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73rd MEETING

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C O N T E N T S

P R O C E E D I N G S

DR. SMALLWOOD: Good morning and welcome to the second day's session of the 73rd Meeting of the Blood Products Advisory Committee. I am Linda Smallwood, the Executive Secretary. Yesterday, I read the statement of conflict of interest that pertains to this meeting. It is available for anyone's review if you so desire.

At this time, I would like to ask if there are any declarations to be made regarding conflict of interest on the topics to be discussed this morning. If there are none, then I would just like to announce that we have a very tight schedule today with a complex subject. We would ask that all speakers please adhere to the time frame allotted so that we can complete the agenda for today.

I would also ask, as far as protocol is concerned, when speaking at the mike, please give your name and your affiliation and please speak into the mike since we are having the proceedings recorded.

At this time, I will turn the meeting over to the Chairperson, Dr. Kenrad Nelson.

DR. NELSON: Thank you, Dr. Smallwood.

The first items are some committee updates. The first is the Summary of the FDA/PPTA Workshop on Comparability of Plasma Derivatives. Dr. Chang?

Committee Updates

Summary of FDA/PPTA Workshop on Comparability of Plasma Derivatives

DR. CHANG: Thank you, Mr. Chairman. Good morning, everyone.

[Slide]

My name is Andrew Chang. I am a special assistant to the director, Division of Hematology in the Office of Blood Research and Review, CBER, FDA. In the next 15 minutes I am going to give the committee an update on the FDA/PPTA co-sponsored workshop, entitled Comparability Studies for Human Plasma-Derived Therapeutics. This one and a half day meeting was held in the Doubletree Hotel, in Rockville, on May 30 and 31.

[Slide]

The objectives of this workshop include to evaluate the implementation of the FDA comparability policy to plasma-derived therapeutics; obtain better understanding of the FDA's and industry's concerns and expectations; and improve comparability approaches for plasma-derived

therapeutics.

[Slide]

For the benefit of this audience, I will give a brief introduction to FDA's comparability guidance as it is related to the discussion during this workshop, followed by the agency's experience and the results of the workshop. Also in the interest of time, I will not be able to cover all the topics that were discussed in the workshop. I have chosen issues that might be of interest to this audience.

[Slide]

In April, 1996 FDA published a guidance entitled, FDA guidance concerning demonstration of comparability of human biological products, including therapeutic biotechnology-derived products. As you know, plasma derivatives is one type of biologic product so this guidance actually covers plasma-derived products.

[Slide]

The comparability policy has resulted from a desire to reduce the regulatory burden for manufacture changes. It is stated in the guidance that the FDA may determine that two products are comparable if the results of comparability testing

demonstrate that the manufacturing change does not affect safety, identity, purity or potency. This policy allows for changes in the product characteristics if they have no adverse effect.

[Slide]

As referenced, this slide illustrates our idea of what comparability is. Comparable stays in between identical and different.

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In the guidance, the 1996 comparability guidance, the following testing strategy for demonstrating comparability is stated: There are three levels. The first level includes in vitro, and sometimes in vivo, analytical functional studies. These could be chemical, physical, immunological or bioassays.

The next level, the second level is a preclinical study, such as animal pharmacokinetic, animal pharmacodynamic study and a toxicity study.

The last level, which is the third level, is a clinical study. This could be clinical pharmacokinetic, immunogenicity and clinical safety and efficacy studies.

The one thing I want to emphasize here is that the comparability testing is not necessarily a

hierarchical system where one result leads to another level of testing. Sometimes this system is complementary. For example, if the testing at a preclinical study finds some differences, that may trigger some additional in vitro analytical studies.

[Slide]

So, what is FDA's experience since 1996, when we published the comparability guidance, related to the plasma derivatives?

[Slide]

I have just a quick review of what plasma derivative products have been licensed by the FDA. Basically, there are four different categories of plasma derivatives. The first is the coagulation factors, including antihemophilic factor, including von Willebrand Factor complex.

I am not going to go through this list; I will just point out some categories. The next one is albumin and plasma protein fraction. We also have a group of protease inhibitors, such as alpha 1 protease inhibitors which you are all familiar with and, lastly, the family of immunoglobulin products. This list may not be a complete list but I just put this here to give you a review of what

products we are dealing with.

[Slide]

In addition to the plasma derivatives, we also have five licensed recombinant coagulation factors, such as the BeneFix, which is recombinant Factor IV; ReFacto, and so forth and so on, Kogenate and Recombinate. We also have one drug substance, recombinant antihemophilia factor for further manufacturing.

[Slide]

In the past five years FDA has received 70 to 100 prior approval supplements. For those of you that are not familiar with the term "prior approval supplement" I want to briefly say that a prior approval supplement is a supplement that is used to support a specific manufacturing change. We deem this type of change as significant, and the product made after the change cannot be released to the market for distribution until the agency approves it.

The number of supplements, as you can see here, remained relatively steady during 1997 to 2001. The 2002 data is up to May of this year. Another thing I want to point out to you on this slide is that at the top of the slide there are

some numbers. These numbers indicate the number of the major supplements that required clinical data to support the approval. Totally, we have six such major supplements with clinical data, and three of them actually are efficacy supplements for new indications. The other three involve manufacturing changes such as formulation changes and major process changes. So, roughly we have about 1.31 percent major supplements that require clinical data to support a change. If you take out the three efficacy supplements, we only have roughly about 0.7 percent of the supplements requiring clinical data.

[Slide]

So, what is our regulatory approach? I want to emphasize here that up till now we have regulated major manufacturing changes on a case by case basis. The following three factors are important in terms of determining what type of data will be required. First, we have to deal with so many different types of products. Product is important. Also, the type of manufacture changes and, lastly, the risk analysis and assessment that the agency makes for that particular manufacturing change.

[Slide]

For the benefit of this audience, I include two general examples to illustrate the scope of change and the regulatory requirements. This example includes the type of changes, such as a new facility with no change in in-process control, no change in specification, and demonstration of in vitro comparability.

A second type of change includes new assay, new standard for quality control and lot release. Lastly, we have quite often received a one-time exception supplement. For those of you who do not know what a "one-time exception supplement" is, basically it is a company that sends in a request to the agency for release of some of the lots that were manufactured with minor, or sometimes major, deviations from their license.

To handle this type of manufacturing change, the review mechanism that we have is under the prescription user fee program, for which we have a four-month review time. For some of the applications, such as a new facility, we also require a pre-approval inspection.

[Slide]

Another type of manufacturing change which

we consider very major manufacturing change is a new facility with alternate process; changes in specifications for drug substance and drug product; demonstration of comparability, and this demonstration includes three tiers of analysis which I mentioned earlier. Under PDUFA 2 we have ten months review time and data supporting this kind of manufacturing change includes in vitro biochemical/biophysical characterization, preclinical studies, bridging clinical studies, and normally involve human pharmacokinetic data and sometimes will require safety and efficacy clinical data. Pre-approval inspections are always required for this kind of manufacturing change and in some cases, and very often, a new proprietary name is used. A company normally voluntarily phases out their old process but the agency has no requirement to make a commitment of time for this transition.

[Slide]

In conclusion, comparability approaches apply to both plasma- and biotech-derived biologics. In our experience, clinical data have seldom been required to support manufacturing changes, however, major concerns remain.

[Slide]

Concerns related to plasma protein therapeutics are the following, which may not be a complete list but I have pointed out some major things: Poorly defined starting material. We have source plasma versus recovered plasma that we had extensive discussion yesterday about. We have different pool sizes used for the manufacturing. Lack of robustness of the manufacturing process, minor changes with major impact. We have learned this lesson a long time ago and this is still the case. Introduction of a vasoactive substance, such as PKA that Dr. John Finlayson mentioned for some of the cases yesterday. Low purity; neoatigenicity. Impurities, as I quoted here, may be active and may affect activity or absorption. Often this type of product is highly complex; and heterogeneous proteins; history of viral transmission.

[Slide]

Lastly, I want to give you some of the major results that came out from this workshop.

[Slide]

It is the agency's impression that the plasma derivatives industry welcomed the agency's comparability policy. Comparability approaches

have been successfully used to expedite the implementation and approval of manufacturing changes.

[Slide]

Due to the complexity of the products and processes, it is unlikely, in the near future, to have a formula to decide what is comparable. Judgments will always be needed. Up till now, as I mentioned earlier, we still use a case by case approach. Due to the complexity and the reasons I mentioned earlier, there are many specific concerns for this type of product.

[Slide]

In conclusion, this workshop has fostered a better understand between the FDA and industry on the various topics related to the demonstration of comparability of human plasma-derived therapeutics. This workshop has also prepared both parties for more focused discussions to advance the goal of providing consumers with safe, pure, potent products in the most expeditious manner. I thank you for your attention.

DR. NELSON: Thank you, Dr. Chang. Are there any questions?

[No response]

The next item is a summary of the AABB Conference on Oxygen Therapeutics, Toby Silverman.

AABB Conference on Oxygen Therapeutics and Transfusion Alternatives

DR. SILVERMAN: Thank you, Mr. Chairman. I attended the AABB Conference on Oxygen Therapeutics and Transfusion Alternatives on May 30th to 31st of this year, and I am going to give you a brief summary of the discussions that occurred at that meeting.

[Slide]

AABB convened a conference to discuss a variety of topics, to include red cell transfusion, transfusion risks, perceptions of transfusion risks, alternatives to allogeneic red blood cell transfusion, and future directions for a class of products known as oxygen therapeutics, as well as other transfusion alternatives.

[Slide]

The meeting structure was essentially as follows. I have rearranged some of the order of the talks to organize them into subject groups. There was an introduction and outline of the issues by the conference chairs. There was a discussion of the impact of red blood cell alternatives;

logistical and control issues; and then a number of scientific discussions to include cancer and cancer treatment related anemia, the efficacy of transfusion, and the ethics of so-called bloodless medicine. There was a discussion of the military needs for oxygen therapeutics. There were a number of manufacturer presentations, and then the meeting concluded with my presentation.

