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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH
CIRCULATORY SYSTEM DEVICES PANEL

MEETING

TUESDAY

SEPTEMBER 11, 2001

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regarding its accuracy**

The panel met at 8:00 a.m. in Salon 8 of the Gaithersburg Marriott Washington Center, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, Doctor Warren K. Laskey, Acting Chairman, presiding.

PRESENT:

Warren K. Laskey, M.D., Acting Chairman
Salim Aziz, M.D., Member
Michael D. Crittenden, M.D., Temporary Voting Member
Robert A. Dacey, Consumer Representative
Thomas B. Ferguson, M.D., Temporary Voting Member
Michael Morton, Industry Representative
Janet T. Wittes, Ph.D., Member
Megan Moynahan, M.S., Executive Secretary.

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A-G-D-E-N-D-A

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P-R-O-C-E-E-D-I-N-G-S

8:03 a.m.

1
2
3 DOCTOR LASKEY: Good morning. My name is
4 Warren Laskey. I am an interventional cardiologist
5 from the University of Maryland, and I'd like to call
6 this session to order.

7 This morning's topic is a discussion of a
8 pre-market application for the Cryolife BioGlue
9 Surgical Adhesive. I'd like to have Megan Moynahan,
10 the Executive Secretary, read the conflict of interest
11 statement.

12 MS. MOYNAHAN: Thank you. The following
13 announcement addresses conflict of interest issues
14 associated with this meeting and is made part of the
15 record to preclude even the appearance of an
16 impropriety.

17 To determine if any conflict existed, the
18 agency reviewed the submitted agenda for this meeting
19 and all financial interests reported by the committee
20 participants. The conflict of interest statutes
21 prohibit special government employees from
22 participating in matters that could affect their or

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1 their employers' financial interests.

2 The agency has determined, however, that
3 the participation of certain members and consultants,
4 the need for whose services outweighs the potential
5 conflict of interest involved, is in the best interest
6 of the government.

7 Therefore, a waiver has been granted for
8 Doctor Janet Wittes for her interest in firms that
9 could potentially be affected by the panel's
10 recommendations. Copies of this waiver may be
11 obtained from the agency's Freedom of Information
12 Office, Room 12-A-15 of the Parklawn Building.

13 In the event that the discussions involve
14 any other products or firms not already on the agenda
15 for which an FDA participant has a financial interest,
16 the participant should excuse him or herself from such
17 involvement, and the exclusion will be noted for the
18 record.

19 With respect to all other participants, we
20 ask, in the interest of fairness, that all persons
21 making statements or presentations disclose any
22 current or previous financial involvement with any

1 firm whose products they may wish to comment upon.

2 DOCTOR LASKEY: Thank you. At this point,
3 I'd like to have the panel members introduce
4 themselves starting with Mr. Morton.

5 MR. MORTON: I'm Michael Morton. I'm the
6 industry representative, and I'm an employee of W.L.
7 Gore and Associates.

8 DOCTOR CRITTENDEN: Michael Crittenden,
9 cardiac surgeon, West Roxbury V.A., Harvard Medical
10 School.

11 DOCTOR FERGUSON: Tom Ferguson, cardio-
12 thoracic surgery emeritus, Washington University, St.
13 Louis.

14 DOCTOR AZIZ: Salim Aziz, cardiac surgeon,
15 University of Colorado, Denver.

16 DOCTOR WITTES: Janet Wittes, statistician
17 from Statistics Collaborative here in D.C.

18 MR. DACEY: Robert Dacey, consumer
19 representative from Boulder County, Colorado.

20 MR. DILLARD: Jim Dillard. I'm the
21 Director of the Division of Cardiovascular and
22 Respiratory Devices in the Office of Device Evaluation

1 for the Food and Drug Administration.

2 DOCTOR LASKEY: And, again, Warren Laskey,
3 interventional cardiologist and to my right hand is.

4 MS. MOYNAHAN: Megan Moynahan. I'm the
5 Executive Secretary of the Circulatory System Devices
6 Panel.

7 DOCTOR LASKEY: Thank you. Thus far,
8 there were no individuals requesting time to speak at
9 the open public hearing. Has that changed? Then
10 Megan.

11 MS. MOYNAHAN: I'd like to read through'
12 the voting status statement for today.

13 Pursuant to the authority granted under
14 the Medical Devices Advisory Committee charter and
15 dated October 27, 1990 and as amended August 18, 1999,
16 I appoint the following individuals as voting members
17 of the Circulatory System Devices Panel for this
18 meeting on September 11, 2001: Michael Crittenden and
19 Thomas Ferguson.

20 In addition, I appoint Doctor Warren
21 Laskey to serve as panel chair for the duration of
22 this meeting.

1 For the record, these people are special
2 government employees and are consultants to this panel
3 under the Medical Devices Advisory Committee. They've
4 undergone the customary conflict of interest review
5 and have reviewed the material to be considered at
6 this meeting.

7 DOCTOR LASKEY: Thank you. Sorry to get
8 out of order. If there were no individuals who
9 request time at the open public hearing, I open and
10 close the public hearing. Thank you.

11 We divert for a moment. We have a little
12 bit of ceremonial function to pursue, so I'll turn
13 things over to Mr. Dillard for a moment.

14 MR. DILLARD: Thank you, Doctor Laskey.
15 I appreciate it. It's my honor occasionally to get to
16 really highlight some of the service that you all
17 really provide to us. It's with great pleasure today
18 that we'd like to honor Doctor Michael Crittenden.
19 Michael has served for many, many years on this panel
20 and has been one of the real stalwarts and leader from
21 the cardiovascular surgery perspective and has really
22 been one of the people that we've looked to time and

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1 time again to not only serve in his role as a full
2 voting member of this advisory panel but from time to
3 time, like today, bringing him back for his services.

4 Michael, I'd certainly like to extend my
5 gratitude for all the years of service that you've
6 dedicated to the agency as a special government
7 employee and, for that, I've got a plaque for you and
8 I'd like to just read a nice little note that Doctor
9 Henney, before she retired, wrote about your service.

10 "Dear Doctor Crittenden, I'd like to
11 express my deepest appreciation for your efforts and
12 guidance during your term as a member of the
13 Circulatory Systems Devices Panel of the Medical
14 Devices Advisory Committee. The success of this
15 committee's work reinforces our conviction that
16 responsible regulation of consumer products depends
17 greatly on the participation and advice of the non-
18 governmental health community.

19 In recognition of your distinguished
20 service to the Food and Drug Administration, I am
21 pleased to present you with the enclosed certificate,
22 And it's signed Doctor Jane Henney, Commissioner of

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1 Food and Drug Administration."

2 The plaque reads, "In recognition of
3 distinguished service to the Circulatory System Panel
4 of the Medical Devices Advisory Committee term from
5 March 18, 1998 to June 30, 2001," and it's signed in
6 addition by Doctor Jane Henney and David Feigal, the
7 Center Director for Devices and Radiological Health.

8 With that, Michael, thank you very much.

9 DOCTOR CRITTENDEN: Thank you.

10 (Applause)

11 MR. DILLARD: And with that, I'll turn it
12 back over to you, Doctor Laskey.

13 DOCTOR LASKEY: Thanks, Jim, and
14 congratulations again, Mike.

15 At this point, I think we can get on with
16 the task at hand and the sponsor's presentation.

17 MS. MOYNAHAN: And just a reminder for the
18 folks who are speaking to introduce yourselves and
19 state your conflict of interest.

20 DOCTOR VANDER WYK: Mr. Chairman, members
21 of the panel, good morning. I am James Vander Wyk,
22 Vice President, Regulatory Affairs and Quality

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1 Assurance, for CryoLife.

2 This morning I will be introducing the
3 BioGlue Surgical Adhesive for vascular and cardiac
4 repair. Further presentations will be made by David
5 Fronk, Vice President, Clinical Research, concerning
6 non-clinical performance, Doctor Joseph Coselli of
7 Baylor College of Medicine, a participant in the
8 BioGlue Surgical Adhesive IDE trial concerning
9 clinical trial data and concluding, Doctor Joseph
10 Bavaria of the Hospital of the University of
11 Pennsylvania, also .a trial participant, providing a
12 clinician's viewpoint.

13 Additional CryoLife personnel and
14 consultants present and available for further
15 discussion include the individuals listed here.

16 In the following few slides and two brief
17 videos, I will present the regulatory history of
18 BioGlue Surgical Adhesive, its mechanisms of action,
19 operation of the delivery device, and several examples
20 of clinical applications.

21 BioGlue Surgical Adhesive was first
22 approved for use in the United States in June of 1998

1 under an IDE for repair of acute type A aortic
2 dissections.. Two years later; a second separate
3 investigative arm was added to expand the trial to
4 cardiac and vascular repair. Using interim data,
5 CryoLife sought and was granted a humanitarian device
6 exemption in December of 1999 for acute thoracic
7 aortic section repair.

8 To date, institutional review boards
9 representing over 600 hospitals have approved the use
10 of BioGlue for this indication. We estimate more than
11 5,000 patients have been treated in the U.S. under
12 this HDE.

13 In January of this year, CryoLife
14 submitted a PMA application for BioGlue Surgical
15 Adhesive to be used as an adjunct to standard methods
16 of cardiac and vascular repair such as sutures or
17 staples to provide hemostasis.

18 BioGlue Surgical Adhesive may be used
19 prophylactically or after a leak is detected to bond
20 tissue layers, seal, reinforce anastomoses in cardiac
21 and vascular surgical repairs.

22 In Europe, CryoLife received a CE Mark in

1 November of 1997 for the adhesive permitting its use
2 for sealing, reinforcing and adhering tissue in
3 vascular repair and in March, 1999 for sealing air
4 leaks in pulmonary tissue repair. This approval was
5 followed by similar approvals in Canada and Australia.
6 The approval process is ongoing in Japan. To date,
7 Cryolife has received commercial distribution
8 authorization in over 36 countries.

9 At this time, we have not received any
10 reports of adverse events involving deaths or serious
11 injuries attributable to BioGlue or reports of
12 reactions or immune responses from the use of over
13 45,000 units commercially distributed world-wide.
14 There has been no withdrawal of approval in any
15 country nor any causes or actions to do so undertaken
16 in any jurisdiction.

17 In our first video, we introduce the
18 simple components of the BioGlue Adhesive system and
19 demonstrate the assembly of the delivery device. In
20 the basic starter kit, we have the main trigger-
21 activated unit, a cartridge plunger, a dual chamber
22 cartridge pre-filled with the adhesive components, and

1 a tortuous path mixing tip of which four are supplied.

2 To assemble, the cartridge locks are
3 released, the ratchet plunger is inserted into the
4 base unit oriented by size and then pulled fully back.
5 The cartridge, which requires only room temperature
6 storage, is also oriented by barrel size, inserted
7 into the slot in the base, and locked in place.

8 After removing the cartridge tip cap, a
9 mixing tip is connected to the cartridge.
10 Corresponding notches aid in aligning the tip. Final
11 attachment is achieved-by turning the locking ring at
12 the base of the tip, either by hand or with a twist
13 ring tool as illustrated here.

14 In the last assembly step, the plunger is
15 advanced to the cartridge fill point. The device is
16 now ready for priming which must be done only
17 immediately prior to adhesive application.

18 The active components of BioGlue Surgical
19 Adhesive are 45 percent bovine serum albumen and 10
20 percent glutaraldehyde mixed in a 4:1 ratio. In this
21 ratio, there is a slight stoichiometric excess of
2'2 aldehyde groups over free amine groups. The

1 glutaraldehyde reacts with free amino groups of
2 protein, first of the BSA, then tissue, forming
3 permanent covalent bonds.

