

FOOD AND DRUG ADMINISTRATION

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NEUROLOGICAL DEVICES PANEL
OF THE
MEDICAL DEVICES ADVISORY COMMITTEE

June 12, 1998

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P R O C E E D I N G S

(11:08 AM)

MS. SCUDIERO: Good morning. We would like to begin. We are running just a little bit behind, but not too much. We are ready to begin this meeting of the Neurological Devices Panel.

I am Janet Scudiero. I am the Exec Secretary of the Panel, and I, also, serve the Division as Coordinator for Classification and Reclassification Efforts.

I would like to remind everyone that you are requested to sign in on the attendance sheets which are available at the tables by the door. Agenda and other Panel information, including how to find out about future meeting dates of the Panel are on the phone line and how to get meeting transcripts is at the door.

This and other Panel meeting information, including Panel meeting summaries is now available on the net. Advisory Panel meeting activities are described in the general information folder listed on the CDRH home page.

I am now required to read two statements into the record. The first statement is the appointment to temporary voting status.

Pursuant to the authority granted under the Medical Devices Advisory Committee Charter dated October 27, 1990 and amended April 20, 1995, I appoint the following as voting members of the Neurological Devices Panel for the

duration of this meeting on June 12, 1998, Constantine A. Gatsonis, PhD, Anne C. Roberts, MD and Robert W. Hurst, MD.

For the record, these people are special government employees and are consultants to this Panel or another panel under the Medical Devices Advisory Committee.

They have undergone the customary conflict of interest review and have reviewed the material to be considered at this meeting. This is signed by D. Bruce Brillington, MD, Director, Center for Devices and Radiological Health on May 13, 1998.

The other statement is the conflict of interest statement that was prepared for this meeting. The following announcement addresses conflict of interest issues associated with this meeting and is made a part of the record to preclude even the appearance of an impropriety. To determine if any conflict existed the agency reviewed the submitted agenda and all financial interests reported by the Committee participants.

The conflict of interest statutes prohibit special government employees from participating in matters that could affect their or their employer's financial interests. However, the agency has determined the participation of certain members and consultants the need for whose service outweighs the potential conflict of interest involved is in the best interests of the government.

A waiver has been granted to Dr. Alexa Canady for her financial interests in firms at issue which could potentially be affected by the Panel's deliberations. The waiver allows her to participate fully in today's discussion.

Copies of this waiver may be obtained from the Agency's Freedom of Information Office, Room 12A15 of the Parklawn Building.

We would like to note for the record that the agency took into consideration certain matters regarding Drs. Alexa Canady, Everton Edmonston, Constantine Gatsonis, Robert Hurst and Anne Roberts.

Drs. Canady, Edmonston, Gatsonis and Roberts reported interest in firms at issue on matters not related to what is being discussed today. Since these issues are not related to the specific issues before the Panel, the agency has determined that they may participate fully in today's discussion.

Dr. Hurst reported a past financial interest in a firm product at issue. Since this is a past involvement, there is no continuing conflict of interest. The agency has determined that he may participate in the Panel's deliberations.

In the event that the discussions involve other products and firms not on the agenda for which an FDA

participant has a financial interest the participant should excuse himself or herself from such involvement, and the exclusion will be noted for the record.

With respect to all other participants we ask in the interest of fairness that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you, and I will now turn over the meeting to Dr. Canady.

DR. CANADY: Hello, my name is Alexa Canady, and I am the Chairperson of the Neurological Devices Panel. Today we will be making recommendations to the FDA on the reclassification of the arterial embolization devices.

I would like to note for the record that the voting members present constitute a quorum as required by 21 Code for Federal Regulations, Part 14.

For this part of the open meeting I would like to have the Panel reintroduce themselves. I am Alexa Canady. I am Professor of Neurosurgery at Wayne State University in Detroit and Vice Chairman of the Department of Neurosurgery.

DR. KU: My name is Andrew Ku. I am an interventional neuroradiologist at Allegheny General Hospital in Pittsburgh.

DR. GATSONIS: I am Constantine Gatsonis. I am a

biostatistician at Brown University.

DR. ROSSEAU: I am Gail Rosseau. I am a neurosurgeon, Director of Cranial Based Surgery at Chicago Institute of Neurosurgery and Neuroresearch.

DR. WITTEN: I am Celia Witten. I work for the FDA as the Division Director of the Division of General and Restorative Devices.

DR. EDMONSTON: I am Tony Edmonston. I am Clinical Assistant Professor of Neuro-oncology at MD Anderson and Clinical Assistant Professor of Anesthesiology at ET Health Science Center.

DR. ROBERTS: Dr. Anne Roberts, Professor of Radiology at University of California, San Diego and an interventional radiologist.

MS. MAHER: Sally Maher, Director of Regulatory Affairs for Johnson & Johnson Professional, and I am the industry representative.

MS. WOJNER: Anne Wojner. I am an Assistant Professor of Nursing at the University of Texas in Houston and President of Health Outcomes Institute, and I am a consumer representative.

DR. WALKER: Cedric Walker. I am Professor of Biomedical Engineering at Tulane University, a voting member.

DR. HURST: I am Robert Hurst. I am an Associate

Professor of Radiology, Neurology and Neurosurgery at the University of Pennsylvania, Director of Interventional Neuroradiology, University of Pennsylvania.

DR. CANADY: We would like to thank very much the distinguished Panel for giving their time to study these issues with us today.

We could begin our meeting, I think at this point with the presentation from Mr. Dillard.

MR. DILLARD: Thank you, Dr. Canady.

