easy questions. Can I use starch in a balanced salt solution and have a clinical benefit, not a theoretical one? The study that Dr. Haynes said couldn't be ethically done is the one where you use Hespan because we agree that there are bleeding problems.

I am going to focus on the patients who received starch in balanced salt solution well above what everyone thinks will be a safe range. More than 25 cc's per kilo body weight per hour. Both of these studies are investigator-driven. This was part of our QA process. They were not funded.

Next slide. Keep on going. Keep on going. I am going to tell you what this showed.

[Slide.]

Most of our patients were trauma patients, lesser amounts with sepsis and a small amount, the

lowest monitored patients were just there for postop fluid management. In this group, they started off with a low pH with only Hextend resuscitation. They cleared about 80 percent of their lactate. They received almost 40 cc's per kilo bodyweight over the first twenty-four hours, well above what you would expect. Improvements in pH.

For this group, sepsis patients, about two-thirds of the lacate cleared consistent with hyperlactatemia. Not much of a change in pH. Same thing for the postop patients because they were pretty normal.

[Slide.]

What you are missing here are the two other groups of patients, but these are the trauma patients. What you see here in pink is no change in coagulation profile and increase in coags more than 0.2 seconds in PT or PTT or a decrease. The very patient population with hemorrhage, with holes in tissues, with inflammatory activation, we would expect a huge bolus of starch. If it was the starch to have a problem, the coags got better.

Only in 25 percent of these patients were on a massive transfusion protocol. The rest were

not. These patients that had an increase also had their chloride concentrations go up. They had brain injury and we could not get the neurosurgeons to let go of the chloride.

You will see that, in these other two groups, the major portions are no change in coagulation, no change at all.

[Slide.]

This was that same study that Dr. Gan had shown you.

[Slide.]

What you would have seen here is a giant bar that says this group that had the high chloride groups, the Hespan and normal saline, had a hyperchloremic metabolic acidosis. This will be flat where they received Hextend and LR. So there is an important profile difference between these two.

[Slide.]

There is a program called STORMACT, Strategies to Reduce Military and Civilian Transfusion. This was driven by the Military, by Joint Special Operations Command that had a whole host of other people that contributed. This came out of the Resuscitation Research Conference in

Bethesda.

[Slide.]

The Military is limited to FDA-approved plasma-volume expanders. You see the list here. You have approved them.

[Slide.]

When we decided which fluid to use, because the soldiers currently carry saline or LR, they wanted less space, less weight, a repeatable dosing for fluids. What we arrived at, in terms of safety, was starch.

[Slide.]

We created this fluid algorithm that you can't see terribly well but the central feature of it is hydroxyethyl starch in a balanced salt solution because of the trauma data that has been shown here and the difference in coagulation times that you get with hydroxyethyl starch in saline. They would not agree to use that.

This fluid algorithm, those fluids, are currently in use by our Special Forces people so this has already been embraced.

[Slide.]

What this allowed us to do was to create an algorithm for fluid resuscitation, transfusion

using things like hemoglobin-based oxygen carriers.

Factor VII, VIII for clotting.

Cytokine manipulation for antioxidants and cell repair.

[Slide.]

But the central core is the fluid resuscitation. The safety of this kind of a fluid, in terms of coagulation, resuscitation and absence of coagulopathy sets this apart from everything else that you have heard and, thankfully, everyone else presented that data that said starch and saline is bad.

I would encourage you to think about this as you review your warning indication, that the warning is not molecule-specific but carrier specific because there are valid clinical difference between the two.

So thank you for bearing with the very abnormal slides. I will be happy to take questions.

DR. NELSON: Dr. Moskowitz is next. Would it be possible for you to do it in five minutes?

DR. MOSKOWITZ: My name is David Moskowitz. I am over at Englewood Hospital and Medical Center over in New Jersey.

[Slide.]

What I wanted to start with, essentially the first slide shows that, in 1994, the New Jersey Institute for the Advancement of Bloodless Medicine and Surgery was formed at Englewood Hospital. We have become a very worldwide referral center for blood-management cases. We perform about 225 noncardiac cases per year that require our services and that are associated with major blood loss.