4 This process is initiated immediately in
5 the mixing tip and continues on contact with the
6 tissue. With synthetic material a vascular graft,
7 BioGlue adheres by mechanical bonds as it polymerizes
8 within the interstices of the graft material.

9 The unpolymerized BioGlue is stable in the
10 body for greater than one year. Any reabsorption that
11 does occur is a slow process. This is typical of any
12 glutaraldehyde cross-linked protein such as enforcing
13 heart valves. In areas of resorption, there is
14 evidence of cellular infiltration accompanied by
15 collagen formation in a normal healing process.

16 Regarding safety issues of sourcing the
17 BSA, all serum is derived from cattle, only of U.S. or
18 Canadian origin, which are slaughtered in USDA-
19 inspected abattoirs. The purification process of the
20 source BSA is capable of a 16.2 log reduction of the
21 BSE based upon testing inoculated samples. This
22 material holds a certificate of suitability from the

1 European Pharmacopoeia.

2 Three examples of clinical use of BioGlue
3 are presented in the following video. They are
4 typical of the methods used and results obtained.
5 These video segments were selected to illustrate
6 prophylactic application of the BioGlue in commonly
7 encountered anastomotic repairs and are used in a
8 repair of an actively bleeding site in a vascular
9 graft.

10 In this first section, we are observing
11 the repair of the distal end of an aortic dissection.
12 Excess tissue is removed in a normal manner to prepare
13 for joining to a vascular graft. Thrombus and blood
14 is removed from the false lumen. The BioGlue is
15 primed immediately to prior to the first use by simply
16 expelling a small amount onto a disposable sterile
17 material. The false lumen is obliterated and the
18 walls adhere together by filling the false lumen with
19 BioGlue.

20 After the graft is -- in this case, a
21 Dacron graft, BioGlue is applied to the anastomotic
22 site to prevent bleeding. Since BioGlue reinforces

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1 the often friable tissue, pledgets may not be required
2 in the repair.

3 We are now observing the proximal repair
4 of the same dissection. As before, BioGlue is used to
5 obliterate the false lumen after removing thrombus and
6 blood. Notice that no clamping or other special
7 manipulations are required. In these examples, no
8 pledgets were required nor is there any accessory
9 equipment necessary to activate the adhesive. After
10 sealing an adhesive set-up, the anastomoses is checked
11 for leakage.

12 This next video example illustrates the
13 use of BioGlue to seal a Dacron to Dacron vascular
14 graft anastomoses in a thoraco-abdominal aneurism
15 repair. The adhesive begins setting immediately and
16 achieves functional strength within two minutes. The
17 flow is restored and the anastomoses is checked for
18 leakage.

19 In this final segment, we are observing a
20 suture link that has developed in a PTFE vascular
21 patch used in a carotid endarterectomy. The blood
22 flow is interrupted, the field is dried, and BioGlue

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1 is applied to the bleeding site. While it is
2 necessary that the site is dry to enhance the binding
3 of the BioGlue to the site, it can be observed that
4 there is a small amount of blood present showing that
5 there is some tolerance for residual fluid. When flow
6 is restored, the site is checked for leakage.

7 Thank you. This concludes my opening
8 remarks.

9 At this time, I would like to introduce
10 David Fronk, Vice President of Clinical Research, to
11 present our non-clinical data.

12 DOCTOR FRONK: Good morning. My name is
13 David Fronk. I'm the Vice President of Clinical
14 Research for CryoLife. I'd like to take the next
15 several minutes and share with you the non-clinical
16 performance results of our BioGlue Surgical Adhesive.

17 Specifically, I will summarize the
18 following: in vitro shear strength, biocompatibility,
19 in vivo animal studies, histopathology, and
20 immunotoxicity testing results.

21 BioGlue was designed to be a high strength
22 adhesive capable of withstanding the forces and

1 pressures of full systemic arterial pressure. Using
2 a mechanical shear test methodology which simulates
3 clinically relevant loading, the shear strength of
4 BioGlue was compared to both Fibrin-thrombin and GRF
5 and glues. GRF or gelatin resorcinol formaldehyde
6 glue, is a comparable adhesive available in Europe.
7 Results show that the BioGlue is at least fourfold
8 stronger than either of these other adhesives.

9 Biocompatibility testing was performed
10 using ISO 10993 standards. These tests were conducted
11 using derivatives of polymerized BioGlue. ISO
12 standards were used to define passing results. The
13 mild to moderate results for the cytotoxicity tests
14 were expected.

15 As described by Doctor Vander Wyk, the
16 mechanism of action of BioGlue utilizes the
17 glutaraldehyde present in the polymerized BioGlue to
18 bind to the surrounding tissue. Therefore, any
19 cytotoxicity is acute, localized, and isolated to the
20 first few cell layers of the tissue. Additional
21 biocompatibility tests and their conclusions are
22 listed in the table shown.

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1 I will now report on a series of four
2 different animal efficacy experiments conducted with
3 BioGlue. The goal of these models was to evaluate the
4 safety and effectiveness of BioGlue in a variety of
5 different clinical indications. The aim of the first
6 experiment was to study the effectiveness of BioGlue
7 as a surgical adjunct in the repair of acute aortic
8 dissection. An aortic dissection model was developed
9 that allowed for BioGlue to be used to obliterate the
10 false lumen by adhering and reinforcing the dissected
11 layers of the aorta and sealing the repair. Control
12 animals received conventional repair techniques,
13 namely suture closure of the false lumen.

14 Results from the study clearly show the
15 potential clinical benefits of BioGlue. When compared
16 to controls, the animals receiving BioGlue had
17 decreased rates of acute post-repair rupture of the
18 aorta, redissection of the distal surgical repair
19 site, dissection progression, and chronic dissection
20 formation.

21 To evaluate the ability of BioGlue to seal
22 large diameter synthetic anastomoses, a Hemashield

1 interpositional aortic bypass graft was sewn into the
2 thoracic aorta of a coagulopathic sheep. Hemostasis
3 of the anastomoses was controlled, either by BioGlue
4 or Surgical, a commercially available hemostatic
5 agent. Animals were monitored for rate of blood loss
6 and total post-operative drainage.

7 Again, the benefit of BioGlue treatment as
8 compared to control was demonstrated. Both the rate
9 of blood loss and total blood loss was significantly
10 reduced in the animals receiving BioGlue as an
11 anastomotic sealant.

12 The two previous studies demonstrated
13 BioGlue's effectiveness on large diameter native
14 tissue and synthetic grafts. To further assess its,
15 utility in small diameter repair, a glued anastomosis
16 study was conducted on coronary artery bypass grafts.
17 This evaluation included both an in vitro assessment
18 of anastomotic burst strength and an in vivo goat
19 study.

20 Though not recommended by this PMA
21 application, the anastomoses in this study were
22 completed using BioGlue as the primary means of

1 joining and sealing the vessels. This was done to
2 assess the feasibility of a glued anastomoses to
3 facilitate attaching coronary artery bypass grafts
4 during beating heart bypass procedures.

5 The in vitro results clearly demonstrated
6 BioGlue's ability to adhere the joined anastomoses.
7 All 12 glued anastomoses easily withstood two times
8 normal systemic arterial pressure, 10 of which
9 withstood pressures in excess of 500 millimeters of
10 mercury without leakage or dehiscence. In the goat
11 model, all animals survived surgery and all grafts
12 remained patent, non-stenotic, and free of
13 interluminal BioGlue.

14 The final animal study evaluated BioGlue
15 on small diameter synthetic anastomoses. In a growing
16 pig model, a PTFE graft was placed as an
17 interpositional graft. The proximal anastomoses was
18 performed using BioGlue while the remaining distal
19 anastomosis which was sutured served as the control.

20 All animals survived the procedure and
21 completed their course of follow-up. All but one
22 graft remained patent which the surgeon investigator

1 attributed to technical failure at the time of
2 surgery. Even though the animals gained up to 60
3 kilograms during the study, the BioGlue anastomosis
4 remained firmly adhered and sealed to the growing
5 proximal aorta and did not dehys or leak.

6 I would now like to turn your attention to
7 the histopathologic assessment of BioGlue. The
8 following three slides show a time course of tissue
9 response to BioGlue from the aortic dissection animal
10 model study. BioGlue, which can be seen on the left
11 side of each photomicrograph, appears amorphous pink
12 in HNE staining. At seven days, we observe a tight
13 position and homogeneous layer of BioGlue between the
14 layers of the dissection. A slight infiltration of
15 mononuclear cells is present but, in general, there is
16 little evidence of an inflammatory response.

17 At 31 days, BioGlue is again shown to be
18 adhered to the host tissue. Entrapped red blood cells
19 remained at the tissue glue interface and no evidence
20 of inflammatory response is seen. At 91 days, we
21 continue to observe the firm position between BioGlue
22 and the vessel wall. Also at this time, the cellular

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1 response shows signs of an inflammatory response
2 characterized by fibrosis.

3 A one year explant from the coronary
4 artery bypass graft goat study showed the longer term
5 histologic effects of BioGlue and its response to
6 small vessels. There is a lack of inflammatory cells
7 present and the BioGlue remains intact as seen in the
8 lower left hand corner. To compare the tissue
9 response in humans, we have included a 90 day explant
10 from a patient who underwent a repair of a Type A
11 aortic dissection using BioGlue. As seen in this
12 montage of photographs of different magnifications,
13 there's a paucity of inflammatory cells present. This
14 appears to be less than previously noted in animals.
15 BioGlue is present and firmly opposed between the
16 layers of the dissection.

17 To contrast this response in humans, the
18 following is a histologic section through suture
19 material from this same patient. There is a
20 significantly greater inflammatory response associated
21 with the suture material as compared to the, BioGlue.

22 To summarize the histopathology findings,

1 we believe that the histopathologic observations of
2 BioGlue are consistent with a typical foreign body
3 reaction. This is analogous to what is seen with
4 other long-term implants.

5 Finally, I would like to review the
6 immunotoxicity testing results of BioGlue. Per the
7 FDA's testing guidance, I will address the following:
8 hypersensitivity, inflammation, immunosuppression,
9 immunostimulation, and autoimmunity. Data from the
10 various biocompatibility in animal studies were used
11 as the basis for these analyses.

12 Several evaluations of hypersensitivity-
13 based immunotoxicity were performed. The Buehler
14 test, which doesn't used adjuvant, and the Kligman
15 test, which uses adjuvant, were conducted using
16 topical exposure of BioGlue extract. The passing
17 results from these two classic hypersensitivity tests
18 showed a severity of zero which, by definition, is
19 characterized as a grade one weak allergenic potential
20 response.

21 I would like to elaborate on the
22 previously listed antigenicity test in guinea pigs.

1 This study had two parts: an active systemic
2 anaphylaxis test and an antigen antibody test. For
3 the anaphylaxis test, guinea pigs received a
4 subcutaneous application of either BioGlue or bovine
5 serum albumen as a sensitizing dose. At 14 days, the
6 animals were challenged with an additional dose of
7 intravenously administered adjuvant added extracts of
8 BioGlue or BSA. A saline control was also
9 administered.

10 As can be seen, the animals showed a
11 significant anaphylactic reaction to bovine serum
12 albumen but, on average, less than a weak reaction to
13 BioGlue. Again, for ISO standards, a weak reaction is
14 defined as a grade one passing response.

15 The second part of this experiment look at
16 the antigen/antibody potential after exposure to
17 BioGlue or bovine serum albumen. Eleven days after
18 'sensitization, diluted sera from the guinea pigs were
19 tested against BioGlue, bovine serum albumen, and a
20 vehicle control antigen using ELISA techniques. The
21 bar chart summarizes these data. The three paired
22 bars represent the original sensitizing agent. Within

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1 each paired bar are two lanes showing the titer level
2 to re-exposure of either BioGlue or bovine serum
3 albumen antigen. As you can see, animals that
4 received either BioGlue or BSA had low levels of
5 antibody against BioGlue. Animals sensitized with
6 BioGlue had higher titers of antibody against the
7 bovine serum albumin antigen.