Good morning and welcome, once again, Panel, distinguished members, as well as the audience. What I would like to do here at first before we get to the second portion of the open discussion today is do what we traditionally like to do which is update you from all that good hard work that you have given us over the last year to 2 years and tell you that we have made some progress on what your recommendations have been, and so, to that end, I would like to first give just a real quick general discussion about the Division.

We have talked about this already this morning. So, I will be brief, but for the benefit of the other industry personnel in the audience today, a couple of people of note I would just like to introduce you to, Pauline Fogarty who is our most recent addition to the Division.

She is our Associate Director for Program

Operations, and she is the person that we have, also, got spearheading the effort to try to coordinate the neurology integration into our Division from the Division of Cardiovascular, Respiratory and Neurology Devices.

She will be a good contact person, as well as Ms. Scudiero who is the Executive Secretary for the Panel for issues that might be associated with neurological products.

We did not keep the Neurology Devices Branch intact as a separate Branch with a Branch Chief when we made the administrative move from one Division to another Division of the Neurological Products because in the transition there currently was not a Branch Chief per se and the staff had gone down to pretty much two members.

So, it was our task to take a look at the product areas and see where it might integrate very appropriately into our divisional structure, and I think some of the thinking at the current time was that many of the products that were being reviewed in the neurology area were products that either had similar or a little bit different indications for use, perhaps, functional indications versus a pain indication where the product for pain would be reviewed in the Neurology Branch and for function would be reviewed in our Restorative Branch, and there was about one-half or three-quarters of the products that seemed to be reviewed in both of the Divisions, and so, it made a lot of

sense for us to integrate what was currently being done into the Division as well as keep this Panel and keep it intact.

So, from that standpoint just in summary on our staff it wouldn't surprise me from time to time if both Panel members and industry alike will work with a number of the people that are actually on this list.

So, you may come to love and enjoy many of the names here and hopefully we will be able to introduce you to some of them from time to time, also.

Okay, Stephen, to the heart of the activity here from the update standpoint, in chronological order, reverse chronological order September 15, 1995, this Panel met with a little bit different make-up, but generally to talk on embolization devices which, of course, is the topic of conversation today.

At that point in time the discussion was not centered around reclassification or potential reclassification of the devices. It was more generalized discussion about clinical end points, study designs, what is the needed data that if one were to be developing an embolization device the kind of information that would be useful not only to you as Panel members but hopefully to us at the FDA.

We thought that was very productive and as a matter of fact since that and since the next portion which I

will do on reclassification and actually getting information on the embolization devices that is why we are where we are and that we are here today to discuss that.

So, I think that was a good segue almost 3 years ago now to where we have gotten to today. More recently, March 14, 1997, we got together and discussed the Medtronic D brain stimulator which in fact was approved by the agency on July 31, 1997 and just by way of giving an update the indication that went out was unilateral thalamic stimulation for tremor suppression.

June 27, 1997, we met to discuss the Cyberonics NeuroCybernetic Prosthesis, the NCP. The agency approved that device July 16, 1997, for reduction of seizures for patients with partial onset seizures age 12 and over.

October 1997, the beginning part of October was actually when DGRD acquired the neurology product area and since then we have been trying to integrate it in and do a good job and keep up with what the FDA is trying to do which is keep our review times in line and expectations high and provide good customer satisfaction and get the products to market as soon as they are ready.

We are trying to do that now with the neurology product area. So, we will continue to work in that direction.

In November 1997, the new law was passed, Food and

Drug Administration Modernization Act, FDAMA which gave us some generalized principles that I thought I just might mention.

Congress really tasked us at the time with a number of things, and one of them is very open communication and interaction, not only with sponsors, manufacturers but with our Panel, also, and so it came with quite a bit of new pieces in the legislation that we are going to be working on and rolling out even over the next year, but from the standpoint of some take-home messages that I think will be important, Congress said, "FDA, you need to cooperate."

That was really the take-home message. Use the resources outside the agency as well. Let us move forward in public health, and I think to that extent we are certainly trying to do that.

Some of the other, I think, important points and I think that have been very beneficial to our program is that they did give us the ability now to recognize standards and recognize consensus standards and use standards in our review process so that what we are not doing is duplicating perhaps what a manufacturer has already done in order to meet a standard, that declaration of conformity with that standard may suffice in some circumstances for not providing that section of an application to us.

We find that very beneficial at this point in time.

The other was to really shore up our classifications and to make sure we have clear direction with our Class III, Class II and Class I products, as well as giving us the ability and actually the direction to exempt many of the Class I products so that we can focus our attention in the areas that they are really of highest risk which we would consider to be a Class II, Class III area.

There are lots of other pieces to FDAMA. Our web site at this point is full of new guidance documents and full of new regulations, 46 to be exact, and there will be more rolling out. So, I think if anybody is interested make sure to tune in and take a look at our web site.

The final slide, just quickly, to give you a general feel of what the neurology product area did last year, as well as what you participated in, and of course, the PMA number ought to be 2 instead of 1, but in the 510(k) area we rendered 149 final decisions.

Most of those were substantially equivalent for products to go to market, two original PMAs, and actually in terms of the amendments and the supplements the amendments were other amendments that were submitted to those originals, and the supplements, we came to closure on 11 supplements.

The IDE is a larger area. While 27 seems like a small number, many of those do come in in terms of

supplements, expanding studies, looking for new indications for use, and so, you can have actually multiple studies in the originals, and I think that is where a number of those supplements are captured.

So, it is not an insignificant workload by any stretch of the imagination. It has brought a fairly big chunk of work to us, but it is very interesting, and I think based on our current resource situation that we will be turning to you as the Panel to give us guidance in all of these product areas.

So, you can give yourself a little bit of a hand, too, for helping us out in this area last year, and for that we thank you, and I will turn it back over to you, Dr. Canady.