[Slide]

The impact of oxygen therapeutics on the current transfusion environment, there is and remains a public perception that allogeneic transfusions are not safe for a number of reasons. First, known infectious risk; a concern about emerging infectious risks; and then further, a concern about the noninfectious hazards of transfusions, affectionately known as NISHOTS. There is a desire for alternatives to be used to reduce or eliminate the risks of blood transfusions.

[Slide]

Here are a number of transfusion alternatives that were mentioned or discussed at the meeting: Predeposit autologous transfusion; hemodilution; intraoperative autologous donation;

pharmacologic therapeutics; apheresis to reduce donor exposure; viral inactivation of a variety of transfusion products; and, finally, oxygen therapeutics.

[Slide]

There are a number of competing technologies for oxygen delivery that were identified in discussions at this meeting. These include intravenous allosteric modifiers of hemoglobin function; hemoglobin from transgenic animals and pathogen-reduced red blood cells. One that was new to me was in vitro red blood cell culture, and a number of others.

[Slide]

What is the impact of transfusion alternatives? You see a number of question marks for everything here on the slide. What is the demand for allogeneic blood donors for the manufacture of such products? Unknown. Whether there will be an improved outcome in trauma is unknown. Whether there will be an impact on the volunteer blood donor pool is unknown. There are many implementation questions that remain. The first is where will such products be stocked. Pharmacy or will they be controlled through the

blood bank? What will happen in terms of collection of source red blood cells for such products? How will such products be reimbursed? Then, what choice of agents to stock either in the blood bank or in the pharmacy?

[Slide]

How and where will oxygen therapeutics be used? First how, will they be used for initial resuscitation? Will they be used as a bridge to transfusion? Will they be used as adjunctive therapy for, for example, radiation treatments to enhance oxygen delivery to tumors? Will they be used as a transfusion alternative? Will they be used as an oxygen therapeutic?

Where and by whom will such products be used? Will they be used on the battlefield? Will they be used at the accident scene? Will they be used in the transport vehicle, such as an ambulance? Will they be used in the hospital and, if in the hospital, where? In the OR, in the emergency room, in the cath lab? Will they be used by oncologists? Will they be used in physicians' offices?

[Slide]

Who will control and how will control of

products be maintained? First, who will control? Will it be the pharmacy? Will it be the blood bank? Will it be both? Will it be neither?

What control and oversight issues remain? What will be the initial and then what will be the total dose of such products to be used? How will use of the product be monitored? Will there be a utilization review committee? What will happen in terms of the clinical laboratory and how will the clinical lab handle the interference that invariably is associated with the use of a colored product in terms of the readouts for some of the clinical chemistry laboratory tests? Who will control and how will quality control be maintained? Finally, who will have oversight or who will evaluate transfusion or infusion reactions?

[Slide]

The scientific discussions. The first was a discussion of cancer and treatment-related anemia. High dose hemotherapy and autologous stem cell transplantation can be performed without the use of blood or platelet transfusion. We heard that stem cells are cryopreserved with albumin; that pre-transplant use of erythropoietin and intravenous iron help reduce the need for red cell

transplantation; that there is no mortality when high-dose chemotherapy is delayed until the total hemoglobin level is at least 11 g/dL. There is a question as to whether high-dose chemotherapy should be delayed until platelet recovery has occurred. Thrombocytopenia can be managed with antifibrinolytic agents. And, there was no significant bleeding with platelet counts above 5000.

[Slide]

Efficacy of transfusion, there are a number of considerations: What is the level of anemia that adversely affects outcome? What is the level of anemia at which transfusion has been demonstrated to reverse poor outcome? I think what you can gather from this is that there are an awful lot of questions and not an awful lot of answers.

[Slide]

The efficacy of transfusion, there is one adequately powered trial in the world literature that suggests that total hemoglobin of 7 g/dL as a threshold is safe in ICU patients, but the data may not be generalizable overall. There are observational data in patients with cardiovascular disease that suggest that a higher total hemoglobin

level may be needed in such patients.

One of the conclusions was that it is likely that the most important factor related to outcome is whether or not the patient has had outstanding medical care or less than outstanding medical care. Then, there is a question as to whether to use alternative treatment when there is increased risk and transfusions have improved outcome.

[Slide]

There was a discussion of the ethics of bloodless medicine. The standard of practice was described. Blood transfusions are indicated when specified conditions pertain, however red blood cells are a scarce resource. Patients may refuse transfusion. There was a discussion of the use of informed consent and decisional capacitation and also a discussion of the outcomes of clinical research on bloodless techniques. There is a range of practices that are the product of accumulated medical experience but, as you have seen, there are very few clinical trials.

[Slide]

Decisional capacity, there are four conditions that pertain in order to determine

whether a patient is decisionally capacitated. The patient must be able to understand his or her medical condition. They must be able to understand the medical alternatives which include no treatment at all. The patient must be able to understand the risks and benefits of each alternative and express a choice about those alternatives. For refusal of a high benefit and low-burden treatment, the patient should have a stable set of personal values that can be ascertained, and must have the ability to apply those values to the clinical situation.

[Slide]

Finally, the last two talks for the conference included military blood use. For the military, delivery of blood or transfusion products is logistically difficult and it is very difficult to position appropriate products where they are needed. Not all products are available where they are needed. For example, platelets cannot be shipped because of the time lag between the date of notification of need and the date of arrival at the scene, which can be as long, if I recall correctly, as 10 or 11 days. Therefore, untested whole blood is collected for platelet transfusion in the combat arena. Finally, the frozen blood inventory is

reaching its 10-year storage limit.

[Slide]

There were a number of manufacturer presentations which I will not summarize here. We were updated by Alliance Pharmaceutical Corporation, Amgen, Biopure, Hemosol and Northfield Laboratories.

[Slide]

A very brief overview of the talk that I gave, there are some considerations when looking at clinical trials for oxygen therapeutics. Whether one should look at trials as urgent versus elective use; trauma versus surgery versus medical use; or whether blood is available as opposed to blood not being available.

[Slide]

We made a number of recommendations, that studies in both trauma and elective surgery are probably needed for best initial understanding of the benefits and risks of oxygen therapeutics in the broadest spectrum of situations where and when such products might be used, generally as alternatives to red cell transfusion. An indication for use where and when blood is not available is best supported by studies in both

elective surgery and in trauma. Safety evaluation should be performed in stable elective surgical settings before using a product in unstable or traumatized patients. Finally, the FDA may accept applications for elective surgical indications alone.

In general, the discussion at the meeting suggested that there might be other places for use of oxygen therapeutics, particularly as adjunctive therapy or for medical indications or indications other than surgery or trauma. That seems to be the new message coming out of this particular meeting. Thank you very much.

DR. NELSON: Thank you, Toby. Questions? No? We had a request for a brief presentation from Anthony Castaldo, from the Hereditary Angioedema Association.

Public Presentation

Hereditary Angioedema Association

MR. CASTALDO: Thank you, Mr. Chairman. Good morning. My name is Anthony Castaldo, and I am here today to briefly discuss issues associated with gaining FDA approval for plasma-derived purified C1 inhibitor concentrate. This drug is the only treatment available for acute attacks of

hereditary angioedema, HAE, and has been used safely and effectively in Europe and other parts of the world for over a decade.

Although I am a board member of the association that represents patients with this severe, debilitating, and life-threatening disease, it is important that I mention up front that statutes governing the ethical conduct of government employees preclude me from representing the HAE Association during today's proceedings. Accordingly, to ensure strict compliance with federal statutes that prohibit a government employee from representing a third party before any governmental entity, I would like to state for the record that technically I am not appearing on behalf of the association or in my capacity as a board member. I appear today as an advocate for the severely affected HAE patients in my immediate family. That takes care of 18 USC 205.

HAE patients were recently informed that the results of a Phase III clinical trial of Baxter International's C1 inhibitor concentrate product were not favorable enough to obtain FDA approval. Patients suffering from HAE are once again left with little near-term hope for an acute attack

therapy. This outcome is tragic in light of the unanimous view among participating investigators who are convinced that Baxter's C1 inhibitor concentrate is an effective and safe acute attack therapy.

By way of background, HAE is a rare condition in which a genetic defect causes a deficiency in the plasma protein C1 inhibitor. Dysfunctional C1 inhibitor protein permits production of vasoactive peptides that alter vascular permeability and cause edema. Accordingly, the disease is characterized by episodic swelling of the extremities, face, bowel wall, and upper airway. Studies of affected kindreds have reported mortality rates of over 30 percent, with death most frequently caused by asphyxiation due to airway closure.

We are constantly reminded of the inherent danger posed by hereditary angioedema. Over the past 18 months, I have received information regarding the untimely deaths of three patients who were active participants in an informal email support group for HAE patients. Two of these patients, by the way, were enrolled in the Baxter clinical trial and were unable to get to the trial

site in time for treatment.

The fact that the Baxter C1 inhibitor product will not be licensed in the United States is shocking for many reasons. Foremost among them is the fact that this product boasts a decade-long track record of safe and effective use outside the United States. Moreover, the same product was proven safe and effective in a well-designed NIH-funded study conducted by three respected scientists who published their results in a 1996 paper that appeared in The New England Journal of Medicine. It is, indeed, ironic that the day Baxter notified us of the trial failure marked the one-year anniversary of a study out of Europe in the Archives of Internal Medicine that assessed 193 cases of HAE-related laryngeal edema, all successfully treated with C1 inhibitor concentrate.

In light of the foregoing, there looms an obvious yet quintessential question, how could a demonstrably life-saving therapy, with a proven track record of efficacy and safety, be judged a failure? Investigators who participated in the trial immediately knew the answer, and it continues to haunt the HAE patient community. To meet the mandated primary clinical endpoint, the trial had

to demonstrate that C1 inhibitor concentrate was effective within one hour from commencement of an infusion. In contrast, studies that garnered C1 inhibitor concentrate approval in Europe assessed efficacy within a four-hour window.