8 Based on these hypersensitivity tests, we
9 believe that there is a low risk of hypersensitivity
10 reaction by the repeated use or long-term 'exposure of
11 BioGlue. Once sensitized, other medical devices or
12 medicines containing bovine serum albumen
13 theoretically may induce an anaphylactic reaction.

14 Please note: in recognition of this
15 potential, clinical trials and product labeling has
16 always contraindicated patients with a known
17 hypersensitivity to bovine products, In addition, as
18 previously stated, we have received no reports of
19 reactions to BioGlue in over three and a half years of
20 clinical use.

21 Looking at inflammation as a sign of
22 immunotoxicity, you will recall from the previously

1 shown photomicrographs, we conclude that there is no
2 evidence of an abnormal inflammatory response to
3 BioGlue.

4 With respect to immunosuppression, our
5 tests revealed no evidence of post-resistance-based
6 immunotoxicity. Similarly, our tests revealed no
7 overt evidence of immunostimulation.

8 The *Handbook of Toxicology* recommends the
9 histopathologic assessment of organs, particularly
10 kidney and thyroid, for identifying signs of
11 autoimmunity. Review of these results from our 90 day
12 subcutaneous study in rats revealed no evidence of
13 autoimmunity. This is clearly demonstrated in the 90
14 day rat kidney histopathology. Note the lack of
15 observable inflammation in either the glomerulus or
16 renal arterioles.

17 In summary, we believe that the results
18 from the non-clinical testing demonstrated that
19 BioGlue Surgical Adhesive is biocompatible and
20 effective for its intended use.

21 I would now like to introduce Doctor
22 Joseph Coselli who will address the IDE clinical

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1 protocol and clinical results.

2 DOCTOR COSELLI: Doctor Laskey and panel,
3 I'm Joseph Coselli. I'm a cardiovascular surgeon in
4 Houston, Texas with Baylor College of Medicine. I
5 have had in the, past nor do I have today no financial
6 interest in the company involved. They are, however,
7 compensating me for my expenses of being here this
8 morning.

9 I'd like to present to you the information
10 with regards to the clinical trial. Hemostasis is
11 critical to the success of cardiovascular surgery. To
12 all of us involved in conducting these procedures,
13 this is intuitive as well as it to most of our
14 patients. Also well known is that re-operation for
15 bleeding is associated with significant morbidity,
16 mortality and expense. It's certainly a drain on our
17 clinical resources. Immediate hemostasis has the
18 potential to decrease the need for blood products and
19 associated risks thereof.

20 The current hemostatic devices are
21 difficult to use. These would include devices which
22 are of similar ilk but are not able to be stored at

1 room temperature, difficult to apply, etcetera.

2 The objective that the trials seek was to
3 demonstrate a decrease in the frequency of intra-
4 operative anastomotic site bleeding in patients
5 receiving BioGlue as an anastomotic prophylactic
6 sealant as compared to patients receiving standard
7 surgical anastomotic repair. This was done as a
8 multi-center trial allowing each of the individual
9 surgeons conducting the procedures to proceed, both
10 with their usual techniques and in the environments in
11 which they were comfortable in treating their
12 patients.

13 The primary end point focused upon
14 anastomotic hemostasis at each of the repaired
15 anastomoses. Hemostasis -equated to that the
16 anastomosis did not require any additional agents,
17 additional suture placement, pledgets or other
18 hemostatic agents or even more BioGlue to control
19 bleeding at any point, during the course of the
20 operation following completion of the initial
21 reconstruction.

22 Success was evaluated twofold. 1) by

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1 anastomosis. There were multiple anastomoses carried
2 out in most of the patients and by patient on an
3 individual basis. A single failed anastomosis
4 constituted a patient failure. Data was accumulated
5 throughout the, trial. on a number of secondary end
6 points to include the volume and type of blood product
7 replacement; the use of additional hemostatic agents,
8 returning the patient to the operating room for
9 bleeding or re-opening the patient for bleeding,
10 procedural complications, and mortality.

11 The study design included a prospective
12 randomized control multi-center trial. The study
13 group was comprised of standard repair for whatever
14 that particular surgeon at that institution generally
15 used plus the additional application of BioGlue
16 prophylactically. The control group was the use of
17 the standard repair without the glue.

18 Uncontrollable bleeding in the control
19 group allowed the surgeon to opt out to cross over to
20 BioGlue. This actually did occur in one patient
21 undergoing a transverse aortic arch replacement in one
22 institution where the distal anastomosis, the tissue

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1 was so friable that the surgeon felt that bleeding was
2 an immediate risk to the patient and, consequently, in
3 the trial there was one single cross over. The
4 patient did survive.

5 With regards to sample size, assumptions
6 were made -- and I might add that these were based
7 upon information derived from the various institutions
8 and were, I think, exceedingly conservative. The rate
9 of anastomotic bleeding was estimated at 15 percent,
10 BioGlue reducing bleeding to achieve five percent, and
11 that most of the patients, the overwhelming majority,
12 would have at least two anastomoses and actually quite
13 a few of the patients had multiple anastomoses. Five,
14 six, seven, eight or more.

15 The power calculation really estimated a
16 sample size of 142 patients to include a potentially
17 inflated group for possibly a 10 percent dropout and
18 10 percent cross-over for uncontrollable bleeding.
19 The actual dropout for primary end point was zero and
20 the cross-over was one single patient, as I've already
21 mentioned. The study enrollment stopped at 151
22 patients.

1 Inclusion criteria involved patients
2 undergoing a cardiac or vascular surgical repair and
3 patients who, or their legal authorized
4 representative, was willing and able to give prior
5 informed written consent.

6 Exclusion criteria included proteins with
7 a known hypersensitivity to albumen, bovine products
8 or glutaraldehyde in patients treated with an
9 investigational product who have not completed an
10 ongoing study. Also, patients excluded included those
11 undergoing repair of intra-cerebral circulation and
12 patients undergoing repair of acute thoracic aortic
13 dissections which was covered under a separate arm of
14 the study and the BioGlue HDE.

15 The centers are listed here, and they
16 included Houston, Philadelphia, Indianapolis, Orlando,
17 Florida, Atlanta and Loma Linda, and all of the PIs
18 were considered to be accomplished cardiovascular
19 surgeons.

20 The study enrollment of 151 patients was
21 randomized to 76 BioGlue for the treatment group and
22 75 randomized to the control group. One control

1 patient, was I mentioned before, was crossed over to
2 the BioGlue side. The safety data for that patient is
3 included with the BioGlue group, but the efficacy data
4 is excluded from all of the analysis. The two groups,
5 the treatment group and the control group, based, as
6 you can see here, on gender and race, were virtually
7 identical and quite homogeneous.

8 The variety of procedures carried out were
9 indeed diverse and they included quite a number of
10 cardiac procedures, aortic procedures; and peripheral
11 vascular operations. The distribution of these
12 categories for the treatment group and the control
13 group, however, was statistically similar. W i t h
14 regards to achieving the primary end point, both by
15 patient and by anastomosis, it was statistically
16 significant in favor of the treatment group using the
17 BioGlue.

18 With regards to secondary end points --
19 and here is shown the use of intra-operative blood
20 products, both by volume and by category of components
21 -- the treatment group using BioGlue and the control
22 group were essentially identical with no difference.

1 Similarly, the use of post-operative blood products,
2 again shown here listed by component, was identical,
3 both for the BioGlue group and the control group.

4 Interestingly, again focusing on secondary
5 end points, additional hemostatic measures -- three
6 columns on the right -- were identical with the
7 treatment group and the control group. However, the
8 use of pledgets for the primary anastomosis was less
9 in patients in the BioGlue group than in the non-
10 BioGlue group. What this indicated to us was that
11 surgeons as the trial progressed were evolving to use
12 less pledgets during the construction of their initial
13 anastomosis than they might have been otherwise as
14 they developed comfort with the use of the material.

15 With regards to the use of hemostatic
16 measures as shown on the right, the use of BioGlue did
17 not preclude or interfere with the use of additional
18 efforts to secure hemostasis when it was felt to be
19 necessary. With regards to mortality, there was no
20 statistically different significance between the
21 control group and the treatment group.

22 Procedural complications. There was no

1 difference with regards to hemorrhage, infection,
2 inflammatory response, irreversible morbidity,
3 ischemia, myocardial infarction, organ system and
4 multiple organ failure between the control group and
5 the treatment group.

6 There was a difficult to explain reduction
7 in neurological deficits, primarily in the form of
8 significant stroke, in the treatment group with the
9 use of BioGlue. In discussing this with the other
10 investigators, clearly in the treatment of many
11 patients with regards to the replacement of the
12 transverse aortic arch and aortic root, etcetera,
13 bleeding frequently translates into episodes of
14 hypotension and hypotension in such patients is
15 related to the development of stroke in such patients.
16 This possibly is an explanation for this particular
17 data .

18 With regards to other complications -- and
19 they are diverse because of the diverse procedures,
20 types of procedures used in the trial. Everything
21 from, as I've mentioned, root replacement to
22 peripheral vascular procedures -- include such things

1 as paraplegia, pleural effusion, kidney failure,
2 pulmonary failure, stroke, thromboembolism, thrombosis
3 and other, and there's no statistically significant
4 difference here.

5 Product-related complications were few.
6 There was one implication where the glue was
7 incidentally applied to non-target tissue which was
8 treated simply by removal with sharp dissection of the
9 glue separating it from the surrounding tissue, and
10 this was resolved without any additional sequelae
11 whatsoever.

12 There was one failure of BioGlue to adhere
13 and the surgeon at the time felt that it was applied
14 to a field which was too wet at the time, re-cross
15 clamping, achieving a dry field and reapplication of
16 BioGlue resulted in a successful therapy. The risk of
17 these problems and complications are specifically,
18 however, provided in the labeling that we had
19 available to us.

20 In summary, anastomotic hemostasis as the
21 primary end point was statistically superior in the
22 BioGlue group, both by patient and by anastomosis.

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1 Procedural complications were similar between the two
2 groups and second end points, post-operative blood
3 product administration, the need for re-operation for
4 bleeding and mortality, were not statistically
5 different. BioGlue significantly, however, decreased
6 the need for pledgeted sutures to reinforce the
7 vascular tissue at the time of the primary
8 anastomosis.

9 To conclude, BioGlue is more effective in
10 achieving immediate anastomotic hemostasis when
11 compared to standard repair. BioGlue is safe as a
12 standard repair, and it decreases the need for
13 pledgeted sutures to reinforce vascular tissue.

14 Next, Doctor Joe Bavaria will give us the
15 clinician's information. Thank you.

16 DOCTOR BAVARIA: I'm Joseph Bavaria, a
17 cardiac surgeon and professor of cardiac surgery at
18 the University of Pennsylvania in Philadelphia.

19 Regarding disclosure, I have no equity
20 interest in Cryolife or any sort of position within
21 the company. However, I am compensated for today's
22 presentations and the time today, and I was a primary

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1 investigator in the study obviously.

2 At the University of Pennsylvania, our
3 clinical trial had 43 test and control subjects which
4 were equally distributed between cardiac surgery
5 patients and vascular surgery patients. The
6 investigators were myself as primary investigator and
7 Doctor Jeffrey Carpenter, who's a peripheral vascular
8 surgeon who performs some of the peripheral vascular
9 operations.

10 Today I wanted to go through five cases
11 that demonstrate various applications and various
12 issues regarding BioGlue in the clinical arena.