These cases, on average, have a transfusion rate at our hospital of about 10 percent. These include prostates, hips, knees. It is much higher in the general population.

[Slide.]

Just to show how effective it is, the arrow is 1994. As you can see, there is a steady decrease.

[Slide.]

We have had a 50 percent drop since the Year 2000 in packed red-blood-cell units in the total hospital based on our program. As a matter of fact, the operating room uses less than 5 percent of the total hospital blood supply per year in blood products. Most hospitals use somewhere around 70 to 90 percent. Barring we don't do liver

surgery, it is still a significant number.

[Slide.]

In the Year 2000, this is where I came in, we were granted the certificate of need to perform cardiac surgery. It was based on that we can create a model center for the research regarding blood conservation and cardiac surgery. To date, we have done 452 cardiac cases. That is not just CABG or bypass and valve and a combined. It has to do with aortic procedures, ascending, descending, which are very high-risk cases.

[Slide.]

As you know, blood conservation requires a bunch of techniques, not just one or two techniques and not just one person involved. It is multimodality and multidisciplinary. In addition to the standard, what most places don't do is what we do. We use on-site, lab-guided transfusion therapy. That is the thromboelastogram we have alluded to in addition to heparin concentration on bypass. So we can rule out other causes of bleeding that are often missed in these other studies in addition to the standard lab tests. We combine them altogether to come up with a plan.

We also perform acute normovolemic

hemodilution. I will show you in a second. And we tolerate anemia.

[Slide.]

This is acute normovolemic hemodilution. The patient comes to the operating room. We remove a significant amount of blood. We store it next to the patient. The patient tolerates the procedure anemic but normovolemic. At the end of bypass, we give them the blood back. Removing the blood allows you to lose dilute blood and, in addition, you also prevent that blood from being exposed to the negative effects of bypass.

[Slide.]

Here is a case, a patient who underwent spine surgery. Two-and-a-half liters of blood were removed. The fluid of choice was hydroxyethyl starch in a balanced salt solution or Hextend. The patient did not bleed afterwards. This is a very high-risk scoliotic surgery where just scraping the spine can cause release of factors that can cause bleeding. The patient didn't bleed, didn't require transfusion of any blood product.

[Slide.]

So, in order to tolerate our maneuvers during our cardiac surgery, you must be euvolemic

or normovolemic.

[Slide.]

That means you must have a normal circulating blood volume in order for this to be effective.

[Slide.]

What we use is we use colloids greater than crystalloids. We use it for specific reasons. I know this topic has come up today, why don't we use more crystalloids. I think it is a very simple answer. There is data out there that there is probably better rheology with the colloids than the crystalloids in the microcirculatory level and delivering oxygen to the tissue, to the cellular level.

In addition, there is less third-space loss which is a common problem and that can increase the distance oxygen must travel to the tissue. Also, there may be some evidence that increase in plasma viscosity may improve tissue oxygenation. Therefore, by keeping the arterioles more open, you can deliver oxygen better.

You also want to avoid crystalloid because you need more to attain more normovolemia. You create an iatrogenic-induced anemia which can also

lead to a coagulopathy which I think is a major problem in cardiac surgery. This leads to inappropriate use of blood products.

For all our cardiac cases, we use synthetic hydroxyethyl starch in a balanced salt solution. We feel it is safe. We don't feel there is any increased risk of bleeding and we also think it is lower cost than other colloids out there.

[Slide.]

Here is a paper that we presented in the Canadian Journal of Anesthesia. This is cardiac surgery. This is a gentleman, a Jehovah's Witness patient who underwent removal of renal-cell carcinoma that extended into his right atrium. The incision goes from his sternum down to his pubis bone. It is associated with a significant amount of blood loss, up to at least 5 to 9 units per case reported in the literature.

This patient, we used hydroxyethyl starch in a balanced salt solution, 2 liters. We didn't need any more because we also do acute normovolemic hemodilution. The patient received no blood, no blood products and left ten days after the hospitalization.

[Slide.]