Perhaps the most compelling evidence of the C1 inhibitor clinical trial design deficiencies was articulated in an email from Dr. Andrew Grant, a trial investigator from the University of Texas at Galveston. I quote, my patient, TA, with HAE was admitted to this hospital with complete obstruction of his airway. He survived the day only because he has a permanent tracheostomy which he could open. Within 20 minutes of starting his C1 inhibitor infusion he noticed some improvement, which continued over the next four hours to the point of near resolution. But until one hour, his course was not at all clear. Thus, he probably would have been judged and listed by me as a trial failure at one hour, thus, another proof that the study design was hopelessly flawed, closed quote.

Additional analysis performed by one of the study's principal investigators shows just how close we were to getting approval for this vital and critically needed therapy. This scientist

evaluated the clinical trial data set using 80 minutes instead of 60 minutes as the endpoint. Even this relatively small additional time increment produced a striking difference in the number of treatments that would have been reported as a positive response, and likely would have altered the study's final result.

In conclusion, the only treatment shown effective for abating dangerous and painful acute attacks of hereditary angioedema is replacement therapy using plasma-derived purified human C1 inhibitor concentrate. The human suffering that will result from the lost opportunity to gain approval of C1 inhibitor concentrate motivates HAE patients to pick up the pieces and try again. This has become more complicated since the trial failure appears to have prompted Baxter International's decision to cease worldwide production of its C1 inhibitor product.

At this juncture, HAE patients are left without any near-term hope for an acute attack therapy. However, HAE patients are working feverishly to interest another company in conducting a clinical trial with their C1 inhibitor product. I urge the FDA staff to work with the HAE

investigator community to establish a more rational and fair C1 inhibitor concentrate clinical trial design. To be sure, this is a crucial factor that will influence drug company decisions on whether another C1 inhibitor concentrate clinical trial will be conducted in the United States. Thank you for your time, and I would be happy to answer any questions.

DR. NELSON: Thank you. Toby?

DR. SIMON: Is the plasma useful--we realize it has a lot of disadvantage to a concentrate in view of the volume, but how useful is it in treatment?

MR. CASTALDO: FFP, there is just not enough inhibitor. I can give you an example of my daughter before we got access to the factor. We actually got compassionate use of it because of the severity of my daughter's disease. We literally used gallons of FFP and it just doesn't work effectively at all. Some patients report some efficacy but, generally speaking, because of the other substrates that are in plasma and the possibility of attack exacerbation, it is not an effective therapy. Furthermore, it is a 24-hour resolution at best, and generally it is not

considered an effective therapy for this indication.

DR. HOLLINGER: Is it found in cryoprecipitate?

MR. CASTALDO: I am sorry?

DR. HOLLINGER: Is the factor found in cryoprecipitate of this inhibitor?

MR. CASTALDO: I don't believe so.

DR. NELSON: Yes, it sounds like it is a fairly complex problem. As I put it together from your presentation, it appears that the trial was designed with a certain endpoint which wasn't met but still there was a benefit. Then, the FDA, I think, required the manufacturer to satisfactorily meet the endpoint and they met another endpoint and, therefore, it wasn't licensed and the company decided not to proceed. So, it is a very difficult situation. I don't think the committee can do much, except we are very thankful for the information.

MR. CASTALDO: Well, we note that the staff is here--

DR. NELSON: And we are hoping, if there is any progress or change on this, that maybe we could discuss it at a future meeting.

DR. EPSTEIN: Just a few things. First of all, I appreciate your remarks. On the other hand, this was not a topic on the agenda and we didn't come prepared to really deliberate it.

MR. CASTALDO: Right.

DR. EPSTEIN: But that said, the first point is that the product does remain available for compassionate use so the patients have not entirely been abandoned either by the company which makes it available, or by the FDA that permits the compassionate use.

The second point I would make is that, you know, it is a fundamental error in clinical trial assessment to take a failed trial and to draw a circle about an observation and to say that you have now validated the new endpoint. This is a heresy; it violates all statistical principles. I am sure Dr. McGee would agree with me. You simply can't go about it that way. When that happens what has actually occurred is that you have generated a new hypothesis which you then should test prospectively. That is the only way to know whether you have committed an error of logic.

So, the normal response, and true in this case, would be to say to the company, well, it

looks as if it might have efficacy with this other endpoint which would appear to have clinical benefit if shown true, and you need to redo the trial prospectively with that endpoint in mind, or the new target. You can't just draw a circle around a result and say that was our target; we met it. You have to have the target and then do the study.

So, you know, it falls to the company to decide whether to pursue a trial with a different endpoint and, of course, to convince people that this different endpoint is also a clinically meaningful endpoint. I would just submit that most of the enlightening exercise needs to be directed towards the company to address patient need.

MR. CASTALDO: Yes, and we agree. In fact, that is what this testimony basically says today, that we just hope that staff would be willing to work with our physician investigator community that is going to work, hopefully, with another company to design a trial that would be more in accordance with what we observed to be the response, the pathophysiological response to the therapeutic.

But I agree with the reasoning that you

have posited here. One of the things that we have heard anecdotally from our discussions with various individuals who represent different companies which make this factor is that if there were some notion that there could be an endpoint that would be more in accordance with what the European trials have done, then a company would be more willing to come into the market. That is basically what we are looking for. In the next trial, hopefully, the design will be a little different than the one we currently have.

DR. HOLLINGER: In terms of numbers, how many people in this country do you know of that have this deficiency in terms of powering of studies, and how often do they have a problem? Once a year? Once a week?

MR. CASTALDO: Yes, one of the things about this disease is that the presentation is highly variable among patients. The epidemiological data on the disease is not very good. There is a very wide spread. It is between 1 in 10,000, which would give you a patient population of 28,000, to 1 in 50,000, which would make around 5500.

You know, there is an association of

patients and I can tell you that that association generated upwards of 2000 letters to the Baxter chairman, in response to their decision to exit this market, to see if we couldn't change his mind and have him come back and do another trial and try to go for a different endpoint.

Again, as I mentioned before I looked at the time requirement and I crossed a few things out of my statement today, but the current available therapy is anabolic steroids, 17-alpha alkylated androgens, and they do provide prophylaxis in some patients but most of those patients, in my experience, still have what we call breakthrough attacks. Moreover, trauma is a big part of this disease. Many attacks are induced by any form of trauma. As a result, if you are going to have oral surgery or any other kind of surgery, in Europe it is customary to have a prophylaxis dose of C1 inhibitor concentrate to ensure you don't have associated edema with that. But most patients, I would say roughly speaking maybe on the more severely affected side of the continuum would probably have attacks anywhere from once a month to once every two weeks, not withstanding androgen therapy. That excludes a whole other tragic

population of children, and there are a lot of very severely affected children out there, for whom, of course, anabolic steroid therapy is contraindicated.

DR. NELSON: Thank you. The next item is requirements for premarket submissions: in vitro diagnostic software and instruments, Diane Gubernot.

Requirements for Premarket Submissions: In vitro Diagnostic Software and Instruments

MS. GUBERNOT: Thank you. Good morning.

[Slide]

There will be three of us presenting on this topic this morning, and we will also have John Murray, who is a software expert from CDRH, in the audience, if there are questions.

I am Diane Gubernot. I am a reviewer in the Division of Emerging and Transfusion Transmitted Diseases. The presentation is on the requirements for premarket submissions for in vitro diagnostic instrumentation and software related to donor screening and all HIV diagnostic assay systems.

[Slide]

The issue is that software/instruments are

becoming increasingly complex due to the development of automated platforms for testing and, therefore, the applications are becoming more complex. Some manufacturers have expressed confusion regarding premarket submission requirements for software related to blood typing, donor screening and HIV diagnostic assay systems.

[Slide]

The objectives of this presentation are, one, to summarize the regulations and guidance documents applicable to the software systems for premarket applications; two, to provide specific information to the manufacturers on the content of submissions to expedite the review process.

[Slide]

Three, to inform manufacturers of the standards for level of concern determination which apply to CBER-regulated donor screening and HIV diagnostic assay systems.

[Slide]

For software development, manufacturers must follow the quality system requirements, the QSR, found in 21 CFR 820. The general principles of software validation is a guidance for industry which should also be followed. It describes how

certain provisions in the QSR apply to software. It is a very useful document. This is true for device applications that are submitted to CDRH and to CBER.

[Slide]

When submitting software and instrument applications to CBER, or applications that contain a software component or an instrument of an assay, manufacturers should follow the guidance for content of premarket submissions for software contained in medical devices. This is a CDRH guidance document available on our website. By following this, this will expedite the review process.

In addition, manufacturers of blood bank software should follow reviewer guidance for a premarket notification submission for establishment computer software, which we refer to as BECS. This guidance is specific for 510(k)s for BECS.

[Slide]

The applications may be premarket notifications, which are 510(k)s. These are for substantially equivalent devices. Premarket approval applications, PMAs, are usually submitted for diagnostics. Biologic license applications,

BLAs, are for donor blood testing. If you are confused, please contact us prior to submitting.

[Slide]

Blood bank and HIV diagnostic instrument and software devices may be stand-alone software, such as blood establishment computer software. It could be software that is used in conjunction with automated instruments. It could be software that controls an instrument or software that collects data and results from an instrument. Or, it could be automated and semi-automated instruments containing firmware, which is embedded software. Although people may not perceive instruments to be software, they do contain software and, therefore, the guidance applies. An example would be an automated pipetter or an analyzer. Also, accessories, such as barcode scanners, should be part of the application. I mention barcode scanners, they are important data input and part of the system for sample traceability and unit traceability.

[Slide]

The CDRH guidance for premarket submission includes definitions for major, moderate and minor level of concern; a flowchart for determining the

level of concern for your device; and required documents to be submitted based on the level of concern determination.

[Slide]

The level of concern is a term used by FDA and industry to determine which software design documents are required to be submitted in an application. Therefore, it determines the depth of the review. The required verification, validation and testing activities performed by a manufacturer are not limited to the scope of the application submission. Therefore, the application should be a xeroxing exercise.