13 The first patient is a 77 year old female
14 who has a past medical history of previous AAA repair,
15 abdominal aortic aneurysm repair, a right carotid
16 endarterectomy, hypertension, hypercholesterolemia,
17 insulin-dependent diabetes, peripheral vascular
18 disease and was smoking up to the day of surgery. She
19 had a distal aortic anastomotic problem from her
20 previous AAA repair.

21 The arteriographic data reveals an eight
22 centimeter Crawford Type III thorical abdominal aortic

1 aneurism. A Crawford Type III aneurism is an aneurism
2 that includes the abdominal aorta as well as half of
3 the thoracic aorta.' You can see that she has a
4 previous III graft right in here. This is where the
5 anastomosis was. She has left renal artery
6 involvement of this aneurism. She has a left iliac
7 occlusion. As you can see, this only has one limb and
8 obviously a previous AAA graft.

9 This operation included five separate
10 anastomoses. The proximal anastomosis was tissue to
11 polyester and the mid-thoracic aorta are tissue to
12 graft. The distal aorta was polyester to polyester
13 secondary to a previous AAA graft. She had a
14 mesenteric segment. The mesenteric segment includes
15 a patch graft to the celiac artery, SMA artery and
16 right renal artery. That's a side to side anastomosis
17 tissue to polyester. And she had a separate left
18 renal artery bypass as a side branch which actually
19 includes two anastomoses, the graft to graft
20 proximally and the distal anastomosis at the tissue at
21 the renal artery. So five anastomoses. She had 100
22 percent hemostasis at all sites in this operation.

1 The second operation is abdominal aortic
2 aneurism repair. I chose this particular one. This
3 patient actually did not do well. He died four or
4 five days later, but I wanted to present this to show
5 exactly how we can get out of a pretty serious
6 situation. This is a 79 year old very elderly frail
7 gentleman who has a history of TIA, COPD, alcohol
8 abuse, and again, current tobacco use. He had a
9 common femoral artery aneurism as well, and his
10 medications included aspirin and Plavix.

11 He had a six centimeter abdominal aortic
12 aneurism and the proximal anastomosis involved
13 accessory renal artery vessels. The distal
14 anastomosis was to the aortic bifurcation. This is
15 the proximal anastomotic site right here which shows
16 that this aorta is very friable. Under a little light
17 in the area here, you can see that there's actually a
18 lot of calcium intra-luminal here which basically is
19 an indicator of an aortic wall which is basically
20 falling apart.

21 This patient had two anastomoses, that
22 proximal aorta which was tissue to polyester, and the

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1 distal aorta which was tissue to graft as well. The
2 proximal aorta was extremely friable and tore during
3 the end to end proximal anastomotic completion. This
4 was prior to BioGlue application. This was just
5 during the actual reconstruction. We had to take the
6 clamp off, reclamp at a higher level, excise that
7 portion of the aorta, and redo this anastomosis at a
8 higher level. Again, the aorta was extremely friable.
9 Proximal anastomosis was redone and reinforced with
10 BioGlue at this time. The distal anastomosis achieved
11 primary hemostasis as well as a proximal anastomosis.

12 There was significant operative bleeding
13 due to vessel friability, and my partner, Doctor
14 Carpenter, credits BioGlue with operative survival.

15 The third patient is another thoroco-
16 abdominal aortic aneurism. It's a different type.
17 It's a Type I thoroco-abdominal aortic aneurism which
18 includes the entire thoracic aorta and the upper
19 portion of the abdominal aorta. This is a 48 year old
20 female who has anxiety, hypertension, again current
21 tobacco use, and a very symptomatic aneurism.

22 The radiographic data shows an eight

1 centimeter or maybe even larger Type I thoroco-
2 abdominal aortic aneurism. This aneurism had
3 significant compressive symptoms, as you can see here,
4 with the cardiac structures completely squished up to
5 the level of the sternum here. This is the left
6 atrium which has almost no cavity as well as left
7 ventricular compressive symptoms. There was anterior
8 displacement of the cardiac structures.

9 She had a two anastomosis Type I thoroco-
10 abdominal aortic aneurism repair. The proximal aortic
11 anastomosis was done at the level of the distal aortic
12 arch at the left subclavian artery. The distal aortic
13 anastomosis was also performed at tissue to polyester
14 and was just proximal to the celiac access but infra-
15 diaphragmatic. There was 100 percent primary
16 hemostasis achieved at both anastomoses and no blood
17 transfusions required.

18 A little point here is when Doctor Stanley
19 Crawford, who performed 1,509 thoroco-abdominal
20 aneurysms and reported this in 1991 or 1992, this was
21 a 30 year experience that ended in January of 1991.
22 Every single one, 100 percent of the patients who had

1 heart which is the aortic root tissue to polyester
2 anastomosis. We have a distal ascending aortic
3 anastomosis way up at the level of the first part of
4 the aortic arch, a right main coronary transfer, and
5 a left main coronary transfer which may be actually
6 the most important of the four anastomoses which is
7 back here. You can't see it on this picture.

8 This is quite different than your standard
9 aortic valve replacement which basically only has one
10 single aortotomy suture line. The hemostases achieved
11 was a primary hemostases achieved at all locations and
12 there was no blood utilization required in this
13 patient. BioGlue was placed on all four anastomoses.

14 The last patient is a very significant
15 patient, in my opinion. This is a patient who I
16 believe would not have survived in an earlier era.
17 This is a 50 year old gentleman with hypertension,
18 coronary disease, renal failure, and is hemodialysis
19 depending. He actually had hemodialysis the day
20 before hospitalization. He also has current tobacco
21 use. He presented with- an acute Type A aortic
22 dissection. This patient was part of the Phase I HDE

1 study.

2 Intra-operative TEE revealed a dissection
3 flap noted at the aortic root, a complex dissection
4 lap with moderately severe aortic valve insufficiency
5 which is typical in patients presenting with acute
6 Type A aortic dissection. What was most impressive
7 about this patient was that his baseline hemoglobin is
8 only nine to begin with. We got that from the
9 hemodialysis records. He presented with a hemoglobin
10 of approximately seven and basically not a single
11 functioning platelet in his whole body, which is
12 typical.

13 We took the patient and actually prior to
14 surgery, actually while he was on the table prior to
15 incision, primed his cardiopulmonary bypass machine
16 with FFP and packed red blood cells as a CPB prime
17 because we didn't think we could get out of this any
18 other way. And we proceeded with repair. The repair
19 included a BioGlue placement into the false lumen
20 right here of the distal anastomosis as a hemi-arch
21 basically obliterating the false lumen and sealing the
22 adventitia to the intima and creating a quote/unquote

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1 neomedia or a new media basically of BioGlue.

2 That was the first application of BioGlue
3 and then at the root after re-suspension of the aortic
4
5 valve, placed BioGlue in the false lumen at the aortic
6 root sealing the adventitia to the intima and
7 obliterating the false lumen at the aortic sinuses.
8 And this is how we apply BioGlue in these patients and
9 then after the graft is put in, we put an additional
10 application on the grafting anastomosis.

11 Surgical outcome of -- catastrophic
12 presentation. He had an intimal flap extending into
13 his left subclavian artery. He had innominate and
14 left carotid artery flaps repaired utilizing a Dacron
15 graft, as I just said, and he was discharged on day 30
16 in good condition. The key here was he received an
17 incredible amount of blood products, as is typical of
18 an early era type aortic dissection, and the only spot
19 that he was not bleeding from to my eye was the
20 BioGlued areas. In over 200 -- aortic dissections,
21 he's the only patient I've seen who actually bled
22 through the interstices of the graft after completion

1 of the operation.

2 This concludes my presentation and the
3 presentation for CryoLife. Thank you, Doctor Laskey,
4 for chairing this session.

5 DOCTOR LASKEY: Thank you, gentlemen, for
6 that illuminating presentation.

7 We'd like to turn now to the FDA
8 presentation and our lead reviewer for this PMA is
9 Lisa Kennell.

10 MS. KENNEL: Good morning, panel members
11 and audience. My name is Lisa Kennell and I was the
12 lead reviewer of the CryoLife BioGlue PMA. My
13 presentation today will focus on the regulatory
14 history of the BioGlue, a summary of the clinical
15 study, and an overview of the non-clinical testing
16 issues about which we would like some panel discussion
17 and the questions for the panel.

18 This next slide lists the main team
19 members who helped in the review of the PMA, some of
20 whom are here today. There were others who are not
21 noted on the slide for the sake of brevity.

22 There has been a regulatory history with

1 the BioGlue and some of the information provided in
2 previous submissions led us to the PMA we are
3 reviewing today. I would like to take a few minutes
4 to go over this history with you as it may provide
5 important background for today's discussion.

6 The first involvement that the Division of
7 Cardiovascular Devices had with this biological
8 adhesive was the Investigational Device Exemption
9 submitted in 1998. The study was first proposed for
10 the use of Bioglue as an adjunct to Type A ascending
11 aortic dissection 'repair.

12 Shortly after the IDE study was approved
13 for this patient group in June of '99, the sponsor
14 opted to take advantage of a relatively novel
15 marketing submission called an HDE or Humanitarian
16 Device Exemption. These exemptions are granted for
17 patient populations or diseases that are rare, that
18 is, less than 4,000 cases in the U.S. per year, and
19 for whom there are no options or the options are
20 inadequate.

21 Another major distinction between the HDE
22 route to approval and the PMA route is that FDA

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1 considers only the safety and probable benefit of the
2 proposed device under an HDE and not the effectiveness
3 when granting approval.

4 In their HDE submission, CryoLife expanded
5 the patient population to include both Type A and Type
6 B descending dissections.

7 After granting approval of their HDE, the
8 sponsor began to have protocol deviations in the areas
9 of randomization, consent and off label use. FDA
10 encouraged the sponsor to modify their protocol to
11 capture some of the off label use so that they could
12 assure that the ultimate label and indication covered
13 the gamut of patient populations and diseases desired.
14 Thus began the cardiac and vascular study arm, which
15 is the subject of today's discussion.

16 I have placed a slide containing the
17 indication for use of the BioGlue verbatim from the
18 proposed instructions for use to keep in mind during
19 our discussions today. The sponsor proposes to
20 indicate, the BioGlue for adjunctive use with standard
21 methods of cardiac and vascular repair such as sutures
22 or staples to provide hemostasis.

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1 The next set of slides gives an overview
2 of the clinical study. The use of the BioGlue was
3 randomized to standard surgical hemostases methods.
4 The sponsor wanted to show a 10 percent improvement in
5 hemostasis using the BioGlue. To accomplish this, a
6 sample size of 86 patients per treatment group was
7 estimated, factoring in cross-overs and loss to
8 follow-up. Since there was only one cross-over, the
9 study was completed after entering only approximately
10 75 patients per group.

11 Patients needing cardiac or vascular
12 repair who gave consent were entered. Those who had
13 sensitivity to bovine material, glutaraldehyde or
14 albumin who had another investigational device who
15 needed intra-cerebral circulation repair or acute
16 thoracic aortic dissection repair were excluded.

17 This slide shows that the majority of the
18 patients had the BioGlue used adjunctively to repair
19 aneurysms. A few needed repair of peripheral or
20 carotid vessels and the rest of the cases involved
21 root dilation or valve surgery.

22 The primary end point was anastomotic

1 hemostasis which was defined as no need for additional
2 agents to control bleeding at any time. Secondary end
3 points included exposure to donor blood productions,
4 additional hemostasis agents needed, re-operation for
5 bleeding, major and minor adverse events,; mortality
6 and collection of cost benefit data such, as bypass,
7 cross-clamp, operative time and time in the ICU and
8 hospital.

9 FDA noted the following outcomes from the
10 study. The superiority hypothesis of 10 percent
11 improvement in hemostasis was met when considered
12 using either a patient denominator or an anastomosis
13 denominator. With the exception of the number of
14 pledgets used for the repair, no improvement in the
15 secondary end points was noted when using the BioGlue.