Thank you.

DR. CANADY: Thank you.

Do the panelists have any questions for Mr. Dillard?

If not, then we will move to the open session. This is the first of two open sessions. Do we have anyone interested in addressing the Panel at this time?

Very good or not very good.

(Laughter.)

DR. CANADY: We will now proceed with the discussion of the reclassification of the arterial

embolization device. We will start with the FDA presentations, then have a reading of the FDA questions and a coordinated industry presentation.

Then we will have a general Panel discussion on this topic followed by a more focused panel discussion aimed at answering the specific FDA questions. Before we complete the new classification worksheet and supplemental worksheet we will have a second open public hearing.

Then we will complete the reclassification worksheet and supplementary worksheet and vote on those as our recommendation to the FDA.

I would like to remind public observers at this meeting that while this meeting is open for public observation, public attendees may not participate except at the specific request of the Panel.

We will now begin with the FDA presentations, Mr. Dillard?

MR. DILLARD: Good morning. Thank you, Dr. Canady. I would like to first introduce the team that has been involved with the artificial embolization devices in looking at the 515(i) submissions, Lieutenant Commander Keith Foy who is a biomedical engineer.

Following my brief, let us hope it is brief, background about where we are and how we got here with artificial embolization devices he is going to give you

currently what the devices are, the MDR reports and the current status, and then Dr. Jerilyn Glass who is a neurologist in our Division is going to talk to you about what the literature has told us about artificial embolization devices.

So, with that I will jump right into it.

What I would like to do just briefly is set the stage for your discussions today, talk a little bit about classification. You have heard about it a couple of times and been trained on it. So, I will be brief and very specific towards embolization devices.

The one point I would like to make about the embolization devices is just to make sure that we are all working from the same page and that we are talking about neurovascular and neurological uses for embolization devices.

We certainly have more generalized cardiovascular and peripheral cardiovascular uses, but those types of intended uses for perhaps similar products are not what we are asking you to discuss today.

I will update you briefly on cyanoacrylates and perhaps give a little insight as to why those are not a particular class of products that are on the table for discussion today and why that is.

I would like to briefly tell you about the 515(i)

process, about calling for information and the information that you are currently looking at, how and why we got that and then just task you with a couple of things for today's meeting that may help clarify what you need to be doing..

Medical device, I don't think we really need to define it. The only thing that as you have seen a couple of times today, the salient point here, and I think the point that is appropriate, certainly for cyanoacrylates and perhaps is a debatable issue, but No. 3, does not achieve intended use through chemical action.

Transitional devices, cyanoacrylates which I will go into some detail were a pre-amendments drug or looked at as a pre-amendments drug, and so at some point in time we thought there was some chemical action perhaps for that product area even though by current definitions today we probably are talking about a medical device, but this is the criterion we try to use when we are talking about a medical device and trying to make a differentiation between a drug, a biologic and a device. This is the arena we live in.

Classification, again, just for today, classification and reclassification is really something you should keep in the forefront of your mind is that Congress gave us the ability and really tasked us with saying that we need to place products in the lowest regulatory class for a reasonable assurance of their safety and effectiveness. I

think we all need to remember that.

What is the appropriate and the lowest appropriate class for the kinds of products that we are talking about, and we do have to go to advisory committees for these kinds of recommendations, and so that is why we are here today.

Class I, Class II, Class III, I think are pretty well defined it is a risk-based classification category, and the concept of classification is Class I, and products should be in Class I if the general controls alone are sufficient to provide reasonable assurance of safety and effectiveness.

If general controls are not by themselves, in and of themselves, enough to provide reasonable assurance of safety and effectiveness, the next question you should ask is are there special controls that when combined with the general controls will then provide reasonable assurance of safety and effectiveness. If so, Class II is the appropriate classification.

If not, and if general and special controls combined will not provide that reasonable assurance, then Class III is the appropriate classification for the type of product.

Next slide?

Classification from the 19 Classification Committees that met in the late seventies and early eighties

what we came out with was about 30 percent of the devices were Class I, and most of the devices are Class II devices with a small proportion as Class III devices.

This is a large amount of devices for 140 categories. I think last year we did somewhere on the order of between five and six thousand 510(k)s alone which are predominantly Class II devices although some Class I devices in terms of the clearance process.

So, it is not an insignificant amount of work in the 510(k) program and actually with the Food and Drug Administration Modernization Act we have now exempted almost all of the Class I devices as I think I said earlier, and so, you will see us concentrating much more of our effort in that sort of final 70 percent that you see at the bottom of that overhead.

Embolization devices for neurological use. Back in November 1978, the Classification Panel met and defined an artificial embolization device as an object that is placed in the blood vessel to permanently obstruct blood flow to an aneurysm or other vascular malformation.

In the proposed rule just so you don't have to go back and read it, the proposed rule stated that we, as well as the Panel believed that it ought to be a Class III device, and this was based on the fact that it was a permanent implant and that the device was difficult to aim

and get to selected target site.

At the current time, 22 years ago, there was insufficient clinical information known about predominantly the effectiveness of the product and that the Panel felt at the time that there was insufficient clinical information to develop a performance standard, and that is actually what was proposed in the proposed rule, and the risks that were noted at the time were infarction of nervous tissue and tissue toxicity of materials, biocompatibility kinds of concerns at the time with some of the materials that were being used.

FDA concurred with that and then subsequently --

Next overhead?

-- the FDA published the final rule in September 1979. There was one comment that was received in the comment period between the proposed and the final rule, and that comment actually recommended that the products be Class II devices, and the comment went on to state that there were 15 years of experience even up to that point, that the submitter believed that the safety had already been established and that really was not an issue of the product. It was an issue that depended upon the user and the user's ability and training to be able to place the embolization devices.