We have alluded to this study by Dr. Bennett-Guerrero. It is an abstract. What we find is that it corroborates with our clinical beliefs that the hydroxyethyl starch in a balanced salt solution is equivalent to albumin with respect to blood products, percentage of patients being transfused these blood products, and the reexploration for bleeding while the hydroxyethyl starch in normal saline has a higher incidence of transfusion and the lactated Ringer's has a lower incidence. We don't use solely lactated Ringer's for the reasons I mentioned before.

[Slide.]

Let me just give you our data. I looked at only CABG--valves and CABG valves. These are the heart cases that have been reported in the literature. We have done a total of 359 cases. There is how they are split. Most of them are bypass that require just grafting. Others are valves and CABG valves.

The age is a very respectable 70 years of age. They are elderly patients. The reoperation rate; these people present for their second and third heart operations or even one person who had their fourth heart operation is 10 percent.

The Parsonnett score--that is a risk score--it is an overall general score--is 17 which is a moderate risk to this patient population. In addition, the bypass time is two hours which is very respectable.

[Slide.]

We use the hydroxyethyl starch in a balanced salt solution for all the cases requiring colloid. We use anywhere from 500 to 2 mls intraoperatively and we keep using it postoperatively. Coagulopathies; we rarely see coagulopathies. This is because we have on-site coagulation monitoring that includes not only the thromboelastogram but also the heparin concentration.

So if the surgeon sees that there is bleeding, what we do is we go back, make sure there is no residual heparin and we make sure that there is no abnormality on the thromboelastogram. Most of the time, these tests show us that it is surgical or mechanical bleeding.

Our average test-tube drainage is only 429 mls in 24 hours. That is lower than most reported studies. Only two patients have come back for reexploration. One of them had a surgical cause,

so we have only seen one out of 359. There is a very low transfusion rate. 10 percent have received packed red-blood cells.

DR. NELSON: Could you summarize. Your data are interesting, but we have seen it. Otherwise, we are not going to be able to discuss the question.

DR. MOSKOWITZ: Okay. The summary is basically we are a blood-conservation institution and we use hydroxyethyl starch in a balanced salt solution without reservation.

We might as well go to the last slide.

[Slide.]

There is no significant relationship between the amount of Hextend and chest-tube drainage. The r-squared value is 0.02.

[Slide.]

Just to show the nation average versus ours. We are much lower.

[Slide.]

So we use it, hydroxyethyl starch in a balanced salt solution. It is our only colloid that we use. No increased risk of bleeding. I feel that you have to use transfusion-guided therapy on site, meaning all the tests that I have

mentioned. We use in all cardiac and noncardiac cases including patients who are Jehovah's Witnesses where there is no blood bank and that they are high risk. We use it without reservation and we recently added it as our prime in our bypass circuit.

DR. NELSON: Thank you. It is very impressive. My secretary is a Jehovah's Witness so, if she needs surgery, I will send her to you.

The last person, Keith Berman. Is he here? If he is here, I wonder if you can limit your remarks to under five minutes.

DR. BERMAN: Thank you very much for inviting me. I wanted to speak about one subject, but while he is preparing the slides, I think that the comments I make reflect the comments of a number of anesthesiologists that I have spoken to, and surgeons. I think that one thing with regard to these Hextend data--and, by the way, the one set I don't know anything about is the UCSF series by Dr. Shaughnessy. I have never seen that before.

In all the other studies I want to submit that, as opposed to issues concerning patient comparability and whether something is statistically significant, in the other studies

presented by Dr. Gan, I want to suggest that the study design, itself, is very seriously flawed in several of those studies and raises some serious questions.

These are the views of a number of anesthesiologists that I have spoken with beginning with the Phase III trial in which conventional hydroxyethyl starch and saline were administered to patients in volumes of up to 5 liters. In the literature, you will find a rare reference to anyone using more than 1,000 to 1,500 liters.

In the second study, I just want to mention, involving the 47 patients randomized, these were elderly, geriatric patients who are already at risk for hyperkalemic acidosis. The study design, I think it is worth noting, that Hextend is essentially, in essence, very, very similar to hetastarch--it is hetastarch in a base of lactated Ringer's.

So, in clinical practice, it is very common, if not standard practice for many surgeons and anesthesiologists to take lactated Ringer's and hang it with hetastarch for some of the very reasons we have seen. It is a source of calcium. It is lactated. It buffers. That is why the

lactated Ringer's was developed in the first place.