16 With respect to safety results shown on
17 the next several slides, only neurological deficit was
18 observed to be significantly different between the two
19 groups in favor of the BioGlue. The non-clinical
20 testing methods were acceptable and covered the all
21 important issues. However, there is information
22 provided in the submission relating to immunogenicity

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1 testing about which the FDA would like to have some
2 discussion and comment from the panel today.

3 With respect to the issue of
4 immunogenicity, the firm conducted a gamut of studies
5 to address this issue which are summarized in the next
6 several slides. They conducted several sensitization
7 tests in which adjuvant and ELISA testing for antibody
8 production was assessed. They also assessed
9 compliment activation and the amount of unbound bovine
10 serum albumen protein after various polymerization
11 times ranging from one and a half minutes to 24 hours.
12 Both the BCA and Lowry methods were used for this
13 assessment. Biodegradation was also assessed in vivo.

14 Results of these studies suggested low
15 titers of antibody to BioGlue and albumen were
16 observed in the ELISA assays in the sensitized
17 animals. Unbound protein was found in the Lowry assay
18 but not in the BCA assay and varied biodegradation
19 reactions were noted from encapsulation or local
20 inflammatory response to degradation.

21 We solicited review and comments from
22 Doctor Henry Hornburger who is a consultant on the

1 Division of Clinical Laboratories Clinical and
2 Biochemical Immunology Devices Advisory Panel and the
3 Director of Clinical Immunology at the Mayo Clinic.
4 The next slides summarize his comments. He noted that
5 the data are inconclusive but that there are
6 antibodies produced that are specific to BioGlue and
7 albumen and that T lymphocytes probably persist that
8 could respond to BioGlue or related proteins upon
9 repeated exposure.

10 He further noted that these may not be
11 indicative of a clinically significant immune
12 reaction. He further indicated that a transitory
13 immune response is not likely to be clinically
14 significant but may prime the immune system for
15 subsequent exposures which could be clinically
16 significant. If antigen persists at the implant site,
17 there is a theoretical risk of immune complex mediated
18 diseases.

19 He recommended that it would be difficult
20 to design additional animal studies to evaluate the
21 human risk. Furthermore, he recommended that product
22 labeling should include warnings in the labeling

1 regarding use in patients who are sensitive to bovine
2 products -- which is already in the labeling -- and in
3 those with a prior history of immune-mediated
4 diseases. In addition, he recommended a warning about
5 repeated use and a post-market clinical and in vitro
6 study to assess antibody production.

7 We have the following questions for the
8 panel, separated into those relating to safety,
9 effectiveness and labeling issues. Questions relating
10 to effectiveness include, #1, the sponsor proved their
11 primary hypothesis of a 10 percent improvement in
12 hemostasis which was defined as no need for additional
13 agents during the procedure but did not show an
14 improvement in the secondary end points. Please
15 discuss the clinical implications of the primary and
16 secondary end point data.

17 #2, the sponsor states in the submission
18 that, quote, "Our clinical investigators believe that
19 the routine use of BioGlue in these patients will
20 allow them to modify their blood management protocol
21 and should minimize the potentially life-threatening
22 complication of post-operative hemorrhage." Please

1 comment on whether there is adequate information to
2 support the statement.

3 Questions relating to safety and
4 effectiveness, #3, based on the information provided
5 in the pre-market approval application, please discuss
6 whether the information supports reasonable assurance
7 of safety and effectiveness of the BioGlue.

8 Questions relating to safety and labeling.

9 One aspect of the pre-market evaluation of a new
10 product is the review of its labeling. The labeling
11 must indicate which patients are appropriate for the
12 treatment, identify potential adverse events with the
13 use of the device, and explain how the product should
14 be used to maximize benefits and minimize adverse
15 effects. Please address the following questions
16 regarding the product labeling and safety.

17 #4a, please discuss the findings of the
18 immunogenicity testing, especially as they relate to
19 both physician and patient labeling issues. Should
20 patients be advised of specific adverse events to be
21 aware of that may suggest they are experiencing a
22 sensitization reaction from the BioGlue?

1 #4B, the sponsor conducted several animal
2 studies to assess the potential for BioGlue to elicit
3 an immune reaction. The information from these
4 studies suggests that there may be a potential for
5 sensitization to the bovine serum albumen and related
6 proteins in the formulation. Information from the
7 clinical studies is limited to assessing the product
8 with short-term follow-up. Please discuss whether
9 sensitization has been adequately addressed with the
10 clinical data as supplied or are additional post-
11 approval studies needed to assess the immune potential
12 of BioGlue?

13 #5. Please comment on the indications for
14 use section as to whether it identifies the
15 appropriate patient population fortreatmentwiththis
16 device. The indications verbatim from the labeling
17 again are, quote, "BioGlue Surgical Adhesive is
18 indicated for use as an adjunct to standard methods of
19 cardiac and vascular repair such as sutures or staples
20 to provide hemostasis." End quote.

21 #6. Please comment on the directions for
22 use as to whether they adequately describe how the

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1 devide should be used to maximize benefits and
2 minimize adverse events and, finally, #17, do you have
3 any other recommendations regarding the labeling of
4 the device?

5 Thank you for your attention.

6 DOCTOR LASKEY: Thank you,

7 I'm going to open the panel portion now by
8 having our lead reviewer, give his review and ask
9 questions of the sponsor. After his portion, we'll
10 all the other members of the panel to also question
11 the sponsor. In the interest of just staying on
12 schedule, I'd like to confine each panel member's
13 delivery to 10 minutes or less. Doctor Aziz, thank
14 you.

15 DOCTOR AZIZ: First, let me say I very
16 much enjoyed listening to both the company's
17 presentation and also the cardiovascular surgeons who
18 were both experts in their field, Doctor Coselli and
19 Doctor Bavaria.

20 I was just going over the in vivo and in
21 vitro testing. I think a lot of the times what we
22 find in animals really doesn't actually translate into

1 the clinical setting. This may be one of those sort
2 of situations. I must say I was looking at the
3 antibody ELISA testing. There did seem to be an
4 elevation in antibody generation, but it seems that
5 for the large number of clinical cases it doesn't
6 translate into a clinical problem. But I think that
7 clearly should be watched over a period of time to see
8 if that does propose to be a problem.

9 I'm going to focus most of my questions to
10 its use in the clinical situation and a couple of
11 these questions are targeted towards Doctor Coselli.
12 Patients with aortic dissection are particularly
13 troublesome and difficult, and I think there have been
14 improvements, particularly in the grafts that we have
15 now compared to what we had years ago. The collagen-
16 impregnated grafts. But still, I think technically
17 they are quite a challenge, as all of us know.

18 A lot of the times when you have the Type
19 A dissection or Type I DeBakey dissection, when you
20 apply the glue, you clearly showed that you are
21 obliterating the false lumen at the point at which you
22 are applying it. But the false lumen distally clearly

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1 still stays in the patient. Am I right in assuming
2 that?

3 DOCTOR COSELLI: I believe you're right in
4 assuming that. I think that the patency of the distal
5 false lumens in a complex issue. Patency of the false
6 lumen requires in flow and out flow. One of the
7 things that was done to reduce that was this open
8 distal anastomosis under hypothermic circulatory
9 arrest eliminating the potential for cross-clamping
10 the aorta proximal to the -- artery creating a
11 fracturing of the inter-lining which would allow
12 either in flow or out flow.

13 Other sources include the suture line and
14 then finally, distal openings between the true and the
15 false lumen generally at sites of branch vessels. The
16 first situation, using hypothermic arrest eliminating
17 the cross-clamp, takes that off the table. The
18 BioGlue addresses the second issue. In other words,
19 that the actual passage of suture through! the tissue
20 as a source of entry or exit from the false lumen.

21 The remaining one, the openings due to a
22 tearing away at the level of the branch vessels, is

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1 really not addressed in this particular approach.

2 DOCTORAZIZ: When you applied the BioGlue
3 and you obliterate the false and true channels, at
4 least in a localized fashion, then you don't have to
5 apply any felt at the point you do your vascular graft
6 anastomosis. Am I right in assuming that from what I
7 saw in the video?

8 DOCTOR COSELLI: Absolutely right.

9 DOCTOR AZIZ: When you have a dissection,
10 obviously you look for the tear. Now, can the glue be
11 used to obliterate the tear or should the tear be
12 removed and your graft should actually be interposed?

13 DOCTOR COSELLI: The way we've managed
14 these, if the tears in the ascending aorta are in the
15 arch, we try to eliminate the tear as part of our
16 replacement effort. If the tear is well down into the
17 descending or below and we're treating a Type I
18 dissection, then we've in effect taken an acute I
19 dissection and converted it to an acute III for
20 continued medical management.

21 I think where this particular product has
22 altered what we've done is that before, I've been

1 concerned about spiraling tears in and around the base
2 of the brachial cephalic vessels. We've always
3 wondered whether or not should we replace the base of
4 that vessel with a separate inter-position II graft or
5 not and we've placed pledgeted sutures inside the
6 lumen in order to try to secure the situation and to
7 allow for a hemi-arch or a bevel approach without
8 being overly concerned with extension into the head
9 vessels. I actually encountered this particular
10 situation last Friday night on a case.

11 What the BioGlue allows us to do is is to
12 seal the false lumen at the level of the brachial
13 cephalic vessels and take that particular concern
14 again off the table.

15 DOCTOR AZIZ: If you were doing a valve
16 conduit, is there any danger of the BioGlue, for
17 example, getting onto the valve itself? Do you see
18 that as a potential danger?

19 DOCTOR COSELLI: I don't believe that it
20 would be appropriate to allow the glue to get down
21 onto the valve tissue. Consequently, what most of us
22 have done, it's very simple to avoid it. It is a

1 matter of just taking some moist gauze and placing
2 that down inside the root covering the valve leaflets
3 while the application is carried out into the false
4 lumen.

5 Also, the applicator tip for this
6 particular device is a fine enough instrument that you
7 can pretty well easily control the amount of material
8 that you're extruding from the device and control
9 where it's going and it isn't. It's not something
10 that is just running all over the field by and large.

11 DOCTOR AZIZ: There's another subset of
12 patients who I think might be benefitted from its use
13 which I think was included in your cases. Patients
14 with traumatic aortic tears where the tear is really
15 localized and you may get obviously a little
16 dissection very, very localized. A number of patients
17 have addressed, that issue in terms of doing primary
18 anastomosis, though most people don't do that. But it
19 seems to me that this might provide the impetus for
20 really using primary anastomosis techniques. What
21 would your thoughts be on that?

22 DOCTOR COSELLI: I haven't used it for

1 that particular purpose, but I certainly would
2 consider it.

3 DOCTOR AZIZ: And in the cases of
4 patients, could this also be used as a patch repair
5 for venous tears and atrial tears? For example, if
6 you had a right atrial tear and you were using circ
7 arrest to sort of try to control that, both the
8 investigators -- could you see this being applied on
9 a pericardial patch and then placing that on the
10 atrial tear to make that easy or IVC tears during
11 redos?.

12 DOCTOR COSELLI: I haven't done that, but
13 I think the utility here would be clear. One of the
14 things that happens when this is applied to the tissue
15 is it takes very friable tissue and makes it far more
16 substantial for the placement and the suture purchase
17 and, although I haven't used it for the inferior vena
18 cava or for the atrium, I think if you had a very thin
19 dilated atrium where that might be a concern, this is
20 certainly something that could be considered.