The final rule, we actually disregarded that

comment and said that we agreed with the Panel recommendation. We didn't believe that there was adequate clinical information either, and so we went on to classify the device as a Class III pre-amendments device which a 510(k) would be required at the time to be submitted prior to marketing.

We have not called for PMAs under Section 515(b). So, if you hear that terminology of proposing a 515(b) or proposing a call from PMA, that has not been done yet.

Cyanoacrylates, just to transition the reason cyanoacrylates are not up for discussion today is because what we are here to discuss are those devices that were pre-amendments Class III devices that were classified under that classification that could be submitted under a 510(k).

Cyanoacrylates as tissue adhesives actually even before the Medical Device Amendments were regulated as a drug by our Center for Drug Evaluation and Research, and so what happened is when the classification came along it was a much different category that we looked at which were those products which were already regulated as a drug versus those products which were unregulated in 1976, as nothing because they were a device that didn't fall under the drug authority.

So, it was a little bit different outcome. It was still a Class III pre-amendments device. It was a Class III

pre-amendments drug first, and we said at the time that instead of going to 510(k) and having a grandfathering time frame before we would call for PMAs we would immediately go to PMAs and require them prior to marketing.

That is where cyanoacrylates are. Another example is bone cements used in orthopedic kinds of applications and a number of sutures were in that sort of realm at the time, also.

Next slide?

The 515(i) process, just briefly what we did is there were a number of devices. It was 143 in total pre-amendments Class III devices that could be brought to market through the 510(k) program. We looked at that back in 1994, and proposed a strategy.

For those devices that we hadn't already made the decision we should call for a PMA or we should reclassify. We really didn't know enough about the information. That is where artificial embolization devices stood for neurological uses, and we proposed in 1994, that manufacturers should submit information to us and try to make a case for reclassification. It is really the whole idea of the 515(i) process.

That information was provided to us. We actually got four submissions, but only three are being considered here because as we looked at those four submissions, one of

them was actually a peripheral application not a neural application of a delivery device. So, that is not one for your consideration today, and then again, just to make sure everybody is clear that we are not talking about the generalized cardiovascular use of embolization devices today.

Next, Steve?

So, at today's meeting what are we asking you to do? With all this regulatory background and this couple of submissions, we are really asking you based on what is in those submissions, based on what you know in your clinical practices, based on what you know as experts in the field and what you have in front of you that there are two outcomes I think that can come out of this, and one of them is that your recommendation could be that the product ought to remain a Class III device, and if your recommendation is that it ought to remain a Class III device, what that signifies to the agency is that you think PMAs, pre-market approval applications should be submitted for not only any new embolization device but the current embolization devices that are on the market.

There is really insufficient information to develop general and special controls. If your recommendation is Class II or Class I then what you are recommending to us that you don't need an individual PMA for

each kind of device.

There are some general and/or special controls that can be applied to assure the safe and effective use of the products, both current products and future products, and so, from that standpoint I think this is kind of the bottom line of what we are asking you to do for those embolization kinds of products, and there was one other thing, Steve, and I think I have got one more overhead, because there is something for us that we think could be confusing today that we would like to clarify, and based on what we are doing today, we are talking about a category of products, but potentially there could be some very distinct products with some very distinct indications or intended uses, and so, we have talked about and thought about that if you look at kinds of products that we are going to be looking at today, coils, balloons and PVA, and you talk about three main indications where most of the literature seems to be, at least from the submissions and at least from what we understand, aneurysms, fistulas and malformations, that conceivably as you are discussing this today, and I think we are prepared to handle it either way, but we could come up, and you might decide that there is a generalized recommendation that might cover all of these possibilities on this matrix if you were to fill it out, but it, also, is conceivable in our minds that the combination of a device

plus an intended use in some applications may be very different than they are in some other applications, and you might have a very different recommendation.

So, Dr. Canady, I think in closing just as you are working with your Panel today, and if you get a generalized sense one way or the other we are prepared to certainly handle the reclassification questionnaire in either of those directions, and we will certainly default to your judgment as to which way you think the Panel might be going.

So, with that I think I will close, and if there are any questions I would be happy to answer them, answer any at this time or later. I will be available certainly for other generalized questions during the deliberations.

DR. CANADY: Do you have other presentations from FDA?

MR. DILLARD: Yes, we do. If you have no questions specifically for me, I will --

DR. ROBERTS: Could I ask just one question, and that is, and I don't want to bog things down right at the beginning, but being a person who is involved with other areas where these devices are used, and since as far as I know there is no one else in the agency that deals with the uses of these devices in the peripheral system, why aren't we talking about this in other areas besides the neural?

MR. DILLARD: I think at this point -- that is a

very good question. Part of the issue has to do with classification and the fact is that two separate panels back in the late seventies, early eighties looked at embolization devices.

We actually have got a neurovascular application classification for embolization devices, and then we have got a peripheral and a cardiovascular classification, also, which was looked at by a completely different panel, and so, we could have put together a joint panel and tried to take them all together with the same issues, and I think when we thought about that the complicating factors just told us we might separate them, and so, it may be that we would do that again, but we might do that under the auspices of another Panel at some point in time. Keep it simple, I think, we took the approach.

DR. WITTEN: I think for the other classification there is a 515(i) that is coming due shortly. So, they are a little behind in getting the information that we had requested.

MR. DILLARD: And I think that this one was just developed a little bit quicker and a little further along, and so, we thought it was a good time to bring this to you all. So, it may be that some of the people that have that particular expertise on this Panel might, also, be asked to serve on another Panel for the same sort of issues.