What Dr. Gan and others did in that 47-patient study was to take conventional hetastarch, which is 0.9 percent saline, and combine it with 0.9 percent saline and then they compared it against Hextend and lactated Ringer's.

If you think for just a moment whether that makes sense, I think the study design, itself, essentially produces an answer that might be desired. There is no calcium. There are no electrolytes. There is no buffering in hetastarch to begin with, so I am wondering if the study should not have been 6 percent hetastarch with lactated Ringer's versus Hextend and lactated Ringer's.

DR. NELSON: Actually, I am not sure that this was submitted officially to the FDA.

DR. BERMAN: No; this was just a--

DR. NELSON: So if you could proceed with your--

DR. BERMAN: Okay.

[Slide.]

I think, with respect to the studies on hetastarch, the retrospective studies, we looked at just the economics of what might happen just in

terms of red-cell transfusions. As we know, there are a number of agents, the so-called oxygen therapeutics blood substitutes, whose primary endpoint is surgical blood avoidance.

So avoiding red cells and other blood components is a worthwhile part. What we did was we just looked at the number of U.S. cardiac surgery cases in 1999 from CDC sources. Altogether, there are just a little over 500,000 adult cardiac surgeries in the U.S. between CABGs, valves and other procedures.

It turns out that there are about 12 million allogeneic red cells in the U.S. and about 10 percent of them are devoted to cardiac surgery. Although there have been estimates that are much higher, we believe it is really closer to 10 percent, not 15 to 20 anymore, for a bunch of reasons that we could talk about outside the meeting.

[Slide.]

There is a company called the Marketing Research Bureau which specializes in blood products and plasma-volume expanders and coagulation factors some of you may have heard of. In late August, 1998, a survey was conducted of 44 cardiac

anesthesiologists across the country. It was determined that about half, taking these overall results, used hetastarch intraoperatively and/or in the cardiopulmonary bypass priming solution.

It became more popular through the '90's for the reasons that some of the speakers talked about. It was cheaper and particularly there were problems with albumin shortages in the early '90s that really drove a lot of hospitals in this direction.

[Slide.]

Looking at the Mayo Clinic findings which we feel very compelling because of some of the points that Dr. Haynes made earlier, it was simply a crossover trial, essentially, single surgeon, about 200-plus patients before, 200-plus patients after. They were well-matched.

I want to suggest that there was a small difference in degree of hypothermia of about 3 degrees, but the literature has several references that suggest small hypothermic differences make no real difference in transfusions. Otherwise, it is really hard to see any difference between these patients, single surgeon. It is as pretty as they come.

Dr. Greg Nuttall, who is I think one of the most highly regarded people in this field, would defend that paper very vigorously in this meeting. The findings from Mayo Clinic were that, on average, there was about half a unit of mean red-cell avoidance per case on the cases where they stopped using hetastarch and reverted to albumin for volume replacement.

Using the assumption from the '88 report that about half of the cases are currently infused intraoperatively with hetastarch and the 500,000 adult surgeries, it suggests that there are well over 100,000 units of blood that are transfused today that might not be transfused if this labeling were changed to reflect these findings.

[Slide.]

They also looked at platelet avoidance. I guess now this committee is not charged with looking at economics but, just in terms of avoidance of donor blood and blood components, that is a worthwhile thing. That works out to a little over 300,000 platelet concentrate units when you use the Mayo clinic data.

DR. NELSON: The committee actually has your handout so I wonder if you could summarize,

because I do want to get to the questions. Otherwise, the meeting will not be productive.

DR. BERMAN: Okay. I tell you what. That is essentially the same kind presentation that was done with that data. The only last thing I need to do is to present the very last slide

[Slide.]

This is a statement that Dr. Curtis Tribble, who could not be here today--

DR. NELSON: The committee also has that. I think everybody has read it.

DR. BERMAN: Okay. That's fine.

DR. NELSON: Thank you.

DR. BERMAN: Thank you.

Questions, Discussion and Recommendation

DR. NELSON: Could we have the questions for the committee again? Does everybody have the questions? Toby?