21 One of the things that we see in acute
22 dissections in the way we used to carry out the

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1 anastomosis, I've personally gotten away from felt
2 strips a long time ago. But because of access into
3 the false lumen at the distal suture line and
4 occasionally at the proximal suture line, you could
5 tell that the false lumen was still patent because the
6 adventitia and the very outer media would bulge and it
7 would be extremely friable and you would encounter
8 oozing through the suture line, even in the face of
9 reasonable hemostasis. This particular material binds
10 the false lumen fairly thoroughly and it enhances the
11 constituency of the strength of the tissue. That
12 particular event just really doesn't occur any more.

13 DOCTOR BAVARIA: I'd like to make a
14 comment on that. We had a case during the dissection
15 THE study. Doctor Michael Acker, one of my partners
16 who Doctor Laskey knows, excellent cardiac surgeon,
17 was doing a mitral valve procedure on a very elderly
18 woman and had a AV groove tear which is almost a
19 universally fatal complication, intra-operative
20 complication. He basically called me up -- he knew
21 that I was using the glue for dissections -- and said,
22 I need the glue, I need it right now. And I called

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1 David Fronk right at that point and said, Dave, I'm
2 going to be using the glue. We have to use this glue
3 here. She's dead if we don't.

4 So I gave it to Doctor Acker, and that
5 patient survived an AV groove tear with. the BioGlue
6 placed in the groove right after the operation.

7 DOCTORAZIZ: In that particular case, you
8 clearly had to have a bloodless field.

9 DOCTOR BAVARIA: Yes. The cross-clamp was
10 on. It was a bloodless field, and the AV groove was
11 coated, so to speak. I think it kind of goes to the
12 finding by David Fronk's suggestion, that some of these
13 anastomoses, sutureless anastomoses, can withstand 300
14 to 560 millimeters of mercury pressure.

15 DOCTOR AZIZ: So this could theoretically
16 be used for VSD repairs intra-operatively.

17 DOCTOR BAVARIA: I'm not so sure the glue
18 should be used intra-cardiac.

19 DOCTOR AZIZ: That's what I was going to
20 come to. I think if it did get into the intra-
21 vascular space, you see that would be a problem per
22 chance?

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1 DOCTOR COSELLI: I would be concerned
2 about it. I think it just should be avoided, and I
3 think it can be avoided.

4 DOCTOR FRONK: This is Dave Fronk. We
5 clearly caution against its use intra-vascularly. We
6 do not have any data to support its use at the present
7 time, so we caution surgeons from using it intra-
8 vascularly.

9 DOCTOR AZIZ: Just a few other questions.
10 Do you see that this could be used in an infected
11 field? For example, if you had a patient who had SBE
12 and you were replacing his aortic valve? Is there any
13 evidence or would you state that there might be a
14 contraindication to using it in patients in an
15 infected field?

16 DOCTOR BAVARIA: First of all, that's a
17 very significant operation. I would think that it
18 could be used in an infected field after you've gone
19 in, you're resected all the endocarditis, you've
20 prepared your graft for anastomosis and basically
21 everything is kind of complete and the last phase of
22 that procedure would be to utilize it at the proximal

1 anastomosis especially. I can see where that would be
2 utilized, could be utilized to get the patient off the
3 table and have a successful operation, although I
4 would also have to say that, as any foreign body, it
5 may be an issue regarding infections similar to a
6 graft.

7 DOCTOR LASKEY: May I just interject for
8 a second. As I was getting uncomfortable with where
9 this was going, I got a little note to remind us we
10 really need to stay within the purview of the indicate
11 of the PMA and the indicated uses. So thank you.

12 DOCTOR AZIZ: Well, I think these are all
13 my questions.

14 DOCTOR LASKEY: Doctor Crittenden.

15 DOCTOR CRITTENDEN: I, too, like Doctor
16 Aziz, want to congratulate the sponsors and the
17 presenters today for an excellent presentation. I
18 just have a couple of questions, but let me just go
19 back to one, point about the intravascular use or
20 problems with intravascular use.

21 -What happens if it inadvertently gets into
22 the blood stream?' Have you done any in vitro testing

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1 just to give a bolus of this intra-vascular to see
2 what happens? I'm just curious that if you lost some
3 inadvertently while you're doing an open aortic
4 anastomosis, is that in and of itself a problem or is
5 it just a bolus that may lodge in the end organ
6 somewhere that's the issue?

7 DOCTOR FRONK: Obviously it will embolize
8 if it releases. The data we have shows that blood,
9 because it is a protein, will stick to the BioGlue if
10 it's administered intravascularly. So you would in
11 essence have a thrombus attached to the BioGlue that
12 could embolize. That's probably the biggest reason
13 for the contra ;use.

14 DOCTOR CRITTENDEN: In the warning
15 section, there was a statement about exposure to
16 nerves. Can you talk about that a little bit? What
17 is the problem with getting the glue on nerves? Is it
18 the glutaraldehyde that affects it?

19 DOCTOR FRONK: We believe that is the
20 case. We also believe that it's very similar to any
21 other product out there. Electrocautery. You
22 wouldn't want to apply electrocautery to the nerve.

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1 It's more of a safety precaution? We do have some
2 data that shows that it does have nerve dysfunction if
3 it's applied to it. We have conflicting data with
4 that. We feel it's the safest thing to advise any
5 surgeon to steer clear of nerve tissue with BioGlue.

6 DOCTOR CRITTENDEN: Doctor Coselli, when
7 you guys resuscitate patients after aneurism repair,
8 dissections, etcetera, do you use mainly crystalloid
9 or choloid? I just want to get to the point of using
10 human albumen in these patients who may have been
11 exposed to this. Is that an issue or is that a non-
12 problem?

13 DOCTOR COSELLI: No, it's really not an
14 issue. We use very little human albumen in our
15 resuscitation efforts.

16 DOCTOR CRITTENDEN: And then Doctor
17 Coselli, going to your presentation, let me just find
18 it here. There's a couple of questions about that.
19 Slide #18, secondary end point additional hemostatic
20 measures. I didn't quite understand the failed
21 anastomosis and the make-up stitches. It said there
22 were 82 percent of these anastomoses that needed make-

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1 up stitches. These are the ones that failed. These
2 are not all of them. Is that correct? Did I
3 understand that correctly?

4 DOCTOR COSELLI: That's correct.

5 DOCTOR CRITTENDEN: Okay. But it was
6 basically the same between BioGlue and the control
7 group. And then the neurologic deficits. Do you have
8 any more insight about that? Just counting them,
9 there was no difference in paraplegia and no
10 difference in stroke. So are you alluding to neuro-
11 psychiatric issues? Is that what was better that made
12 it significantly different?

13 DOCTOR COSELLI: Temporary stroke and
14 neuro-psychiatric, although not statistically
15 significant. I think there was one less paraplegia in
16 the BioGlue group.

17 DOCTOR CRITTENDEN: 'The sponsor is not
18 going to make any claim in that regard, I presume. Is
19 that correct?

20 DOCTOR FRONK: No, we're not.

21 DOCTOR CRITTENDEN: That's all I have.

22 DOCTOR LASKEY: Doctor Ferguson.

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1 DOCTOR FERGUSON: I'd like to echo the
2 comments that were made previously. I think the
3 presentation was one of the most lucid I've been
4 privileged to hear.

5 I have questions which are based on the
6 technical aspects. A couple of them have already been
7 asked by my colleagues. One is that in other systems,
8 particularly the European system, they recommend that
9 when glue is applied, say, through a dissection that
10 for a period of time the two leaves of the dissection
11 be compressed together. You don't agree with that.
12 You don't need that, I gather from your discussions
13 and so on.

14 The question relates, of course, to the
15 fact that if you have two areas of dissection, say, on
16 the proximal part of the dissection which raises the
17 flap near the aortic valve, how do you make certain
18 that the glue that you put in is going to obliterate
19 the space evenly and leave you a definable suturable
20 wall?

21 DOCTOR COSELLI: Actually, it's fairly
22 easy to manage. With regards to the approach of the

1 French with regards to compressing the false lumen by
2 applying some sort of pressure on the inside and the
3 outside, with this particular material, the amount of
4 pressure that's needed is really quite minimal. We
5 have in some cases gently inserted a Foley catheter or
6 other balloon in order to simulate the inter lumen of
7 the aorta in order to have a smooth configuration.
8 It's probably not necessary. The pressure applied on
9 the outside requires no clamps or any special devices.

10 It can be simply accomplished by placing
11 some wet gauze, some moist gauze, on the outside of the
12 aortic wall. It is true that you can get a slight
13 distortion of the inner lining but it's extremely
14 minor and probably insignificant compared to the other
15 distortions which we're creating by our
16 reconstruction.

17 DOCTOR FERGUSON: My question, of course,
18 goes to proper use of the device and whether the
19 instructions for use should include something where
20 you say that the two walls should be held together or
21 not. It's been used enough, I understand, to obviate
22 that and you certainly have not had any problems in

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1 that regard.

2 DOCTOR COSELLI: In our experience, it's
3 been optional and probably not necessary in most
4 cases.

5 DOCTOR FERGUSON: I had a question about
6 the embolic. I think you've answered that for me.
7 And one last question relates to a dry field. I come
8 from an earlier era of cardiac and aortic surgery and
9 dry fields were rare and a luxury, and so I'd like to
10 know how dry you have to have the field. I read in
11 there somewhere about a four or five seconds period of
12 time where you require the field to be dry for the
13 application to work.

14 Have you done any studies or what is the
15 situation if the field is moist and how moist can it
16 get and so forth?

17 DOCTOR BAVARIA: I think the main way to
18 utilize this product is to place it prophylactically
19 prior to release of the cross-clamps. That's the way
20 this product works. It works very well if you utilize
21 that system. Once you have the pressurized aorta, if
22 that aorta is bleeding, I don't think or any other

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1 product actually is going to work very well.

2 DOCTOR FERGUSON: We're talking about
3 applications other than aortic dissection here.
4 That's what we're here today about are others other
5 than dissecting aortas, as I understand.

6 DOCTOR COSELLI: Just from our experience
7 in using this material, the drier the better, but it
8 doesn't have to be absolutely dry.

9 DOCTOR FERGUSON: That's what I want to
10 hear. That's all I have, Warren.

11 DOCTOR LASKEY: Thank you. I, too, would
12 like to compliment you on both a crystal clear
13 presentation and some stellar results. I mean this is
14 typical of controlled clinical trials and I wonder
15 whether this is representative of general use.

16 For example, with respect to the secondary
17 end point failure to find differences there, I think
18 your outcomes were so superb here. Is 1.4 percent re-
19 op standard for the industry or is this just
20 representative of a bunch of great surgeons who were
21 doing this kind of work? What is the number in the
22 literature? I know re-op is a broad category for all

1 the kind of surgery here, but what would be a good
2 comparitor?

3 DOCTOR COSELLI: I think the institutions
4 selected for this trial are representative of, I
5 think, superior clinical work. The numbers are
6 probably lower than what's generally stated in the
7 literature. My personal experience in over 1,700
8 thorac abdominal aortic aneurysms, our bring back
9 rating for bleeding is under two percent. So this
10 particular experience reflects our general work in our
11 institution.

12 DOCTOR LASKEY: I wonder. It's impossible
13 to do a really rigorous blinded clinical trial. You
14 did a randomized trial, yes, and there's no way to
15 blind the operator to the use of the glue because what
16 comes out binds immediately. But it sounds like, as
17 the study went on, you all became converts to this and
18 you tended to want to believe in it, and I think that
19 may have influenced the primary end point, too. It's
20 not truly independent of the arm in which the patient
21 was because you believed in this and it was clear the
22 stuff worked, so you're more likely to stand back and

1 give it time to work as you pressurized the site and
2 allowed the BioGlue to do its thing. Is that true?

3 DOCTOR BAVARIA: I think that's true. The
4 BioGlue works exceedingly fast, especially compared to
5 the European quote/unquote "French glue." It binds
6 with almost 100 percent tissue strength in about two
7 minutes, so you don't have to wait that long, which is
8 important for surgeons. So I think we did become very
9 comfortable with it.