[Slide]

Major level of concern is defined as operation of the software associated with device function directly affects the patient so that failures or latent flaws could result in death or serious injury, or indirectly affects the patient such that incorrect of delayed information could result in death or serious injury of the patient and/or operator.

[Slide]

Moderate level, operation of the software associated with device function directly affects

the patient so that failures or latent flaws could result in noon-serious injury, or indirectly affects the patient such that incorrect or delayed information could result in non-serious injury of the patient and/or operator.

[Slide]

Minor level, failures or latent design flaws would not be expected to result in any injury to the patient and/or operator.

[Slide]

This is a flowchart from the CDRH guidance. It is a little difficult to read, but note the arrows for the boxes. Those are the decisions that I will be going over, the questions that bring us to the level of concern.

[Slide]

The first box, does the software control a life-supporting or sustaining device? The answer is yes for blood establishment computer systems, blood screening systems, blood typing systems because blood is life supporting and sustaining. Sheryl Kotchman will be talking more about that. That would be a yes and that brings us over here.

[Slide]

Then for HIV diagnostics, these would be

no until we get to box number two. Does the software provide diagnostic information as a basis for treatment or therapy? And the answer is yes. So, that bring us over here.

[Slide]

That brings us down to box number three, prior to mitigation could a software failure result in death or serious injury? The answer is yes, so that brings us here to major level of concern. That is a recap with the numbered boxes.

[Slide]

HIV diagnostic instruments and software, FDA has determined these to be a major level of concern. Products that aid in diagnosis, monitor, such as the viral load assays, or genotype HIV, the resistance assays, meet the 21 CFR 809.3 definition of an in vitro diagnostic device. Incorrect test results from use of the devices could mislead physicians regarding treatment decisions, resulting in serious injury.

[Slide]

This is directly out of the CFR definition for in vitro diagnostic devices. in vitro diagnostic products are those reagents, instruments and systems intended for use in the diagnosis of

disease or other conditions, including a determination of the state of health in order to cure, mitigate, treat or prevent disease.

[Slide]

In summary, all software and instrument systems, regardless of the determined level of concern, must follow the QSR for system development. General principles of validation guidance document should also be referenced. The guidance for the content of premarket submissions for software contained in medical devices should be followed to expedite the review process. Seek guidance from CBER prior to submitting an application. Again, the application should be a xeroxing exercise. FDA expects complete and organized submissions, and we strongly encourage early interactions prior to the submissions so that we can go through the guidance documents and discuss the data that should be submitted.

These are CBER software contacts. I work in the Division of Emerging and Transfusion Transmitted Diseases. My phone number is 301-827-3624. Sheryl Kochman, who will be presenting next, is in the Division of Blood Applications. Her phone number is 301-827-3524 and

Richard Potter, in the Division of Hematology, 301-496-2577. If you are unsure whom to call, you may call any of us and we will send you in the right direction. Thank you.

DR. NELSON: Thank you. Next is Sheryl Kochman.

MS. KOCHMAN: My presentation, considerations for premarket submissions for automated blood grouping systems and blood establishment computer software, is just a summary of how we have been doing business, and to put things in perspective for the things that Diane just went over.

[Slide]

I am Sheryl Kochman. I am chief of the Devices Review Branch. My branch covers those devices that are used in tracking donor information, which would be the BECS, and also the devices and reagents that are used in blood typing for transfusable products.

[Slide]

The objectives of my presentation are to confirm that the information just presented by Diane also applies to automated blood grouping systems and blood establishment computer software,

and it is also to remind manufacturers of additional existing guidance that we have.

[Slide]

First, for automated blood grouping systems, the existing FDA guidance for reviewers, premarket notification submissions for automated testing instruments used in blood establishments, which is a draft guidance available on the CBER website, is something that you can refer to. It is still a draft and it states FDA's current thinking on reviewing these devices. It should also be pointed out that this document, while labeled as being a reviewer guidance, also applies to manufacturers.

[Slide]

We also have some other information, that has been around for a while, that indicates our thinking on what we expect these devices to do. So, we also would like to refer people to a memorandum to all licensed blood establishments. The title is changes in equipment for processing blood donor samples, issued by CBER July 21, 1992. This document was initially intended for device users but it provides useful information to manufacturers of automated blood group systems as

it describes some of the expectations we have for what a user is supposed to do to validate and install the system.

[Slide]

We also have a points to consider document, design and implementation of field trials for blood grouping reagents and anti-human globulin, docket number 91N-0467. It is a 1992 draft. The notice of availability for this document was published in May of '92 and it is 57 FR, 18885. This document is also still a draft but it states FDA's current thinking on performance of field trials. This document was intended for manufacturers of reagents but provides useful information to manufacturers or automated blood grouping systems as well.

I also want to reaffirm that the guidance for content of premarket submissions for software containing medical devices, May 29, 1998, is also applicable to this group of devices. As Diane indicated, it is applicable to devices. Again, the general principles of software validation, final guidance for industry and FDA staff is also applicable. Both of these are available on the CDRH website.

[Slide]

I also want to reiterate that the level of concern for automated blood grouping systems is a major level of concern since the affected end product, which would be human blood, is life-sustaining and a defect in the software could result in the transfusion of an incompatible product causing death or serious injury.

[Slide]

For blood establishment computer software, and I will call it BECS for the rest of the presentation, we have a guidance that has been published, reviewer guidance for premarket notification submission for blood establishment computer software. The final was published in January of 1997, and this document is available on the CBER website. There are some things that we found that are not quite clear in this document, and if people have questions about intent or a description of what we are looking for, they should feel free to give us a call and we will help you work it through.

[Slide]

In addition, BECS manufacturers might find some other information that would be useful to them

in a memorandum to all licensed blood establishments. Again, this was recommendations for implementation of computerization in blood establishments. It is a CBER, April, 1998 document. This was initially intended for blood establishment personnel but provides useful information to manufacturers of BECS. It describes some of the things we expect the software to be used in blood banks to be capable of doing.

[Slide]

Again, another memorandum to all licensed blood establishments, requirements for computerization in blood establishments, from CBER, September, 1989. It was initially intended for blood establishment personnel but also provides useful information to manufacturers of BECS in that it describes what we expect the software to be capable of doing.

[Slide]

Just another reaffirmation that the two CDRH guidance documents are applicable to BECS, as well as the CBER guidances that are available.

[Slide]

Again, confirmation that the level of concern for BECS is a major level of concern since

the human blood is life-sustaining and a defect in the software could result in the transfusion of an incompatible or unsuitable product causing death or serious injury.

[Slide]

Some of these documents that I have referenced here are so old that they are not available on the web so I wanted to give people some help in finding some of the older documents. If there is no website address, you can contact our Office of Communications, Training and Manufacturer Assistance. I have the email, the phone number and the fax number for those people. You can also send a letter to that same office if you need additional help. They should be able to refer you to any other help you might need. Thank you.

DR. NELSON: Thank you, Sheryl. Questions or comments? You talked about testing, and so forth, but does FDA require a patient registry, computerized patient registry? The reason I ask this is because I have done a lot of work in international settings and when you go to even a large international blood bank you find that they still have paper records, and it becomes just an impossible situation. My feeling is that all blood

banks in the U.S. are computerized with regard to patient demographics and previous test results, etc., but is that an FDA requirement?

MS. KOCHMAN: No, it is not, not that it be electronic.

DR. NELSON: Because if it isn't electronic it is kind of useless. Thank you. Jim Callaghan?

MR. CALLAGHAN: Good morning.

[Slide]

I am Jim Callaghan. I am from CDRH. I work in the Office of Device Evaluation, the Division of Clinical Laboratory Devices. I am here to talk about CDRH classification policy for laboratory automation. This includes automated clinical laboratory analyzers, reagents and automated laboratory test systems.

[Slide]

These test systems may be considered combination devices. This was discussed in a guidance document, a blue book memo, back in 1986. It was in a premarket notification review program guidance.

[Slide]

Specifically, when any of these analyzers

are regulated as a combination device, the analyzer accessory is classified in the highest of the predicate device classifications of this system combination. There has been confusion on this, and this is why I am bringing that up.

[Slide]

Prior to FDAMA, automated clinical laboratory analyzers were not exempt from premarket notification. Now, since they are class I devices, these analyzers are exempt from 510(k). However, they are not exempt when an analytical claim is made for class I reserved devices, by virtue of the limitations to exemptions under 862, 864 and 866.9, or a class II device. If there is a claim made for a class III device, it would be regulated under the PMA process.

[Slide]

In January, 2000 there was a Federal Register notice exempting class I devices from premarket notification. In this Federal Register notice there were several class I devices reserved from this exemption. In particular, blood banking supplies, vacuum-assisted blood collection systems, blood measuring devices and blood weighing devices. Additionally, quality control materials were

exempted--there are class I devices that were exempted from premarket notification, but they are reserved if they are assay control material or controls that are unassayed, used for blood banking.

[Slide]

The limitations to the exemptions are under 862, 864 and 866.9. They all have the same language. The limitations to exemptions refer to any class I device. They would not be allowed to be exempt from premarket notification if the modified device operates under new technology, such as an in vitro diagnostic device that measures infectious agents by using a DNA probe or nucleic acid hybridization technology, or if it is used for screening purposes, diagnosis or monitoring of life-threatening diseases, such as AIDS or hepatitis.

[Slide]

Additionally, there are other indications that limit in vitro diagnostics from the exemptions, and those would be for use in diabetes management and risk of cardiovascular diseases.

[Slide]

We have covered the analyzer and reagents,

now we need to talk a little bit about laboratory automation systems. When there is a link to the automation system to the analyzer, there is also a link to the reagents and the laboratory automation system would be classified according to this classification of the reagent when we go beyond the transmission of data to and from the analyzer, and the automated laboratory system starts taking over the functions of the analyzers. Then we would require premarket notification. There is a really grey area as to when this kicks in, and we would ask that you call and discuss it with our CDRH people for CDRH, and for blood banking you would have to do the premarket notification.