DR. SIMON: It would appear that, with the hydroxyethyl-starch issue, or the hydroxyethyl-ethyl-starch-in-saline issue, that we have already had these--I don't know if it is a sole manufacturer but the manufacturer present a warning that has been submitted to FDA. So I guess the answer to No. 1 would be yes and, hopefully,

taken care of with regard to that product.

I guess there is going to be quite a bit of confusion in the committee in terms of how this relates to the other product which is in lactated Ringer's which wasn't analyzed for the committee in the same way, but it would appear that there is not the data there to support the bleeding risk. It is the same molecule, but I guess we are being told that the chloride makes a difference.

I think it is difficult to answer that question the way it has been presented here.

DR. NELSON: Jim?

DR. ALLEN: I concur. I guess my suggestion would be to split the question with my answer being urge the FDA to follow Braun's suggested wording change which I, just on quick review, find to be quite acceptable given the data we have heard and I would, at this point, recommend no change in labeling for the other product.

DR. NELSON: Mary?

DR. CHAMBERLAND: My assessment of the morning and afternoon is that, instead of really being asked to vote on Question 1, my recommendation would be to ask FDA to consider the labeling change that had been presented to it by

Braun and to consider and review it.

I feel that there were insufficient data provided to the committee and, by extension, I would assume, to FDA, for me to adequate evaluate the need for a warning statement labeling on the other version of this product.

Also, the information that I have heard today makes me wonder if there are other issues besides excessive bleeding that need to be considered in the FDA evaluation of the need for warning labels. We have heard some data about electrolyte issues and renal issues, et cetera, so I would put that forward as also something that needs to be considered.

In regard to Question 2 and the need for additional trials to extend; I think we have heard testimony that it would probably be very difficult from a human-subjects point of view and the current sentiment among practicing physicians to conduct a clinical trial for hetastarch--for Hespan, whatever it is--but for Hextend, I think, before making a decision about the need for randomized trials, et cetera, again, I would go back and ask the FDA to review the data available or that can be presented to them by the sponsor because, clearly, some of

the data is not preliminary. It hasn't been published. It couldn't be shared in this public session.

So I find myself actually really at a loss to be able to address these questions, at least the way they have been presented and, instead, am falling onto some other recommendations.

DR. NELSON: I have the same thing. The numbers, if you look at the error bars, they are rather wide and whether or not the data are adequate at this point--I think they would need careful review, statistical analysis and comparability data which we didn't have, although it does look like the two products are different. But that is not what we were asked.

So I guess we need some advice from the FDA. One thing is we could modify the first question to say hetastarch, is the evidence for excessive bleeding in cardiac surgery patients who receive 6 percent hetastarch in saline, or Hexa--whatever it is--strong enough to warrant a warning label.

Mark?

DR. WEINSTEIN: We would appreciate advice on that.

DR. NELSON: So why don't we change that first--I think it is fairly clear from a number of studies, even though they are not randomized prospective trials, in the one trial that was a retrospective study that didn't seem to show a difference, there were enough differences in the patients that it looked like that group was exposed less to the pump and other things.

DR. HOLLINGER: And the company has agreed.

DR. NELSON: And the company has agreed, so I think we should support this. So can we make that change, then? Where is Dr. Landow?

DR. LEW: I just wanted to give more opportunity or expand FDA's opportunity to decide on the exact wording of the labeling because, even though the company nicely proactively suggesting some changes, they did mention in their proposal to add on, "However, the risk of bleeding diminishes rapidly." I didn't see a whole lot of data that addressed that, so let's leave it open for FDA to decide what the wording should be but definitely the warning should be there.

DR. NELSON: I think that the FDA will decide on the wording in conjunction, perhaps, with

advice from the company. But, in fact, it is hard for a committee to do a warning label. But I think what we are supposed to vote on is the principle, should there be one.

So I would like to vote on this while we still have enough people here. We will change the--

DR. DiMICHELE: Can I just make one comment? I'm sorry. Could we go over the wording for this because I think we are being asked two things; do we agree that the Hespan people should submit with their own concerns--with their own data and their own concerns, submit this labeling change to the FDA.