So, yes, it is not dead in the water. We just thought we would take this approach.

DR. CANADY: Other questions for Mr. Dillard?

MR. DILLARD: Okay, thank you. With that I think I will introduce Lieutenant Commander Foy, and he will give you the specifics on the background of the device types.

LCMD FOY: Thank you.

Good morning. We will be discussing the 515(i)s submitted by the companies Cook Incorporated, Cordis Endovascular and Target Therapeutics.

I will be presenting some of the background information concerning each device as presented in the 515(i)s and Dr. Glass will be presenting a review of the clinical literature articles presented in the 515 submissions.

For each of the three embolization devices being discussed today, I will provide a summary statement of the cleared indications for use and intended use, a brief device description, examples of the device-related malfunctions discussed in the 515(i)s and a summary for the most recent medical device reports associated with each device, specifically between August 1996 and the present.

I will follow with a list of the FDA's premarket application history for each device, provide a summary total for the supporting literature articles provided by the

submitters, list the submitters reported risks to health, present the submitters proposed special controls and present the submitters recommended classification for these devices.

After Dr. Glass presents the clinical review of the supporting literature I will be reading the FDA questions to the Panel.

The first embolization device to consider will be the embolization coils. Coils have clear indications for use as to reduce or block the rate of blood flow in small or tapering vessels and for embolizing saccular intracranial aneurysms and the management of AVMs, AVFs and other vascular lesions of the brain, spinal cord and spine.

Embolization coils are made from either stainless steel, platinum or platinum/tungsten wire. The wire is soft, flexible, radio-opaque and non-ferromagnetic. Coils are offered in various preformed shapes with and without synthetic fibers such as dacron or nylon. The fibers are added to promote thrombus formation.

The coil ends are blunted by the manufacturer to inhibit puncture of the vessel wall. Embolization coils are delivered to the desired vascular site using a microcatheter and attached either mechanically or by a small electric current. While inside the catheter the coil is straight, and as the coil is fed out of the catheter it reverts to its preformed shape. Multiple coils are generally used.

Next?

This next slide shows briefly some of the device-related malfunctions, such as coil breakage, premature detachment or non-detachment of the coil from the catheter, coil entanglement in the catheter or as a result of interaction with other embolic devices, such as another coil and perforation of the vessel wall.

Later, Dr. Glass will go into some detail about the events and clinical effects of these and other malfunctions which relate to the coils, balloons and PVA particles.

A review of the medical device reporting system information relating to the neurological use of the coil devices showed that the coils had a total of 95 MDR reports. Fifty-five were related to some form of device breakage, either the coil or catheter. Fourteen were listed as premature detachment of the coil. Three were listed as a difficulty in retrieval of the device or catheter, and 23 were listed with key words such as kinked, puncture, uncoiled, stretched or others.

It should be noted that limitations of MDRs include events going unreported, incomplete reporting and not knowing the denominator for the number of devices implanted.

I would like to switch our focus to embolization

balloons. Embolization balloons are indicated for the artificial embolization of symptomatic carotid cavernous fistulae, CCF and internal carotid artery occlusion, ICA, in patients where other medical or neurosurgical means would not be indicated.

Detachable balloons have been made from either silicone or latex. The balloons are offered in several sizes and are placed using a microcatheter. The balloon is inflated with a contrast media, positioned, then detached either general traction or coaxial catheter technique.

Device-related malfunctions include premature detachment or non-detachment of the balloon from the catheter and balloon deflation prior to clot formation. Both of these malfunctions are responsible for migration of the device.

There have been only two medical device reports related to the embolization balloons, one with the key words "balloon rupture and fragmented balloon," and the other as "premature deflation and migration of balloon."

The last embolization device we will be discussing today is PVA particles. PVA particles have been cleared for the vascular occlusion of blood vessels within the neurovascular system and are intended for use in the endovascular management of AVMs and neoplastic lesions.

PVA or polyvinyl alcohol particles are made from

polyvinyl alcohol and formaldehyde. The manufacturer removes the formaldehyde, dries and grinds the resulting foam. The manufacturer separates the PVA particles into a range of sizes between 45 and 2500 microns and provides these particles in about 100-milligram vials.

PVA particles are water insoluble, spongy, white and irregular shaped.

For visualization approximately 10 cc's of contrast agent and/or tantalum powder has been commented to be used and mixed with each 100 milligram vial.

This material is delivered through a microcatheter to the targeted feeding vessels. The particles swell upon contact with blood, saline or contrast media to act like a sponge.

The device-related malfunctions for the PVA particles include clogging of the catheter and particle dispersion, both as a result of inadequate mixing.

There have been no reported MDRs for PVA particles. However, remember the limitations concerning MDR reports discussed earlier.

Here is a summary of the FDA's history of these devices. To date we have cleared sixteen 510(k)s and have reviewed two studies regarding embolization coils. The FDA has cleared two 510(k)s and reviewed six studies involving embolization balloons, and we have cleared four 510(k)s for

the PVA particles.

PVA particles and coils were marketed prior to the Medical Device Amendment of 1976.

The submitters provided a total of 103 supporting literature articles. Sixty-three pertained to coils, 31 to balloons and 35 to PVA particles.

Please note that some of the articles contain information on more than one embolization device. The submitters have listed 11 risks to health which apply to each device. These risks will be discussed later in detail by Dr. Glass.

If you are aware of additional risks to health, we would be particularly interested in hearing you discuss these risks during the deliberations.

The proposed special controls are the same for each device. These were proposed as FDA guidance documents, standards, device labeling and design controls by the submitters.

Based on the information supplied in the 515(i)s each of the submitters has proposed that the coil, balloon and PVA particles be reclassified from Class III to Class II.