10 DOCTOR LASKEY: I think that's
11 understandable. An analogy here is somebody replacing
12 the hole in their sailboat with 5200 sealant that
13 works immediately and you feel awfully good when that
14 water starts coming in. So I can appreciate that.

15 Not that I want to portray these data in
16 any terms other than positive, but let's look at the
17 flip side. You have a 61 percent per patient success
18 rate versus a 40 percent in the control arm, but you
19 have a 40 percent non-success rate with the BioGlue
20 hemostatic. Do you want to just comment on that.
21 Again, this is a best case scenario in superb surgical
22 -centers in highly motivated hands.

1 DOCTOR COSELLI: I think I can try to
2 address that. That, I think, is probably a
3 manifestation of the way the trial was organized. A
4 single stitch on a single anastomosis, even if there's
5 eight or 10 anastomoses, would qualify as a patient
6 failure. That's a very, very low tolerance.

7 DOCTOR BAVARIA: For example, that one
8 case I presented had five anastomoses. So if even one
9 of those anastomoses failed, that would be a patient
10 failure.

11 DOCTOR LASKEY: With respect to the use of
12 polyester versus PTFE, most of the grafts in this
13 trial were dacron. Is that true?

14 DOCTOR COSELLI: Absolutely.

15 DOCTOR LASKEY: And how much PTFE use out
16 there is there for this kind of surgery and what would
17 you expect to see' if there were more PTFE in this
18 trial?

19 DOCTOR FRONK: Obviously in the surgeons
20 that we chose, there was a preponderance of
21 cardiothoracic surgeons, and that's a traditional
22 dacron use. We do have the handful of cases where the

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1 peripheral vascular surgeons did use PTFE. We
2 augmented that in the packet that we supplied to the
3 FDA with some data that we had internationally,
4 looking at its use sealing PTFE and, in all cases, it
5 was successful in the surgeon's minds in terms of
6 sealing PTFE material.

7 MR. CURD: David Curd. I'm a project
8 director in clinical research at CryoLife. About
9 eight or nine percent of the anastomoses in this trial
10 represented PTFE.

11 DOCTOR LASKEY: Right. And I think that
12 reflects the preponderance of this surgery, but really
13 what you're going after is abdominal and lower
14 extremity surgery here and this, I would think, for
15 PTFE might be more. So I just wonder how the results
16 might differ with a material that's going to be less
17 compliant, if you will, to behave as you like.

18 My only other question with respect to the
19 immunogenicity. I was looking for fever data, not
20 that you could ever make sense of that in a post-op
21 patient, but can you just quickly remind me of the
22 febrile status of these folks and was there a

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1 difference?

2 DOCTOR BAVARIA: I don't think we have any
3 data on that. My personal experience is is that there
4 was no difference between the control group and the
5 BioGlue group regarding post-operative fevers or long-
6 term fevers. But I don't have any real data on that.
7 It's just a personal experience.

8 MR. CURD: We did not specifically collect
9 post-operative fever data.

10 DOCTOR LASKEY: Right. Because you have
11 this intriguing entry, inflammatory immune systemic
12 allergic reactions, and they're few in number, but
13 what were you looking for there?

14 DOCTOR FRONK: Obviously, we were
15 addressing any potential concerns there might be with
16 the administration of BioGlue. There was only two
17 patients that experienced an inflammatory and immune
18 reaction. It's important to point out both of those
19 were in BioGlue patients and neither of those were
20 related to the glue. One was after intra-operative
21 administration of an antibiotic. The second immune
22 reaction took place after the intra-operative

1 administration of Protamine to reverse the heparin.
2 So none related to BioGlue.

3 DOCTOR LASKEY: Nevertheless, it would
4 have been nice to have some fever data. Thank you
5 again. Very good.

6 DOCTOR WITTES: I want to echo comments
7 from everybody else. It's very nice to be able to
8 read a randomized study. It's much easier to
9 interpret things and I congratulate you for doing
10 that. I actually like the heterogeneity of the
11 population. I think that actually adds to the
12 strength and the follow-up, of course, is excellent
13 which is great. And the end point is understandable.
14 We sometimes in this panel have end points that we
15 don't understand. It's easy to yes and no.

16 I have actually four questions. Two are
17 statistical comments and then there are two larger
18 questions. One, a question on immunogenicity that is
19 really a clinical question. I have no comment on it.
20 The other is related to is trying to pull together
21 what seems to me an inconsistency in your results in
22 the primary and secondary end points, especially the

1 transfusion-related end points. It actually has to do
2 in part with what Warren brought up in terms of the
3 unblinded nature of the study.

4 So with that as my preamble, the two
5 statistical issues to me are, 1) I don't believe you
6 can analyze by anastomosis the way you have done
7 because they're correlated within a person so that
8 those p-values at 001 I think is an over-statement of
9 the statistical significance. I may have
10 misinterpreted the analysis. My interpretation of the
11 analysis, it was just binomial. Is that true and, if
12 not, have you done an analysis that deals with the
13 correlation, the within person correlation?

14 MR. CURD: Our initial thesis for doing
15 the study was that each anastomosis was an independent
16 observation, that each individual site had an equal
17 chance of bleeding/not bleeding based on anatomy,
18 tissue friability, that type of thing. That's where
19 that came from.

20 DOCTOR WITTES: Did you do the analysis
21 that allows the correlation within a site to be
22 estimated from the data?

1 MR. CURD: No, we did not do that.

2 DOCTOR WITTES: I think you should and I
3 think that should -- my feeling is that that's what
4 should be reported because otherwise, as I say, you're
5 likely over-stating the degree of significance.'

6 The other issue has to do with the cross-
7 over and I struggled with this. My initial feeling
8 was why don't you just call the cross-over a failure?
9 Why did you hurt yourself by removing it? Then I
10 realized of course it's an unblinded study and you
11 have to do that, so I think that was the correct thing
12 to do. But my first thought, as I said, was that you
13 had actually penalized yourself.

14 Let me ask you my imunogenicity question
15 and then go to the big issue. As I understand it,
16 people are going to have bovine protein in their
17 bodies for a very long time. Why is it not a worry in
18 the long term that you would develop some sort of an
19 immune complex or some kind of allergic reaction and
20 how would a person know? What would you know five
21 years down the line? What would you be feeling and
22 why should we not be worried about this?

1 DOCTOR FRONK: I'm going to have Bill
2 Hall, an immunotoxicologist and one of our
3 consultants, to address that question.

4 MR. HALL: My name is William Hall. I'm
5 from Pathology Associates from Frederick, Maryland.
6 I have no financial interest in CryoLife, but they are
7 paying me for my trip down here today.

8 This is a very good question, and we need
9 to look and see exactly what kind of evidence we have
10 so far in the studies. #1, we have some acute
11 toxicity studies that would potentially address
12 anaphylaxis type reactions. #1 is the Buehler test
13 and then the Kligman test, one of which uses Froin's
14 complete adjuvant with it.

15 The third study that was done is the
16 guinea pig immunization study, and the antibody and
17 antibody response was elicited with the guinea pig
18 immunization study. But if one looks at that study
19 critically, the only way -- well; not the only way
20 because we don't know whether or not injection of this
21 material without Froin's complete adjuvant would have
22 produced a response. But this antigen was mixed with

1 Froin's complete adjuvant oil, mycobacterium species
2 and immune response was elicited. The titers were
3 low, however, but they were IGG titers. T h e
4 corresponding anaphylaxis assays were negative in this
5 assay according ISO standard criteria.

6 So basically we have evidence that there
7 can be under extreme circumstances, especially with
8 the adjuvant administration of this material, an
9 immune response. To get an IGG, one needs T-cells
10 also and so, therefore, memory T-cells can
11 theoretically be produced. But if we look at the
12 other part of this assay, the inflammation associated
13 with administration of this material, we have evidence
14 in human, sheep. I've not seen the goats but I
15 reviewed also the rat study where subcutaneous
16 implants were administered.

17 The inflammatory response around each of
18 these was nil or extremely minimal compared to the
19 surrounding reaction that one saw, for instance, on
20 the human graft to the collagen that was administered
21 on that human graft. This was a resected graft that
22 I had an opportunity to look at, but compared to the

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1 BioGlue. And I have photo micrographs of this if one
2 wishes to see the comparison. But compared to the
3 BioGlue, the BioGlue had virtually no host response to
4 the BioGlue and compared with the suture material that
5 was present and compared with the collagen
6 reinforcement that was put onto that graft segment.

7 In the rat, which was a study that was
8 done for 90 days, this was subcutaneous inoculation.
9 Basically with the rat study, the inflammatory
10 response around the BioGlue was minimal and it
11 consisted of very few lymphocytes that were present.
12 There were some macrophages present, but there were
13 not the large macrophages, the activated macrophages,
14 the ones that produced cytokines and kemokines, the
15 ones that attract lymphocytes into the area. These
16 were not present and, if one looked at the
17 macrophages, you could see some material that had the
18 same tinctorial characteristics as the BioGlue itself
19 and the graft.

20 So the evidence that we have for
21 immunogenicity is based primarily on the reaction
22 against the BioGlue itself in a number of species and

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1 the reaction quite frankly is quite minimal and
2 benign. It generally consisted of fibrosis. The
3 worst and most severe reactions were seen in the rat,
4 and these reactions were quite small.

5 DOCTOR WITTES: So you're saying that the
6 long-term should not be any different from the short
7 term. Is that right?

8 MR. HALL: We can not estimate what might
9 happen in the long term from the data that we have
10 except for the minimal reactivity that's present that
11 would suggest an immune response against the material.

12 DOCTOR WITTES: Thank you.-

13 Okay. Now let me ask my questions about
14 primary and secondary end point because naively I
15 would have assumed that if you could cut bleeding
16 early during the surgery that you ought to be able to
17 see some reflection in at least the intra-operative
18 transfusions and you don't and, in fact, what there is
19 is a very small, not statistically significant
20 increase in red blood cells and cryoprecipitate and I
21 think also in the fresh frozen plasma. No, not in the
22 plasma.

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1 But the data -- I mean I tried to get a
2 handle on the data and I couldn't because the data
3 that you present has only a mean and a standard
4 deviation, a minimum and a maximum, and the minimum is
5 zero. So I assume there's a lot of people with zero
6 and that there's a long tail for the red blood cells.

7 The BioGlue group, the range is zero to 22 with a
8 mean of 2.3. The surgical repair is zero to 12 with a
9 mean of 1.9. So we know we got a long tail. We
10 probably have a spike at zero and you cite only one
11 side of the confidence interval. So it's hard to know
12 what is the sort of worse case. So let me put my
13 worse hat on and then tell me why this is not true.

14 You have the patient there. You're now
15 convinced, as Doctor Laskey says, you're convinced
16 that stuff works. So even though there's a little bit
17 of bleeding, you don't suture and besides which, you
18 want to get more successes, so you actually are anti-
19 conservative in the BioGlue group in terms of you're
20 holding back so there will be more success. Not that
21 you're counting, but there's a psychological tendency
22 to do that.

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1 So then in fact what happens is you've
2 held back too much and so you need a little bit extra
3 transfusion. You don't see it in these data because
4 you only have 75 in a group and that's not nearly
5 enough to see more transfusion. So I need to see,
6 first of all, the distributions so that we're not just
7 means and standard deviations, and then tell me why I
8 don't have to worry about this.

9 MR. CURD: I think the appropriate place
10 to begin to answer this question, I think there are
11 some clinical aspects as well. Our statistical plan
12 prior to the study beginning was a non-inferiority
13 analysis which is why you see the statistics presented
14 as you do. I have looked at the medians for these and
15 the medians are almost all zero or one. I mean it's
16 very far towards the left, as you have stated. So
17 that's why the data is presented as it is.