But then, the way the question stands is do we think that there is enough evidence. I think that I might not be able to vote in that regard if the question remains the way it is stated because I think, in both circumstances, I am not sure we have enough data to comment on that particular statement, at least I don't.

So, if the question remains the same, then I may have to vote differently. That's all.

DR. NELSON: You mean is there enough evidence.

DR. DiMICHELE: Is there enough evidence is, I think, a very important--the question says, is there enough evidence.

DR. HOLLINGER: Can you rephrase, then, Question 1 for the vote?

DR. NELSON: My take on it is is the evidence for excessive bleeding in cardiac-surgery patients who receive 6 percent hetastarch in normal saline strong enough to warrant a warning statement in the hetastarch labeling. If the committee agrees. Do you want to vote on that change? Does everybody agree with that? How many agree?

[Show of hands.]

DR. NELSON: How many disagree? You may vote no, but--okay; so we have changed the question slightly. Let's vote on the question, unless there are other comments. We voted first on the change in the wording. Now we are voting on the change in the question.

Linda, do you want a hand vote or do you want to call people or what?

DR. SMALLWOOD: I wanted to read into the record the change in the question; is the evidence for excessive bleeding in cardiac-surgery patients who receive 6 percent hetastarch in normal saline

strong enough to warrant a warning statement in the hetastarch labeling?

DR. ALLEN: That would be hetastarch in saline labeling.

DR. NELSON: Yes.

DR. SMALLWOOD: I want to be clear. The statement that Dr. Allen made--were you asking a question, or were you changing what I read.

DR. NELSON: No, no. He was just clarifying.

DR. SMALLWOOD: Are you ready?

DR. HOLLINGER: But he did make that change from what you read, though. He made sure that it said 6 percent hetastarch in normal saline and then, at the bottom part, in the hetastarch in normal saline labeling.

DR. NELSON: Or we could just say in the product labeling.

DR. HOLLINGER: In that product's labeling.

DR. NELSON: Right.

DR. SMALLWOOD: I am going to try again; is the evidence for excessive bleeding in cardiac-surgery patients who receive 6 percent hetastarch in normal saline strong enough to

warrant a warning statement in that product's labeling?

DR. NELSON: Yes.

DR. SMALLWOOD: I am going to have to do this by roll call, quickly. Dr. Allen.

DR. ALLEN: Yes.

DR. SMALLWOOD: Dr. Chamberland.

DR. CHAMBERLAND: Abstain.

DR. SMALLWOOD: Dr. DiMichele.

DR. DiMICHELE: Abstain.

DR. SMALLWOOD: Dr. Lew.

DR. LEW: Yes.

DR. SMALLWOOD: Dr. McGee.

DR. McGEE: Yes.

DR. SMALLWOOD: Mr. Rice.

MR. RICE: Yes.

DR. SMALLWOOD: Dr. Fallat.

DR. FALLAT: Yes.

DR. SMALLWOOD: Dr. Harvath.

DR. HARVATH: Yes.

DR. SMALLWOOD: Dr. Hollinger?

DR. HOLLINGER: Yes.

DR. SMALLWOOD: Dr. Nelson?

DR. NELSON: Yes.

DR. SMALLWOOD: Dr. Simon, do you agree?

DR. SIMON: Agree with the yes votes.

DR. SMALLWOOD: There were eight yes votes and two abstentions.

DR. NELSON: So that makes the second question moot in the sense that, if we are talking about this product. The other issue is does the FDA want us to vote on anything or say anything about the other product, the Hextend, because, first of all, we weren't given--I mean, we were given data but it was sort of incomplete and not formally reviewed.

DR. WEINSTEIN: I think, actually, it would be valuable if we could have some comments on what we heard today regarding the Hextend if you would like to.

DR. NELSON: Blaine?

DR. HOLLINGER: I think, for the record, at least as I view it, there are definite differences between these two products as we see it with coagulation and, perhaps, even effects on changes in electrolytes and pH which may be related to the carrier rather than to the hetastarch.

I think that there probably is less bleeding. But I think that there does need to be additional information that has been brought up

here in regards to at least one of the larger trials as regards to pump time and cross-clamp time and things like this which need to be looked at. But I do not think it warrants any changing in the labeling of that product at the present time.