I would like now to introduce Dr. Glass who will discuss the clinical review of the 515(i)s.

DR. GLASS: My objective this morning is to go

DR. CANADY: Back to the question because I think Dr. Roberts was right. My question was really more properly No. 4. Any thoughts about the preclinical testing issue from the Panel?

DR. ROBERTS: One thing that I wanted to ask is that I think that it is quite clear from a number of reports and from my own personal experience in using PVA is it really is crucial that the sizing of the particles be accurate so that when they are labeled, you know, 1000 microns that you really have a comfort level that in fact you know a large percentage of those particles are that size, and I honestly don't know how that is quality controlled, and I certainly would like to make the plea that that I think is a very important part of the ibalon(?) or polyvinyl alcohol particles, that that really needs to be carefully quality controlled.

DR. CANADY: Since we are going to have manufacturing controls as part of the surveillance I think we as a Panel can call attention particularly to the sizing and the quality control issue there.

Other comments on this question?

And the final question?

DR. ROBERTS: I tell you what, can I just bring up just on the same lines and that is that obviously we are not here asking for compati- -- we are looking at the device,

over some of the literature that was reviewed that was submitted by the sponsors in response to the 515(i). For this meeting I plan to characterize the majority of that literature.

In other words, I am not going to go over all of it but just the key points in the majority of the articles that were submitted.

The focus is going to be on those articles that describe neurovascular application for these embolization devices. So, in other words, we are not going to cover use of these devices elsewhere in the body although there were a number of articles that described that application.

We are only going to look at the articles that have a sizeable number of patients reported. So, we are not going to go over those that are individual case reports or a handful of case reports by investigators at particular institutions, and the other focus is on where the predominant indications for use are with these various articles, in other words where are these devices used predominantly as revealed in the literature.

I am, also, going to include both articles that were reported on studies done in this country, as well as outside the country. So, we have a little variation there, but I am going to pull them all together.

Next slide?

The literature had a lot of limitations. As you might expect, some of this literature goes back to the seventies, the eighties and of course, the nineties, but often what you do have, even if you have sizeable numbers you still have basically case series done at particular sites.

There tend not to be controls other than an occasional reference to the natural history of the disease or perhaps to surgical outcomes. The inclusion criteria were very variable. In the United States these devices tend to be used on lesions that are non-operable or non-surgical candidates.

That is not true outside this country. A lot of times the definitions of success were not provided or they were very vague. Very rarely did you find anything specific.

There tends to be obviously a radiographic criterion used for an outcome of success, but that often is not very specific.

As an example, what does complete occlusion mean? Rarely did you ever find an operational definition as to how they determined complete occlusion. So, it is possible one site has one way of doing that, and they look at it one way. You know, is 100 percent occlusion what we mean by complete occlusion? Some places might have been using 90 percent

occlusion as complete occlusion as referring to maybe the best they could do.

So, it is hard to really interpret what complete occlusion really means. To make it even harder, often the studies would merely say that for a given lesion so many patients were treated with coils, so many were treated with balloons, but then when it came to the results they didn't break them out by device type. They lumped all the results together. So, that makes it really difficult. It is virtually impossible to tease out the results.

For a given lesion often multiple devices were used. A good example of that is the AVM. Part of it is treated with PVA. Part of it is treated with coils and so forth. So, that adds a little wrinkle into this. Also, of course, you have two treatments involved. So, maybe the end point is after, in fact, two treatments have been used with the patient. They had pre-embolization with a particular device, and then they went on to surgery or radiosurgery, but the results are only given after all of that.

So, what was the result of the pre-embolization; what was the result of the surgical procedure? You really cannot tell. As I mentioned, the information is dated in some cases, and I think you need to recognize that over time the field of neuroradiology, neuro-interventional procedures have gotten much better.

There have been major advances in the field. So, some of the rates of complications, for example, that you see in the more recent studies are much better than they were in the earlier studies. So, you have an evolving field that we are looking at.

There have been variable follow-up periods. As you might expect, early in the literature virtually no follow-up; patient was discharged, and that was the end of it, but certainly over time more and more of the studies have shown a more lengthy follow-up, but still I would have to say that the majority of it when they do give you follow-up, they give you ranges, and they can be very broad, and I would say, "One year to 6 years."

So, it was never the original protocol intent to specify a very definite follow-up period that all patients must complete before the data could be analyzed, but you don't see that in these kinds of studies, especially early on, and then finally, overall there really aren't that many articles in any given category that we are going to come to next.

Next slide?

This is the matrix that Mr. Dillard referred to earlier. On the left you have device types and on the top you have the indications for use, and most of these are in the brain, a few articles on spinal application but very few

in number, and the purpose of this is just to give you an idea of where the majority of the articles fell that met those earlier criteria that I mentioned, a sizeable number and so forth.

So, the way to interpret this would be if you look at the coil articles most of them dealt with the application in aneurysms, occlusion of aneurysms. To a lesser degree there has been some reporting in AVFs.

When it came to balloons most of the literature dealt with aneurysms and AVFs. PVA, most of it dealt with AVMs and to a lesser degree AVFs. So, the smaller X refers to a lesser amount of articles that met our criteria.

Now, I don't want this to imply that there were no articles dealing, for example, with tumors. They are there, but they are very few in number. Likewise, coils certainly have been used for AVMs. Historically they have been used a long time in AVMs, but there haven't been a lot of articles where you have a sizeable number of subjects. So, you know, there weren't that many there to review.

Next slide?

The risks associated with all of these embolization devices can be dealt with in part as a group. For example, all of these devices can have associated thromboembolic events occurring. That can be from blocking vessels that were not intended to be blocked. It could be

from dislodging a clot. There is a host of reasons, but you can have thromboembolic events with all of these devices.