[Slide]

I want to talk about a policy that is different. It is unique to DCLD. It is not used in CDRH and it doesn't apply to CBER. The reason I want to talk about it is to just show you that we are different and the centers are different because of specific issues.

The policy that we use is replacement reagent policy. It is based on a guidance issued in 1996. The guidance is for data for commercialization of original equipment

manufacturers, secondary generic reagents for automated analyzers.

[Slide]

This policy is meant for well-characterized clinical laboratory testing systems intended for use by clinical laboratory professionals.

[Slide]

It is only meant for instruments or reagents that have been previously cleared, and when there is a claim made for a new test system reagent combination. It is also used for the introduction of new instrument family members of previously cleared families.

[Slide]

DCLD feels that there are sufficient controls for these types of claims and test system modifications when there is an acceptable test system validation protocol in place.

[Slide]

We are using an add-to-the-file process to notify the FDA in place of our traditional 510(k). What this policy did for us, because of the numbers of different combinations that would come in--we have thousands of 510(k)s and it would tie up our

resources, so we put this policy in place for DCLD only to address those concerns. We are not recommending that CBER follow this at all. In fact, when the policy was written, it applies to devices intended in support of blood banking practices for class III devices, over-the-counter devices or for exempt general purpose reagents.

[Slide]

In summary, while there are some differences between the centers, we are on the same page. We review devices based on health risks, established guidance and policy and regulations. Thank you for your attention.

DR. NELSON: Thank you. Questions? Dr. Landow is not here? Are you ready? We could take a break now. Maybe we should, and maybe come back at about 9:45.

[Brief recess]

DR. NELSON: The next item on the agenda is reported association of six percent Hetastarch with excess bleeding in open-heart surgery. The topic will be introduced by Dr. Laurence Landow, from FDA.

Reported Association of Six Percent Hetastarch with Excess Bleeding in Open-heart Surgery

Introduction and Background

DR. LANDOW: Good morning, everyone. Here is our agenda for this part of the meeting. I am going to give a few introductory comments about cardiopulmonary bypass and hetastarch, then Dr. Canver will present the argument that hetastarch does not increase the risk of bleeding. He will be followed by Gary Haynes, who will make the opposing argument. Then I will make some closing comments about non-randomized trials and then we will have a discussion of the questions by the committee.

[Slide]

The first question for the committee is, is the evidence for excessive bleeding in cardiac surgery patients who receive six percent hetastarch strong enough to warrant a warning statement in the hetastarch labeling?

The second question is if there is insufficient evidence for a labeling change, should a randomized, controlled trial or trials be conducted to answer this question? If a trial is warranted, please comment on the inclusion and exclusion criteria; what endpoints and differences are clinically meaningful; and what are the major predictors of blood loss.

[Slide]

Hetastarch was approved in the early 1970s. If you look on the label, in terms of this meeting, the indication is for the treatment of hypovolemia when plasma volume expansion is desired.

[Slide]

In the dosage and administration section you will find the following, the amount of six percent hetastarch, usually administered is 500 to 1000 mL. Doses of more than 1500 mL per day for the typical 70 kg patient are usually not required, although higher doses have been reported in postoperative and trauma patients when severe blood loss has occurred.

[Slide]

The warnings on the labeling include this, large volumes of hetastarch may transiently alter the coagulation mechanism due to hemodilution and a mild inhibitory action on Factor VIII, and may result in transient prolongation of prothrombin and activated partial thromboplastin, clotting and bleeding times.

But it also says, and this is the only citation in the warning section, in randomized,

controlled, comparative studies of hetastarch injection and albumin in surgical patients, no patient had a bleeding complication and no significant difference was found in the amount of blood loss between the treatment groups. That is it.

[Slide]

This is a cartoon of a cardiopulmonary bypass circuit. The circuit goes like this, blood leaves the body on the venous side and is pumped by a roller pump into the oxygenator; leaves the oxygenator and then goes through a microfilter, and then returns to the patient through the arterial line.

Before you can put a patient on bypass, the perfusionist has to prime the pump. Here is the pump. The prime is usually colloid that is albumin and then more likely hetastarch. The reason they do this is to get rid of any air because, obviously, if air enters this circuit it will go into the patient. Likewise, you could have what is called an air block where an air bubble in this circuit stops flow entirely and that is a catastrophe because most likely the patient will die.

The second step is to insert canulas into the right atrium and the aorta so that venous blood can leave the right atrium, as I discussed a second ago, and then return back to the arch of the aorta.

The final stage, once the blood is circulating like this into the body, is to stop the heart with cardioplegia solution. The surgeon now has what is called a quiet field and he or she can do whatever needs to be done in terms of vessels, valves, or both.

[Slide]

This is a photograph of a cardiopulmonary bypass machine. I don't know if you can see, but this dark tubing here is coming from the patient. The patient is over here. The venous tubing is here, in dark red. The arterial filter is over here, this little object and I don't think you will be able to see it too well. The roller pump is down here, and here is the perfusionist's hand. He is turning the knob here to increase or decrease the flow as the rate of blood return increases or decreases during the procedure. Then, the blood returns to the patient. I don't know if you can see that but it goes up here, like this, back into the aorta. So, you have a complete circuit. The

perfusionist has to change this constantly. He is constantly watching the patient.

[Slide]

Included in the background package that the FDA sent out to you were five articles. They are all retrospective. Three of them are chart reviews; one was a case-control epidemiology study and one was a meta-analysis.

[Slide]

The first article, by Canver and Nichols, was a chart review of 887 patients, and one of their conclusions or their main conclusion was that use of hetastarch in primary cardiopulmonary bypass circuitry is devoid of any added hemorrhagic risk after coronary bypass. In other words, they added hetastarch into the circuit, into the pump circuit that I showed you before. This is not always done in studies that I am going to talk about in a second. Sometimes the hetastarch is given before the patient goes on the pump; sometimes it is given after, including in the ICY; and sometimes it is given in the pump as well. So, you have various combinations of when hetastarch can be administered.

[Slide]

Knutson et al. studied 445 patients, and they concluded that use of hetastarch may increase bleeding and transfusion requirements in patients undergoing upon heart surgery.

[Slide]

Cope et al. looked at 189 patients and concluded hetastarch infusion produces a clinically important impairment in post-cardiac surgical hemostasis.

[Slide]

Herwaldt conducted a case-control epidemiology study and they divided the subjects into two groups. Cases were predefined. There was a prespecified criterion for what bleeding was. They divided their cases into those that had excessive bleeding and the controls who did not have excessive bleeding. What they concluded was that patient age and hetastarch are risk factors for hemorrhage in patients undergoing open-heart surgery.

[Slide]

Finally, Wilkes et al. conducted a meta-analysis. He looked at 653 patients, and I think it was around 13 clinical trials. His conclusion was that postoperative blood loss is

lower in patients exposed to albumin than to 6 percent hetastarch.

Now I would like to hand the microphone over to Dr. Canver, who will be the first speaker who will speak on this topic, and he will be arguing that hetastarch does not lead to increased bleeding.

Presentation

DR. CANVER: Good morning. I have never been at an FDA-related panel discussion like this so I am very grateful that Dr. Landow asked me to be here.

[Slide]

I am an ordinary cardiac surgeon and I have no connection with Hespan, albumin or any commercial companies at all. The reason that we did that study was for scientific curiosity and to reduce blood product utilization. I am also director of the Heart Institute and head of the Department of Cardiothoracic Surgery. Of course, I do the training.

[Slide]

I think that Dr. Landow summarized the background better than I would do it. As you know, we perform 250,000 open-heart surgical procedures

in the United States every year, and there is an increased interest in doing these operations so-called off-pump, meaning doing them without that machine that Dr. Landow showed us earlier. But still, the majority of the operations require the cardiopulmonary bypass machine, in lay terms the heart-lung machine. The patients are placed on this device while the surgeon quickly treats the disease, blockage, valve repair or whatever, also during heart replacement, such as heart transplantation.

The other thing that is an issue is that we don't have enough blood. The donor pool is very short. Blood is very expensive. Last year alone we paid about five million dollars for blood products at Albany Medical Center, the biggest expense for us. Of course, just imagine the societal issues, nobody wants to get blood products because of HIV, hepatitis and all the societal issues attached to that.

So, I think we have an obligation economically and also societally. Therefore, there are many strategies that surgeons and all care-givers have developed over the years. I think there are many of them, but I think we will focus

today just on hetastarch and colloid administration during cardiac surgery. This is one of the many strategies that we have.

[Slide]

Again, hydroxyethyl starch is a starch. The technical term is amylopectin. It is essentially derived from corn. I think there is some technical information that normally it is degraded or destroyed in the body off-amylase, an enzyme, and to reduce that degradation is attached second or sixth carbon atoms. The molecular weight of the substance is important, and the one we are actually going to discuss, Hespan which is the most commercially available, is 480 kD weight. Low molecular weight, 70 kD, is not available in the United States.

[Slide]

Again, commercially there are two solutions available. One of them is Hespan, constituted in normal saline. Also, it is available as Hextend in lactated Ringer's solution.

[Slide]

The characteristics of Hespan are similar to albumin. I guess I have to say that the argument--you may just say what's the big deal of

albumin versus Hespan? The basic thing actually is the cost. Surgeons and physicians who get involved in this issue primarily are paying less amount of money and providing the same care. With respect to all the properties, Hespan has similar effects to albumin, which expands the vascular volume, meaning that it increases the intravascular space; increases the blood pressure; increases the perfusion, and so forth. It does stay in the system for a long time as well.

There is no antigenicity. I mean, there is no rejection of allergic reactions, or whatever. There are some case reports, but in general it is kind of a neutral agent.

Adverse effects are taken actually from the PDR. These are some reports that have been mentioned. It doesn't mean that it is going to happen all the time but I think it has been reported. When you read it, of course, it is kind of scary that you are going to have salivary gland enlargement, edema and sometimes anaphylactic shock, which is true for everything so this should not really be scaring you that much.