We may come to a different conclusion later, but I did not see any data that seemed to suggest to me that there was an issue regarding bleeding or coagulation problems with this product.

DR. NELSON: I think so. There were some trends in people perhaps that received larger amounts so that it would be good if the data from these trials were submitted to the FDA for review. I think the FDA might consider that given the fact that in one related product we are recommending the label change.

DR. WEINSTEIN: Do you think the FDA should require that this information be submitted for the labeling change?

DR. NELSON: Possibly. We have heard one opinion at least that it was the hetastarch molecule-coating platelets that was the problem. But we have also seen some comparative trials that suggest that there were real differences.

DR. HARVATH: I believe that if any

statements are made in terms of superiority claims of a product or added benefits of a product that any such data must be submitted to the FDA before being allowed to make such claims. I would trust the FDA's critical review of that data to determine whether any such statements could be used in any labeling.

DR. NELSON: I would agree.

DR. HARVATH: Or marketing.

DR. CHAMBERLAND: I think part of this has to fall back to the FDA because, as I understood it from FDA's previous comments, these were licensed as "comparable products." If a labeling change is made in one, then it seems like they are not comparable products. So I think the FDA needs to sort of consider the implications of that because I agree with Dr. Harvath that, de facto, one sort of has a superiority claim associated with it, or inferred, if you will.

So I agree. I think that FDA should require the sponsor to bring forth additional data to evaluate the Hextend product.

DR. FALLAT: I would take Question No. 2 as being applicable to Hextend and, therefore, vote that we vote yes on Question No. 2 that there be

additional studies with regards to that product.

DR. LEW: I don't know about that only because I don't know what excellent studies may have already been done or are in press or about to be written up. So I think we should allow the company the opportunity to bring forward all the studies that have been done and, if that suffices to FDA, fine. But, if not, then we could revisit this.

DR. FALLAT: That's what I meant. I wasn't saying, necessarily, to exclude the studies that have already been presented.

DR. NELSON: The FDA would--we are advisory. We are not writing labels. Thank god. But the FDA would have the option in both products, if they wanted to, to say a product containing hetastarch has been shown, in some studies, to be associated in some patients with excess bleeding, without--there are ways to nuance and wordsmith this, I think.

But I agree. I don't think, by implication of putting in the saline, that we are saying that we agree based on the data presented that the hetastarch in lactate is significantly different or safe or free of--it is just that the

data we were submitted is somewhat convincing that there is some problem with the saline solution.

DR. ALLEN: I think where we are now, we are in the middle, really, of procedural questions and issues. It is my understanding that the FDA can negotiate with Braun and come up with revised labeling but that any other already licensed product is off the table for consideration unless the FDA has evidence sufficient to go back to a company with a licensed product and require them to produce additional information.

This committee has not indicated to the FDA in any way that there is sufficient evidence that the committee thinks that the FDA should do that. So, unless the licenses chooses to bring forth additional information and submit it and request consideration of a labeling change, my guess is that there will not be further action on this unless the company--

DR. NELSON: The one way that they might is if they said, "Our product is superior to the other."

DR. ALLEN: Yes; and that is the company initiating it. The FDA, similarly, could initiate if they think that there is a problem the other

way, but the committee hasn't supported them in that.

DR. NELSON: Exactly. I agree.

DR. ALLEN: I guess I would like to hear if the FDA feels that they would like some direction on that to please give us guidance now.

DR. HOLLINGER: I don't think I heard anything by either of the sponsors here today that said one product was superior to the other in regards to its oncotic properties. We heard a lot of things in regards to its effect maybe on bleeding or other things, but I don't think I saw any data or remember reading much data that suggested that one was any better than the other in terms of what it is really intended to be used for.

I may be wrong. Does anybody else remember anything about that?

DR. NELSON: I think we are still discussing warning labels which has to do with bleeding, not with oncotic problems.

DR. HOLLINGER: Yes; but someone mentioned, as a superior product. I think it is important to say that--

DR. SIMON: The claim for superiority was based on lower side effects.