Likewise you can have vasospasm with all of them and certainly hemorrhage, hemorrhage from perforating a vessel wall, hemorrhage a subtotal occlusion of a vessel. So, the vessel wasn't completely occluded, and then the lesion subsequently hemorrhages.

These things can happen to the targeted vessel, and they can happen to unintended vessels. All of that can lead to neurological deficits. They can be transient, permanent, and ultimately there can be death. So, these are recognized, and they apply to all the embolization devices under consideration this morning.

Factors involved with that are vessel size. We are dealing with small vessels, fragile vessels and very tortuous vessels in the brain. There could be unusual anatomy. So, it makes it difficult to access the lesion.

There can be device design problems or performance problems. Devices can migrate. Certainly the patient is a factor. Patient pre-procedure medical condition can have a big impact, as well as the status of the lesion, and I think we have to remember that some of these patients are very, very sick that come to the neurointerventionalist. They have had a recent subarachnoid hemorrhage. In many respects these are emergency situations.

So, you cannot discount that when you look at all of these results this morning, and then finally a big factor is clinician skill and experience. That sounds pretty reasonable. You have to realize that there are lots of decisions the interventionalist makes. There are decisions about sizing the device. There has to be skill in navigating the vessels and actually getting to the lesion that you want to treat and certainly skill in placing the device appropriately.

Next slide?

This just mentions some of the device problems that can occur. They were alluded to earlier. There are problems with catheters. There can be resistance within catheters. Catheters can kink. The devices themselves can fail. For example, there can be inflation problems, deflation problems with balloons, for example.

Any of the devices that involve detachment, there is a host of problems there. The detachment mechanism can fail. There can be a power failure. The signal on the detachment mechanism can fail, and then there are basic things. You know, devices break; they kink; they bend, and certainly devices like coils can unravel.

I would like to highlight that things certainly are getting better over time, and a lot of that is due to improved patient care and patient monitoring. For example,

anticoagulation has really brought down complication rates, and it is not just anticoagulation during the procedure but for an extended period of time after the procedure, and it is not unheard of for patients to be on medications of a variety of sorts for even a month after the procedure.

There is, also, more experience with pre-procedure provocative testing to assess the amount of collateral flow that the patient has.

During the procedure there is neurological monitoring, especially in awake patients. There is much more availability of emergency procedures in the event of a serious complication, and we have much more improved clinician training than we had, say, 20 years ago.

Next slide?

Many aspects of embolization hold across the different devices. It is important to keep in mind some differences. For example, when it comes to aneurysms and fistulae, embolization is the definitive therapy. You really aim to embolize the lesion, and that is it.

That is certainly not the case with AVMs. AVMs, often surgery or radiosurgery is the goal, an embolization is just a pre-procedure treatment, and then, too, there is the whole thing of parent vessel occlusion. That is an issue primarily with aneurysms and fistulae, and recently in the articles there is more and more of an emphasis on trying to

preserve the parent vessel from which the aneurysm arises or the parent vessel involved in the fistula.

It gets a little sticky, however, when you look at data on this because in some cases it is planned to actually occlude the parent vessel, and we will get into some reasons for that in a little bit, and then it can happen as a complication, and often the results that we will see don't make that distinction.

So, that is something that we will address a little bit.

Next slide?

I am going to spend time on each one of the device indications off that matrix. The first coils to treat aneurysms the treatment of choice for most aneurysms is surgical clipping, but there are always cases where the lesion is not clippable or the patient is non-surgical. So, for that reason coils are an alternative and here we are talking about pushable and detachable. We are talking about coils in general.

There were nine studies that I focused on, and the patient numbers here varied anywhere from 15 to over 400. The follow-up was 6 months to 1 year, and you see there the complete occlusion rates when anywhere from 13 percent to 79 percent, but now, we are back to the problem of what is meant by complete occlusion. That 13 percent, I want to

qualify that.

It was two of 15 patients in one study, and there the definition was exactly 100 percent occlusion. So, that was one of the few studies that really emphasized 100 percent as being what was meant by complete occlusion.

In that study all of the 15 patients were said to have 70 to 100 percent occlusion. So, that was felt to be a significant goal that was reached here.

Underneath that I have broken out in one study it was very interesting. They tried to distinguish which aneurysms seemed to be the most successfully occluded with coils, and there they found that you had the highest success rate with the small aneurysms with the small neck, and that was 71 percent of their patients. This was a result of immediate postembolization angiography.

As I mentioned, parent vessel preservation is certainly becoming more and more the goal, and in two studies they were able to report high percentages here, 93, 96 percent.

In another study they actually mentioned the unintended parent artery occlusion, and there it was quite low. It was only 3 percent, and that was in over 400 patients. So, that was a study where it did break out that we wanted to look at just those that were unintended.

The complication rates for coils in treatment of

aneurysms I have provided there for you. It is important to realize this mortality. Sometimes it is a result of the procedure, but sometimes it is a result of the aneurysm rupturing, the original aneurysm that brought the patient to medical attention, and sometimes it is an aneurysm that reruptures. So, you need to keep that in mind, and often the reasons for the mortality haven't really been distinguished.

More and more interest, too, on aneurysm remnants and in one study they did, again, immediate postembolization angiography looking for small remnants. They call them small fleck remnants, and they found that small aneurysms with a small neck seemed to have the lowest percentage of these remnants right after the procedure.

Some are actually suggesting that maybe surgery be done on these remnants once they are noted, but this is a new issue in the field, and over time we will probably be learning more and more about that.