[Slide]

Again, Hespan has been associated with

bleeding abnormalities. If you look in the literature, you are going to find a lot of experimental studies. There are some dog studies and pig studies and they say that the bleeding is higher compared to other agents. Practically, PT and PTT are the clinical measures we have to measure the bleeding state or coagulation state of the individual and this is slightly increased. Also, platelets, those little, clumpy cells--when you cut yourself these cells go to the cut surface and with spongy areas and essentially stop bleeding. Of course, after you have major open-heart surgery you want these cells to stop bleeding. Again, Hespan is associated with some platelet dysfunction, but also it is well established in the literature that if you reduce the dose, if you limit the dose of Hespan to 500-1000 mL any of these issues or concerns we have are not apparent in a real clinical setting.

[Slide]

Again, I also want to tell you these are the components of Hespan that affect blood coagulation, molecular weight, the lower the molecular weight, the less likely it is that it will interfere with the blood system. Again, let

me say that low molecular weight is not available in the United States. It may be that that is going to be one of the strategies that we need to explore.

Substitution ratio, that deals with how many of this hydroxyethyl--those funny shaped chemical things that I have a hard time understanding myself, but the number of those, the groups are attaching to glucose or sugar molecules. That is what they are talking about. This also affects their influence on the clotting system. Again, attachment to the C-2 ring, carbon-2 ring, is less likely to have clotting disorders. Again, concentration, like six percent versus ten percent, of course, will have an influence.

So, we can make some changes in any of these components and we can anticipate some effects. But the problem is very complex. As you know, in open-heart surgery there are many, many factors involved. First of all, the person having surgery is not the same thing. I may be doing heart transplantation or I may just be doing bypass, putting new vessels on the heart, or maybe repairing a leaky valve. They are all different people and different disease entities.

As Dr. Landow demonstrated earlier, cardiopulmonary bypass or the heart-lung machine itself has negative effects or adverse effects on the clotting system in general. It does promote platelet degradation and essentially makes the platelets rupture and burst, because of the swelling, and then they are dysfunctional, meaning that they no longer can hold onto each other and make big clots to stop bleeding and they are malfunctional. Some of these clotting factors, and I am sure you know that there are 13, 14 clotting factors like hemophilia bleeding disorders, those similar clotting factors, mainly in the liver, are used, meaning there is not enough in the body to help the clotting. Again, the fibrinolysis is one of the factors needed for the finalized shape of the clot and it is utilized and not available in the environment.

[Slide]

Again, cardiopulmonary bypass heart-lung machine is not a normal thing. You are putting bigger than your finger size pipes inside the aorta, inside the right side of the chamber of the heart, and you are taking the blood and you are shuffling about five to six liters per minute.

Then, this blood is not used to going through these rigid tubes. From the sheer force, as the blood is trying to go through these narrow channels, it hits the walls and everything, and all the cells get destroyed. All these destroyed cells will burst and then inside a lot of enzymes, a lot of chemical elements inside the cells will be distributed through the system. That will essentially be our enemy later one.

Again, despite all the bad things we are talking about, most of them are self-limited, meaning that after a successful repair or surgical treatment within 48 hours all these abnormal values return to normal. Therefore, traditionally we put in about three to four chest tubes. I am sure some of you have relatives, or whatever, and you have seen that in open-heart surgical patients with finger size hoses, big hoses. So, we anticipate that up to two days there may be some oozing or bleeding and within two days everything is pretty much back to normal. Again, that low platelet count will be normalized within two to three days.

[Slide]

I will try to summarize what we did, and I think Dr. Landow did a beautiful job. It was

published in the journal Chest, in 2000.

[Slide]

It was a chart review, essentially a retrospective study, but it did have a lot of patients, 887 patients, and we mainly wanted to focus on isolated CABG, meaning that if the patient had aortic valve replacement or the patient had mitral valve surgery or redone bypass, we excluded all of those because we wanted to know purely whether Hespan makes any difference because you can't look at a multifactorial group of patients and expect to get meaningful results.

[Slide]

This how the stratification was done. Of course, this could have been a better stratification if this was prospective but unfortunately it wasn't. We had four groups. The first group had crystalloid, which is a traditional balanced-salt solution and we gave a half liter, and there are only 11 patients. Then we had albumin. Albumin was supposed to be better or superior to the Hespan. We had about 217 patients. Hespan was given to 298 patients. Also, we had another group where albumin and Hespan were used together in 161 patients.

[Slide]

I don't think I need to explain everything to this group but the purpose of this slide is simply to tell you if you look at the patient characteristics, like the person's age and patient's size, patient's ejection fraction, meaning the contraction ability of the heart, and their red blood cell count and their platelet count of clumpy cells, and their overall blood count and also kidney function, they are all identical. So, for practical purposes, I think all these four groups had similar patients with similar characteristics.

[Slide]

Again, as far as what happened in the operating room, those operative events can influence the bleeding rate afterwards as well. Perfusion time, that is, the duration of cardiopulmonary bypass time, how long we kept the patient on the heart-lung machine. The longer you keep the patient, the more likely you are to have bleeding problems because the damage of the machine will be higher on the cells. Again, among those four groups there is no significant difference.

As you know, when we do this operation, we

put a little metal clamp on the aorta. The aorta is a big pipe that comes from the left side of the heart and carries the red blood, clean blood, and you cannot operate on a beating, moving heart, particularly if you are doing valve repair and so forth. So, we put this metal clamp there and exclude the heart from the body while it is being perfused by this heart-lung machine, and we go in and quickly do the job. We put some ice to stop the heart. Then, as soon as we are done whatever we are doing, we start warming and we give a little jolt of electricity and the heart starts beating again. So, the cross-clamp time is also, of course, important but there is no difference among any of the groups.

Again, we did only bypass surgery on these cases, and then the number of the bypasses were essentially similar. Again, the number of arterial grafts was the same.

[Slide]

If you look at the amount of heparin--heparin is the medication we use before we put the patient on the heart-lung machine to prevent any clotting. This simply essentially stops any clotting in the system. At the end of

the operation we reverse that with another medication. Overall, the patients' length of stay in the intensive care unit hasn't changed, and their hospital stay was essentially identical. The re-exploration rate, meaning that the patients had significant bleeding from those tubes, the hoses, and we had to take them back to surgery, in all those groups they were identical.

[Slide]

This is actually I think the most important part because we were very interested in the economics mostly. So, we thought that our utilization of blood and blood products are not any different. If you look at the packed red blood cells, this the bank blood you get from the Red Cross, essentially all the groups are pretty much the same. So, it doesn't matter what combination you use, they are identical. Platelets, those clumpy cells making clots, were similar in all groups. Statistically there was no difference. Fresh-frozen plasma, this is taken from humans and then is essentially rich in clotting factors, and the use of this plasma is similar in all groups.

[Slide]

We also had access to the database and we

had the results after ten years because we were able to track what happened to these patients. You can actually see all those four groups. In the left column is the Kaplan-Meier survival, and years after operation on the bottom, and all those groups essentially overlap each other and there is survival advantage or disadvantage among the groups. Essentially, what that means is whether you use Hespan during surgery or not, it doesn't alter anything up to ten years.

[Slide]

These are essentially our conclusions for the review, and there was no hemorrhagic risk after primary CABG. We also said that the type of prime solution, whether albumin, colloid or crystalloid, has nothing to do with the early outcome or late survival.

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I actually wanted to bring some issues. I am not here to really sell you anything. I mean, I am not here to say Hespan is good or Hespan is bad. I think the issues are more about the facts. These are that Hespan and albumin are volume expanders. They increase blood pressure; useful in traumatic shock or some heavily injured people. I think it

is a good solution. It is much better than crystalloid. So, I don't think we would have too much argument there.

There is also I think universal acceptance that Hespan is cheaper, significantly cheaper. In our hospital, for the last two years we monitored the use of albumin as a criterion for quality improvement, meaning that we don't want to use albumin unless it is necessary because you deplete your bottom line. It is rather expensive.

Again, Dr. Landow summarized all these observation studies, and they did suggest that there is some association with excessive postoperative bleeding. But, again, if you read those study articles, I think they are available, you will find these studies are similar to ours. A doctor was interested and he said I want to write a paper. So, he went and looked at it. I think one of the papers, in the Palo Alto VA hospital, in California, said they had an outbreak of bleeding. Well, again, we have no idea what the operation was; who was the surgeon; what was going on. You don't get outbreaks of this kind just because of the solutions but that was the conclusion.

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Again, I guess the reason I was invited here is because our work suggested that there was no association. I have to admit that I did look around the last five years at what has been published, and we are in the minority. The only advice or I guess opinion I can give you is that in my personal opinion, based on what we did and what I practice, I don't think that Hespan prime during bypass circuitry has any side effects. But I find that whether you use it before surgery, during and after, the studies are inadequate. I think that one needs to focus on the questions, which I think are very valid that Dr. Landow is raising, and I am not certain about the warning label. That is not my expertise. But I am now motivated myself, when I go back to Albany, to try to see if we can do some prospective, randomized studies addressing each issue.

I will stop there. Again, thank you so much for the opportunity to talk here today.

DR. NELSON: Thank you very much. I have one question. In table 2 in your paper, where you compare the four groups and you talked about the time on the pump or cross-clamping time in this table, you said that the groups were comparable.

But, in fact, group one was on for 84 minutes; group two for 103; group three, which was the hetastarch group, for 79, plus/minus 2; and group four for 127. Those numbers sound different to me.

DR. CANVER: Well, I agree with you. I am not a biostatistician and our biostatistician reviewed this commonly called cross covalence test. I don't even know how you do that, but it is essentially based on the numbers--

DR. NELSON: No, no, no.

DR. MCGEE: You know, the rule of thumb is if you just calculate the 95 percent confidence interval and they don't overlap, things are significant. They are not even close.