DR. NELSON: It was based on less side effects.

DR. HOLLINGER: Okay. But I think it is important to point out that they, at least for what they do, they seem to be--

DR. NELSON: Exactly; for the indication, there is no evidence that they are--

MR. RICE: I think there was clear implication, even though they didn't necessarily say it outright. I think because we have already made a decision on one hetastarch product that I think that now they either have to--the Hextend has to prove their position or not at this point if they are going to consider these two products comparable.

Making a new statement on a warning label for the hetastarch in saline, while the other product is a comparably approved product, kind of a Pandora's box has been opened to suggest that it is better, it is different, and that there is a question that I would think the FDA would want to have answered and then, at that point, decide whether they are going to recommend a change in their labeling.

DR. CHAMBERLAND: I guess part of it goes

back to comments that Dr. Lew made earlier on. I guess it is just a point of information for the committee that we don't know. I think you have alluded to the fact that, at least for antibiotics, you can have "comparable antibiotics," although you can have subsequently additional information provided about adverse events about an antibiotic that is considered comparable.

So I don't know whether there is a direct applicability to this particular situation or not that you can have comparable product but one having a warning label about the potential for adverse events. So I think that is what we are struggling with. We don't really know under what sort of regulatory constraints you are under.

DR. LEW: If I can respond to that, although I agree that that is one issue, I do feel that we should make a motion to support FDA to ask the other company to submit some supporting data only because--I think Donna brought out some good points. There was a trend, even with the Hextend, that there might be some platelet problems and there was the von Willebrand's factor that was much lower and just other little subtle things.

So there may be data out there that the

company can just get and bring forward and that is good enough. But I would like to know, myself, and I think it would be worthwhile to give FDA the opportunity to go get that data.

DR. NELSON: I think the FDA would look at the data that is submitted to them and if the company decides not to submit the data, then the hetastarch--our recommendation is with regard to hetastarch in saline because that is the main part of the detailed data that we were originally presented with.

DR. LEW: I thought I heard FDA say they were asking us saying we can ask the FDA, we can recommend, that Abbott or Biotime submit data and that, if we recommend that, they can ask.

DR. NELSON: Do you want us to vote on that, or just the discussion is good enough?

DR. WEINSTEIN: I think the discussion is probably good enough here. You have, obviously, raised the issues here that we are going to have to wrestle with, the idea that these products were originally approved as being comparable both as far as safety and efficacy goes and now we are saying that the 6 percent hetastarch saline will have this warning statement on it that will differentiate it,

but we have heard today that there are potentially differences in efficacy, as I understand it.

Are those legitimate labeling claims? That kind of information has to be submitted to the FDA for application to the label.

DR. HOLLINGER: But, Mark, if you would, please. This all came about because there were several reports in the literature that suggested that Hespan had some bleeding problems. And then you send a letter off to the company I think regarding something about that. I think it came through you back in July or something like that.

I guess the real question is have there been similar kind of reports regarding Hextend.

DR. WEINSTEIN: To the best of my knowledge, no.

DR. HOLLINGER: I think that is important because that is what usually generates these warning labels. The warning label usually comes because of adverse events that are reported, either to the FDA or through some other--either to the sponsor or to the FDA.

DR. WEINSTEIN: Right.

DR. HOLLINGER: So without any adverse-event reports, and so on, then it makes it

difficult, I think, to demand that some warnings be applied to this. I think when they come, then that is another issue.

DR. WEINSTEIN: We will have to examine the MedWatch database.

DR. KOCHMAN: These were papers published over a prolonged period of time for a product that has been approved for a long time. These did not come in as MedWatch reports.

DR. NELSON: Hopefully, everybody can catch their plane or train or automobile or whatever. So thanks. Thanks, again. We will see you in September.

[Whereupon, at 1:55 p.m., the meeting was adjourned.]

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CERTIFICATE

I, **ALICE TOIGO,** the Official Court Reporter for Miller Reporting Company, Inc., hereby certify that I recorded the foregoing proceedings; that the proceedings have been reduced to typewriting by me, or under my direction and that the foregoing transcript is a correct and accurate record of the proceedings to the best of my knowledge, ability and belief.

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