18 Now, as far as the clinical --

19 DOCTOR WITTES: But wait a minute. I mean
20 I agree with you. You don't medians in a case like
21 this because medians are all clumped. You don't want
22 means because they don't reflect it. You need to look

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1 at the highest quartile. It's those people that are
2 getting too many extra transfusions. You have to
3 analyze these data in a very different way from data
4 that don't have clumps at zeros.

5 Yes, I understand that you pre-specify
6 something but when you're talking about worrying a
7 little bit. When something is going in the wrong
8 direction, it seems to me you then say, well, yes, I
9 pre-specified that I'm going to do such and such
10 because I thought it was going to go in the right
11 direction but, given it's going in the wrong
12 direction, I've got to explore the data more.

13 DOCTOR FRONK: I appreciate your comments.
14 Before I let Doctor Coselli discuss this, I think it
15 is important to know that the administration of blood
16 products is multi-factorial and, as Doctor Bavaria
17 presented in one of his cases, he had bleeding through
18 the graft and not at the anastomoses. So sealing the
19 anastomoses is one point which we're interested in,
20 but bleeding can take place for a variety of different
21 reasons. The administration of blood can take place
22 for a variety of different reasons. The

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1 anesthesiologist could do it. It could be used to
2 prime the pump.

3 So again, I appreciate your comments. My
4 concern is the fact that we didn't design this trial
5 per se to adequately control blood utilization per se
6 and to try to train or change institution's criteria
7 for doing blood. We let them do it the way they felt
8 that it was beneficial.

9 With that, I'd rather let Doctor Coselli
10 speak about the clinical implications of that and then
11 maybe we can find out if we're truly answered your
12 question or not yet.

13 DOCTOR COSELLI: The trial was heavily
14 weighted because of the institutions and the people
15 involved towards complex thoracic arterial work. As
16 a consequence, the issues of bleeding are not all
17 anastomotic. There's a smorgasbord of other causes of
18 bleeding. The previous case mentioned is just an
19 example of one of them.

20 One of the things that clinically we saw
21 during the trial and I brought it out in one of my
22 slides is surgeons became more comfortable with

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1 trusting the fact that the glue was going to work and
2 altered, in effect, their even control anastomoses by
3 using less pledgets as the trial went along.

4 We work in an institution with -- in all
5 of this, we didn't as part of the trial alter the way
6 our anesthesiologists functioned. For instance, an
7 institution may have multiple anesthesiologists that
8 deal with these cases and so, even though there was a
9 single surgeon, there was multiple anesthesiologists
10 and they were just going to manage the blood product
11 administration the way they felt necessary for the
12 case at the particular time.

13 Frequently in these types of cases, a lot
14 of the transfusion work is preemptive and they've been
15 doing things a certain way anticipating events that we
16 didn't try to alter as part of the trial. As a
17 consequence, early in the trial, the anesthesiologist
18 would preemptively manage expected bleeding, and
19 appropriately so, and we didn't try to affect that as
20 part of what we were doing, and I think that
21 influenced us.

22 I think in the latter stages of the trial,

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1 just as the surgeons became more comfortable with the
2 fact that they were going to be faced with less
3 bleeding at the anastomoses, the anesthesiologists
4 slowly came onboard but that wasn't specifically
5 targeted as what we were trying to do.

6 DOCTOR WITTES: Thank you. That's very
7 helpful. That's all I have.

8 DOCTOR LASKEY: Great. Just a point of
9 clarification. As I read this, when you did 'your
10 sample size calculations, you did it on a, per
11 anastomotic site. That was your original unit, and
12 then you sort of backed into per patient later on.
13 But your point is well taken. You need to do' the
14 intra-class correlation thing. But your unit of
15 analysis was right from the get go precise.

16 DOCTOR WITTES: I'm not uncomfortable with
17 using that as unit of analysis. I'm comfortable with
18 that method of analysis. That's all.

19 DOCTOR FRONK: Excuse me. Doctor Laskey,
20 can I interrupt just one second. You asked a question
21 earlier about PTFE. I did want to throw up one back-
22 up slide to address that. Here's some data that we

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1 collected from international usage and looking at a
2 variety of different types of material that BioGlue
3 sealed and at various types of procedures that the
4 glue was used on.

5 If you take a look at the far right
6 columns, it's the success criteria rated by the
7 investigator. Yes or no, was it effective in sealing
8 or reinforcing or adhering and whatever they chose to
9 rate the material. As you can see, 35 instances of
10 tissue to PTFE grafts were sealed using BioGlue in all
11 cases. In the 31 cases that they addressed the
12 answer, the answer was yes, it was effective.

13 DOCTOR LASKEY: Great. Thank you.

14 We are pretty much right on schedule.
15 Congratulations to all. So at this point, we're ready
16 for a break but before we break, Jim Dillard had an
17 announcement to make.

18 MR. DILLARD: Thank you, Doctor Laskey.
19 This is a little bit difficult and a little bit odd
20 for me, but I wanted to make a real quick announcement
21 because I think it's going to be important right
22 before break. There's been some activity that's been

1 reported by the news media that there are various
2 activities throughout the United States that are
3 happening, both at the World Trade Center, the
4 Pentagon, the White House has been evacuated, and
5 there's a fire on the Mall downtown. All airline
6 traffic in the United States has been suspended today.
7 I think we have some terrorist activity potentially
8 that is going on and so I wanted to make everybody
9 aware that that's occurring 'before they step outside.

10 Just by way of impact on this particular
11 meeting today, currently I'd like to just consider
12 that we move forward with the meeting, try to move
13 towards completion. If anything changes, we will be
14 monitoring it today. If anything changes and we need
15 to make other arrangements, we will certainly do so.
16 I think under the current situation, it's probably the
17 appropriate thing with all the right individuals here
18 to try to move forward today. I will also be in
19 consultation with both the companies on the break so
20 if anything changes, I will certainly let you know.
21 But why don't we at this point try to break for 15
22 minutes, come back at about 10:20 and we will resume

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1 the activities. Thank you.

2 (Off the record at 10:02 a.m. for a 17
3 minute break.)

4 DOCTOR LASKEY: I really appreciate
5 everybody hanging in here while we move along. First
6 of all, are there any further questions from the
7 members of the panel?

8 DOCTOR CRITTENDEN: Yes. I have two quick
9 questions and then Doctor Bavaria will be probably the
10 best person to answer them. We talked a little bit
11 about the false lumen, Doctor Coselli did, in his
12 initial presentation and in response to some
13 questions. The question I have. We're not saying we
14 don't need to surveil the false lumen any more. That
15 still ought to be followed up over time despite the
16 fact that this may lead to less flow in the long term
17 in the false lumen. Is that not correct?

18 DOCTOR BAVARIA: Let me answer that a
19 little bit historically. The Europeans have been
20 placing glue in the false lumen for years. When you
21 repair a Type A aortic dissection at the distal
22 anastomosis, what we precisely do is we try to create

1 a neomedia of about three to four millimeters thick
2 and about a centimeter in length or depth into the
3 aorta. So we don't do anything targeted in any way to
4 the distal lumen.

5 That strategy may or may not decrease
6 long-term false lumen patency. If it did, that would
7 be a good result. That's what we want. But we don't
8 know whether long-term distal false lumen patency is
9 affected by these surgical strategies.

10 DOCTOR CRITTENDEN: So the follow-up with
11 the false lumen ought to be the same?

12 DOCTOR BAVARIA: The follow-up for the
13 false lumen ought to be exactly the same with BioGlue
14 application as it would be for any previous dissection
15 repair. Absolutely. In fact, false lumen follow-up
16 is probably the most important anatomic follow-up in a
17 dissection that there is and should be life-long.

18 DOCTOR CRITTENDEN: And then the next
19 question is let's say we've resuspended an aortic
20 valve during a Type A dissection and we do an echo
21 post-operatively and, unfortunately, there's more
22 leakage than we think the pace can tolerate and we

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1 need to replace the valve. What is it like going
2 through a glued anastomosis if you have to go back
3 through this again? Can you describe that.

4 DOCTOR BAVARIA: Well, that one case that
5 was presented earlier is a case that I did, and we did
6 exactly that or a very similar operation to that.
7 It's not that difficult. It's a very thick aorta,
8 easily entered, kind of similar to entering a re-do
9 aorta after a graft has been placed with all the
10 fibrous reaction, but it's not that difficult.

11 DOCTOR CRITTENDEN: How about a coronary
12 distal? It seems that some of these were applied to
13 the distal anastomosis for a coronary. What would
14 that be like to take down similar, not much --

15 DOCTOR BAVARIA: Well, first of all, no
16 glue was applied to a distal anastomosis of a coronary
17 bypass graft. The only application of the BioGlue in
18 coronary work was to the buttons of a composite graft
19 proximate to right and left coronary buttons.

20 DOCTOR LASKEY: At this point, I'm going
21 to ask Mr. Dacey --

22 MR. DACEY: In my three years of

1 representing the consumer on this panel and some other
2 panels, I always try to seek out what I call the
3 consumer/patient comfort zone regarding new technical
4 biological treatments, measures, and this is based on
5 the fact that the consumer when they become patients
6 places an enormous amount of trust and faith in their
7 physicians and in the science and in the process
8 including the process we're engaged in today.

9 This is one of the few times in reviewing
10 all the material, and I went over it very thoroughly,
11 that I really don't have any problems from the
12 consumer/patient perspective because consumers and
13 patients really have to trust you and, in this case,
14 I do.

15 DOCTOR LASKEY: Mr. Morton.

16 MR. MORTON: No questions.

17 DOCTOR LASKEY: In that case, we'd like to
18 move to the open public hearing and ask is there
19 anyone in the audience -- do you want to do the
20 questions first? Sorry. Before we proceed with the
21 voting, etcetera, I would like to remind the panel of
22 the questions that we've been asked.

1 Question #1 relating to effectiveness.
2 The sponsor proved their primary hypothesis of a 10
3 percent improvement in hemostasis and that there was
4 no need for additional agents during the procedure but
5 did not show an improvement in secondary end points.
6 We're asked to discuss the clinical implications of
7 the primary and secondary end point data.

8 We really should tackle each of these
9 individually so that at least it was my impression
10 from the discussion this morning that certainly the
11 clinical implications of the primary end point which
12 is adequate hemostasis is fairly straightforward and
13 cogent and the bottom line in terms of surgical
14 procedure. Is that a fair consensus?

15 DOCTOR CRITTENDEN: Yes. I think so. I
16 didn't hear all of Janet's remarks, but I think that's
17 pretty fair, particularly for the primary end point.

18 DOCTOR LASKEY: The clinical implications
19 of the secondary end point data are hard to address
20 because #1, the results were stellar, #2, it's
21 possible there was some investigator bias,
22 particularly as the study went on and the agent proved

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1 its efficacy to stand back, but I think the results
2 speak for themselves. We would have liked to have
3 seen some further testimony to adequacy of hemostasis
4 but those are the data.

5 Is anybody uncomfortable with the absence
6 of differences in secondary end point data?

7 DOCTOR WITTES: My only concern, absence
8 of differences in secondary end point doesn't surprise
9 me because of the sample size and the variability. My
10 only concern is if people are withholding other ways
11 of preventing bleeding during the procedure and,
12 therefore, potentially increasing the probability of
13 transfusion. That's a concern, and it sounds like you
14 don't see that at all.

15 DOCTOR COSELLI: No. The short answer.

16 DOCTOR LASKEY: I think it's hard to
17 argue. Your results really are outstanding.

18 Question #2. Sponsor states in the
19 submission that, quote, "Our clinical investigators
20 believe that the routine use of BioGlue in these
21 patients will allow them to modify their blood
22 management protocol and should minimize the potential

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