DR. NELSON: This could affect the bleeding because, in fact, the group that received hetastarch was on for a significantly shorter period of time. So, it seems to me that would affect the comparison.

DR. MCGEE: That is also true in table 3 for the platelets.

DR. NELSON: Right. You know, I think it is valuable as a preliminary to do a retrospective review, but you need to do a correction, or have comparable patients in order to be sure that, in

fact, there is no effect.

DR. HOLLINGER: These were all done by you in one hospital? Is that correct?

DR. CANVER: Correct, yes.

DR. HOLLINGER: I know they weren't randomized, but how were they selected for each group? You have almost an equal number in every group, so how were they actually selected?

DR. CANVER: It was actually arbitrary. That I think is the drawback with all retrospective studies. The chief perfusionist in the hospital was the driving force behind this, and he was essentially just using one of these combinations without letting us know because we are a teaching hospital and, including myself, none of us really knew what kind of combination the patient had to reduce the bias. But essentially those were arbitrarily chosen by the chief perfusionist.

DR. SIMON: I have two questions. I think you pointed to the concerns with the retrospective versus doing an appropriate prospective, but there are two questions and they relate to your data. One is, if albumin were cheaper than Hespan, would you use albumin instead of Hespan? Number two, you dismissed crystalloid but you had a whole group of

people who did just as well with crystalloid which is even cheaper. Is there a consensus among cardiac surgeons that crystalloid should not be used? Have you stopped using it?

DR. CANVER: I think crystalloid is not utilized in general because it increases the postoperative edema and swelling. Patients gain more weight. It actually makes the patient's respiratory status worse and the patients stay in intensive care longer. So, I think that crystalloid is pretty much out in cardiac surgery.

DR. SIMON: That is not what your data show.

DR. CANVER: Exactly. Well, this data goes all the way to 1995, but I think that albumin, if it is cheaper, yes, we probably would use albumin. I mean, that is probably the right assumption.

DR. MCGEE: I have one more question. Your cases go across nine years. Was the mix of, say, albumin and Hespan the same over those nine years, or in the early years was it more albumin than in the later years?

DR. CANVER: It is the same concentration and the same chemical properties, to my knowledge.

DR. NELSON: No, the same distribution of patients in the four groups over the years? In other words, could there be a temporal effect on other things, other care that might affect the measures of blood loss?

DR. CANVER: Well, I mean I share that concern. You cannot control like that. In the 1990s the people operated on are different than what we are doing now, and in the same thing in the 1980s, it was a completely different set of people. We change our behavior, practice patterns based on what we have done in the past. So, you go back and you look at them and you make some assumptions.

DR. NELSON: These are difficult issues to control but there are methods for adjustment of data where the groups aren't comparable. It is unclear about the comparability of the groups I think.

DR. LEW: One thing that you did mention is that when you use a lot of Hespan there have been noted to be potential problems. I wasn't sure, do you know how much each patient received?

DR. CANVER: We only used priming in the circuitry, like 500 cc. We did not use it postoperatively and we did not use it as a volume

expander later on.

DR. LEW: So, it is just a limited amount.

DR. CANVER: We extrapolated from the experience that trauma surgeons had during shock, and they have used two to three liters of Hespan and they did report increased bleeding problems. But we never really used more than what is recommended.

DR. NELSON: The volume of the pump is 500?

DR. CANVER: Yes, 500.

DR. LEW: But I do think it is worthwhile if you take even this data back to your statistician because it is remarkable that the least perfusion time, the least clamping time for Hespan but they used the most platelets, the most FFP. It just might be worth taking another look at it.

DR. DIMICHELE: As a follow-up to Dr. Lew's question, I was just going to ask do you routinely use thromboelastograms during your procedures to monitor coagulation?

DR. CANVER: Yes, we do. We use ACT, activated clotting time, throughout the pump.

DR. DIMICHELE: Just the ACT?

DR. CANVER: ACT only.

DR. DIMICHELE: And were you able to look at the ACT data? That is recorded, right, in general?

DR. CANVER: Yes.

DR. DIMICHELE: Is there any way that you could have looked at the ACT data during the procedure?

DR. CANVER: It is available but in this set we didn't look at it because ACT is generally when you are on pump during bypass, and you like to give 400 measure. That is pretty much standard. So, it wouldn't give us that much of an answer, and at the end of the procedure we used protamine to reverse the heparin and we would like to see the ACT level constant at less than 150. But in my mind, and practically, I don't think it would give us too much information because as soon as the patient goes to the intensive care unit he will end up with platelet count and PT and PPT, the more traditional parameters, and also the rate of bleeding from the chest tubes. Those would pretty much assess the effect.

DR. NELSON: Any other questions? Thank you. The next discussant is Dr. Gary Haynes.

Presentation

DR. HAYNES: Good morning. I hope you can all hear me.

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My name is Gary Haynes, and I am an associate professor of anesthesia at the Medical University of South Carolina, in Charleston, South Carolina.

I would like to thank the committee, first of all, for the opportunity to speak today about this issue because this is what I have been interested in for some time.

Let me tell you at the outset my interest in this originally started out of a concern with some of the recent marketing that has been conducted for hetastarch solution, suggesting the aggressive use of hetastarch, because I grew up in an environment where I was taught, as our two previous speakers have already pointed out, that the appropriate dose of a hetastarch solution should be 10-15 mg/kg or 20 mg/kg body weight to a total maximum dose of about 1500 cc on any one day. So, that is what prompted some of my concerns about this.

Then, as I looked into this issue more and

more, I thought it is very appropriate to look at what has been going on and to take a look at the use of hetastarch solutions in a very select group of surgical patients, and it is the cardiac patients we are talking about today. So, I have a concern about using hetastarch in all surgical patients. I mention that briefly, but to stick to the point of today, we are looking at this issue in a very select group of patients, those having cardiac surgery for some very particular reasons that I will go over in just a minute.

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Just to give you a little idea of who I am and why I am standing here, talking to you about this, I am a clinical anesthesiologist in an academic practice, taking care of cardiac patients with major transplant surgery, liver transplant surgery, or the anesthesia for those cases at our hospital. We do a lot of them. We are in the top 20 programs in the liver transplant business these days. Consequently, I am one of those guys in the trenches using up an awful lot of blood and blood products.

I am also the chairman of our medical center's blood and tissue utilization review

committee. So, I help try to establish our local guidelines and work with our blood bankers and our clinical pathologists in dealing with the issues of what is appropriate and inappropriate use of these products, and the availability, and working out all the other headaches associated with this at our hospital.

I also sit on the transfusion committee, as a member of that committee of the American Society of Anesthesiologists, and I have had research interest in this for a number of years, which goes back to medical school. I guess that is where my interest really started because my Ph.D. was in pathology and one of my teachers was a hematologist, Oscar Ratnoff, who was the fellow who proposed the cascade mechanism for coagulation. So, I have had this interest for a number of years.

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Without belaboring the point, I would just like to reiterate a couple of things that Dr. Landow and Dr. Canver have already mentioned, and that is a little bit of what hydroxyethyl starch is. It is something that has been around for close to 40 years, one time as an experimental and now a therapeutic modality. In fact, I know the guy who

did a lot of the basic research, a guy who was in Charleston at what was then the medical college of South Carolina, a guy names Lay Thompson, who was a graduate student back introduction he early '60s investigating this as a volume expander, a plasma volume expansion agent.

As Dr. Canver mentioned, most anesthesiologists and surgeons tend to like to use colloidal substances to replenish intravascular volume, simply because it stays in the intravascular space for a longer period of time and we know that if somebody is hypotensive you can fill them up with crystalloid solutions to reestablish blood pressure but you can do the same thing with colloids, but a smaller volume, and they work a little bit more efficiently because they tend to stay in the intravascular space longer. That is why we like to use them.

So, hetastarch is really an amylopectin but what that really means is it is just branching chains of polymeric glucose, just a bunch of glucose molecules strung together. Hetastarch as hydroxyethyl starch groups substituted on the those glucose rings just to retard the metabolism of this. As was mentioned, amylase is what breaks it

down. It is also sequestered in the reticular endothelial system and tends to stay in the circulation for a long period of time.

But when we are using a hetastarch solution clinically, we get it in a plastic bag. It comes in a 500 cc bag, and when we get a bag of this stuff it is a six percent solution of polydispersed substance, which means these branch chains of this hetastarch compound are not all uniform. They vary in molecular size from around 10 kD all the way up to 480 kD or maybe even higher. When it is infused the small stuff, of molecular weight of around 60,000 or less, gets filtered out by the kidneys pretty quickly. So, it is that size and above that stays in the circulation. What is available in the United States for us in clinical use is two forms of this, Hespan, which is six percent hetastarch in normal saline, which has been around for a number of years, and more recently, Hextend, which is the same thing, six percent hetastarch in a lactated electrolyte solution. I think it has been on the market for a couple of years now.

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In contrast to albumin, which has been

mentioned and it is going to be compared to albumin frequently because that is the other colloidal substance that we have for routine clinical use, albumin is monodispersed and one albumin molecule is just like another so they are all the same, with a molecular weight of about 70 kD.

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I think one thing that is important when you look at worldwide literature is to make sure that you are dealing with the same substance because, as was again previously mentioned, in Europe and in Canada there are different hetastarch solutions available that are of smaller molecular weights. Some consider 200 kD medium and some consider it low molecular weight, but those preparations have been used over there, and they also have a different substitution ratio of hydroxyethyl groups to glucose for every 10 glucose units. I don't know if that substitution ratio really has much, if any, effect on the coagulation mechanism or not, but Hespan and Hextend, which are in clinical use in the United States now, are the high molecular weight and that is the type of hetastarch that seems to be associated with bleeding problems. I will show you a study from

Europe in a minute which illustrates that fact.

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One important clarification to make is to make a distinction between some abnormal laboratory test with either of these substances, and make a distinction between that and what is a clinically significant bleeding problem because there are a lot of things we do to patients out of necessity. They are not always the ideal, and they all have some fallout, some risk or some unwanted side effect but we can live with it if the benefit is much greater.

In terms of the laboratory test variation that occurs when patients receive a hetastarch, it has been nailed down for years--in fact, Lay Thompson published, in 1964, a report of giving hetastarch to dogs and showing that fibrinogen levels went down and bleeding times went up. So, we have known this for a number of years. A number of investigators have also documented exactly why this happens, and it is because von Willebrand factor decreases. Consequently, Factor VIII activity decreases and you can get a hypofibrinogenemia. So, it shouldn't come as any surprise that there is a prolongation of the

prothrombin time or the partial thromboplastin time. Bleeding times, of course, really aren't used that much clinically anymore but that is an old that too has been shown to increase in these.

I want to emphasize this point because in a few minutes I am going to show you some data from one of the papers which shows that there are small increases that can be documented in prothrombin times that may be statistically significant but you kind of wonder whether clinically that has a real impact.

I want you to be aware that that happens, but there are also other effects, that Dr. Canver also mentioned, on platelets that we don't fully understand. But, apparently, there may be more than one molecular mechanism for why hetastarch impairs platelet function, but one is that it probably coats the surface of platelets and interferes with the receptor ligand interaction of platelets for their different receptors. Of course, platelet function is extremely important. It is the thing that forms the primary hemostatic plug and that is why we tend to stop bleeding in the first place.

The unfortunate thing is that clinically

we can measure platelet counts and get those results almost in real time; that is not the problem. The problem is we don't have any good test for clinical use of platelet function. So, a lot of times we know that this is happening but we can't measure it or deal with it clinically when we are dealing with patients.

That is the laboratory side. What about the clinical outcomes? The question needs to be asked does hetastarch or anything else really contribute to bleeding? As I mentioned, we have some concerns about this in other groups of surgical patients as well. We will focus on this issue in cardiac surgery patients and as one example of that one problem that comes up is when you are dealing with stroke patients and neurosurgical patients. If a patient has an intracranial aneurysm that bleeds, they are going to have a stroke. The problem in that situation is not just the bleeding but the vasospasm that occurs in blood vessels around that area of bleeding, and the one therapy that seems to work is to load these patients up with volume to expand their intravascular volume to retard that vasospasm.

Neurosurgeons have looked at this. In one

study that is reported here by Trumble, they used large volumes of hetastarch but it was over a period of several days because these patients are in ICUs. Some of the patients developed coagulopathies and some had worsening subarachnoid hemorrhages, and even problems like epidermal hematomas that required surgical intervention. So, there are some subsets of surgical patients where we just don't use hetastarch at all. Neurosurgery is one area; liver transplant surgery; any place where you know the patient has a severe coagulopathy to begin with.

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Both previous speakers did a very nice introduction about what cardiopulmonary bypass is all about. I would just like to add a couple of points about this. One is that when you think about the volume of these priming solutions and the cardiopulmonary bypass, you have to realize--I think the smallest is about 1.7 L and generally when we prime one of those cardiopulmonary pumps we are talking about a volume of about 2 L, a little bit more than 2 L. Most of us, as we sit here, we probably have an effective blood volume of about 5-6 L. So, when you hook one of these pumps into a

patient and you mix these circulations, the effective circulating volume for that patient effectively becomes 6-8 L, of which about a fourth is whatever was priming that bypass pump.

Now, when it is determined that a patient needs some kind of heart surgery, they are brought to the operating room. The anesthesiologist induces anesthesia. Once they have the patient asleep, intubated, put in the different lines, arterial lines to monitor arterial pressure which allows us to sample arterial blood whenever we want, and large vascular access so we can put in pulmonary-artery catheters, watch heart function and infuse large volumes as needed into the venous side of the circulation and sample venous blood as we need, in the first part of the surgery what is going on is the sternotomy is made, the chest is opened, there is potential for bleeding because of direct surgical trauma to the chest, and the surgeon is dissecting out, in the case of a coronary-artery bypass surgery, something like a saphenous vein or internal mammary artery or other artery to graft in and bypass stenotic vessels because you are there to try to prevent myocardial ischemia.

So, there can be some surgical bleeding in that first part of the case but, at some point, you have to stop the heart and work on it. So, in order to manage that we place patients on cardiopulmonary bypass and prior to that either the anesthesiologist or the surgeon injects heparin to anticoagulate the patient because you obviously don't want catastrophic thrombosis going on in the pump. So, we are using a huge blocking dose of heparin, on the order of 300 units/kilogram. Of course, it is given as an IV bolus and has a pretty immediate effect.

The surgeon places the cannulas, as was described, so we can support the patient's circulation. The cardiopulmonary bypass pump can cool and warm the solution so we start cooling patients down. We cool patients in order to reduce the metabolic demand of tissues as some assurance that the patient is not going to have hypoxic injury to any tissue, and also because with that we can circulate blood in the pump at a lower rate. You know, we are circulating our blood right now at 5-6 L a minute. With a bypass pump you are going to do it at about 2.2 or 2.4 so there is less trauma to the blood.

The surgery on the heart is going to be done. After it is completed, you separate from the bypass. If there is any residual heparin effect around, that is reversed with protamine. So, in that middle part of the surgery you have four reasons why you have bleeding in these patients, circulating the blood through the pump; the heparin; the cooling; the protamine that can interfere with coagulation.

So, typically when you see bleeding in these patients it tends to be in this latter part of the case. The important reason for focusing on the intraoperative use of hetastarch in this group in particular is because what we do here is going to have an immediate effect, as would be very reasonable to think, in the immediate period in the intensive care unit. It is important to look at this group because in this group of patients we have limited options if they start bleeding in the intensive care unit. Yes, you can infuse some more blood and if the patient is stable you may get away with that. But the problem is you can't let somebody bleed in their chest. If they become hypotensive or if they are losing oxygen-carrying capacity, the surgeon has to make a decision to go

back to the operating room. That isn't the case necessarily with all the other surgical procedures we have. Sometimes they are a little more forgiving but in this group, if they have to come back to the operating room, you are dealing with patients who are at risk for increased morbidity, mortality, longer ICU stay, longer hospitalization stay, greater stress on the surgical and hospital systems and much greater cost, as you can imagine.

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So, when we look again at why this is an important group, sometimes these patients are on drugs before surgery but those can be minimized.

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You see that once the patient is off the bypass, in the intensive care unit, many of the issues, like running circulating blood through the bypass pump, heparinization and hypothermia all start to resolve as variables. Heparin, you know, is a pretty short-acting drug. Its half-life is two or three hours. So, it is not going to normalize immediately but many of these variables can start to diminish when we get into the intensive care unit.

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What I would like to do is to start to discuss a few pieces of literature. I have divided this into the issue of some patients from earlier studies that have received Hespan or hetastarch preparations postoperatively, and then some early studies where patients received hetastarch intraoperatively and what their results were, and then the more recent papers, all published since 1997 or 1998, on intraoperative use of hetastarch.

If we look at these first papers, these are in cardiac patients back in 1982. These are all small studies. They had two groups of patients, about 30 each. It was a younger age group. As it was mentioned a little while ago, our patient population is changing over time. Older patients tend to have these operations whereas before it was a younger patient group. We have more patients that are reoperated on, having a second or third coronary bypass surgery.

Diehl looked at this, and in this case patients received only hetastarch postoperatively, and found--and also in the Kirklin study as well--this trend towards a higher blood loss in patients who had received hetastarch as opposed to albumin. Maggio compared albumin to Hespan for

volume expansion in the postoperative period. From reading his paper, I am not sure at what point it was given, if it was given first day, second or even third day. So, I am not quite clear what the details were on that. But they also gave fairly small volumes of both of these substances.

Either way, it looks like with hetastarch solutions there was more bleeding in two of the three studies here. Because there is no statistical significance here, there is no reason to think that giving patients hetastarch after the surgery is necessarily contraindicated.

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If we switch to some early studies on intraoperative used of hetastarch, the first one was in 1983 by Saunders. Again, it was a very small study. This was a study where patients received either hetastarch or 25 percent albumin as a priming solution. It was what was going into the pump. Again, a bit of a trend there, not statistically significant but there was more bleeding in the hetastarch group. But they did see that the patients who received hetastarch required actually significantly more blood than those who received albumin.

Bob Sade and Fred Crawford, at my hospital back in 1985, studied hetastarch and compared it to, I think, 25 percent albumin in prime solution. Again, a little bit younger patient population. These were all adults but both of those surgeons do a lot of pediatric surgery so I think some of those were redo pediatric patients. But, again, they couldn't find any distinct difference between the hetastarch and albumin group, although it looked like there was a little higher blood loss in the hetastarch-treated group. Again, as pointed out earlier, this was a study conducted just to see if there was a way of reducing cost because at that time albumin was much more costly than hetastarch.

Boldt did a study in Europe, published in 1993. It was a prospective study where they infused different colloid solutions at the beginning of surgery.

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They looked at actually four different colloid solutions, one gelatin which I didn't include on this slide. Once the anesthesiologist had the patient induced, they just looked at the pulmonary-artery pressures to see if they were low, which would be an indication that the patient was

intravascularly depleted. They just infused one of these different colloid solutions to just double the pulmonary-artery pressure. The ones they used, high and low molecular weight Hespan or albumin, they found that with the high molecular weight Hespan there was significantly more bleeding postoperatively in those patients. As you would expect, that group also received more blood products on the first postoperative day.

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Switching to another study, a more recent one by Cope at the University of Virginia, in 1997, Cope looked at the intraoperative or postoperative use of hetastarch for volume replacement. They did a retrospective review.

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There was a wonderful review by Warren and Durieux in Anesthesia and Analgesia, addressing the issue of hydroxyethyl starch and whether it is safe or not. They made the point--since a statistical discussion occurred a moment ago--of what was needed to have an appropriate study. From that review they quoted an important point, that is, to have a type 1 error of only 0.5 and a type 2 error of 0.1 or 90 percent power, these studies require