One study, too, talked about subsequent surgery that was required, and that happened in 11 percent of patients who received coil embolization, and it was done for incomplete occlusions and to manage complications, and so this just gives you a rough idea of the data regarding coils for aneurysms.

I, also, looked at the discussion sections and was

looking for additional problems that maybe didn't surface in the data but were remarked on in the discussion, and there has been discussion of recanalization.

You can have that in these treated lesions, and there was, also, discussion about basilar tip aneurysms as a special entity that needs to be considered because in one study there was a 24 percent incidence of inadvertent occlusion of the posterior cerebral artery because the origin of that artery is so close to the actual site where they are doing the embolization.

So, I think it is interesting to realize that the anatomy presents some interesting challenges to the neuro-interventionalist.

Next slide?

Coils for the treatment of fistulae, there is very limited information. I think you have to realize that the application, the need for this kind of therapy might be limited. Typically carotid cavernous fistulae are treated with balloons, but there are cases where balloons fail and then the interventionalist may go then to coils.

So, the report here is on three studies, and the patient numbers are really small, three to six. I have given you the occlusion rates, but again, you really cannot make much out of this because the numbers are so small.

In the discussion they do talk about maybe this

kind of therapy is best for the small and medium-size CCFs, and it may be very inappropriate for high-flow fistulae because of the risk of migration.

Next slide?

Balloons, detachable balloons to treat aneurysms. Again, in this country it is for non-surgical patients. It is interesting for you to see in the articles when they actually plan on occluding the parent vessel, and it is pretty clear that it is for lesions where there is no definable neck, fusiform lesions, for example, and if there is thrombus within the aneurysm that may be another case where you want to actually occlude the parent vessel because you wouldn't want to risk dislodging any of that thrombus and then that would entail maybe an ischemic event down the line.

There were five studies here that had a sizeable number of patients, 25 to over 200. The follow-up often was 1 to 4 or more years. Successful embolization rates are given there up to 77 percent, and the parent artery occlusion, you know, again, a wide, wide range, but that entails both the planned and the unplanned. So, it is hard to interpret that.

There is a complication, for example. If a balloon protrudes into the parent vessel, then the interventionalist might have to then occlude the parent

vessel, and you do that as a result of complication, but with the fusiform lesions they intend to do that from the outset. So, that range includes all of that.

The 78 percent though really came from a study where the aneurysms were cavernous carotid aneurysms, and that is a special breed of aneurysm, and it is not unexpected that you would end up having to occlude the internal carotid artery. So, that would not be in the realm of the unexpected.

The complication rates I have given you there for both transient, permanent neurological deficits. There was one study that actually gave a rate for balloon migration that ended up requiring parent vessel occlusion. That was 11 percent, and one study gave a retreatment rate, and that was 11.4 percent, and that was done for subtotal occlusion, balloon shifting, aneurysm expanding or failure to thrombose.

Additional difficulties I picked up in the discussion, sometimes balloons do not perform perfectly to the aneurysm. They may be round or oval, and the aneurysm is irregular in shape. Aneurysms can be too small for a balloon, and then with detaching some of these sometimes traction is applied and that can stretch feeder vessels.

Next slide?

Another big area for balloons is the treatment of

fistulae. Actually many consider it to be the treatment of choice for high-flow direct carotid cavernous fistulae.

Here there were four studies that had sizeable subject numbers, 11 to 200 plus patients. Follow-up in some cases was out to a year, occlusion rates anywhere from 88 to 100 percent, and as I said, they are trying to preserve the parent vessel.

In this case it is the internal carotid artery, and the rates there are 77 to 88 percent.

This is considered pretty much of an advance in that if you look at the historical literature back 10, 15 years ago, you were seeing rates of 59 percent ability to occlude the fistulae and preserve internal carotid artery. So, certainly there have been improvements.

Some people think that you will never get 100 percent preservation of the internal carotid artery because there always will be large fistulae, and often these patients are trauma patients, and you will always have a fistula with a complete transection of the internal carotid artery, and you have no choice then but to occlude it.

Complication rates are given there, and for additional difficulties sometimes the fistulae are too small, sometimes too large or you might have multiple fistulae. Balloons can rupture, and there can be fibrotic bands in the sinus.

Next slide?

We are now going to get into PVA, and most of the literature has it applied in AVMs. A lot of this literature is very difficult to interpret. It is the older literature. PVA has been used to treat AVMs as a presurgical and preradiosurgical procedure. It is used for large AVMs or AVMs in eloquent areas.

It is said to enhance the resectability of the lesion, and some people believe that it has merit in the fact that in some cases it can decrease the neurological symptoms of the patient just with the embolization alone, but most often these patients go on into some kind of surgical definitive therapy.

What makes this so complicated is the fact that PVA is just one of the devices used in treating these, and a given lesion can have PVA treatment of a nidus and then it can have coils, for example, or a liquid adhesive as the treatment for the feeders. So, these are not simple lesions with one device.

There were six studies here with patients numbering 15 to 100. One study went out 2 years, but that is pretty rare, and the success rates really vary in how they describe it, and operational definitions are really hard to come by. You just don't see how they are defining these things.

In one study, for example, one-third of the AVM was obliterated, and this occurred in 56 percent of the AVMs treated. So, at one point it was really important to describe the fraction of the AVM that got obliterated.

Then you see where the goal is complete embolization. So, you might see the percentage given for complete embolization, and that doesn't happen over one session. That might happen over many sessions, and then more recently you have cases where they are looking at PVA as opposed to PVA plus something else, and one study actually looked at PVA plus coils, and they felt that there was a definite angiographic result in 100 percent of the cases treated with the combination whereas patients with PVA alone they felt that was true with only 76 percent.

I have given you there the complications or the rates and then at the bottom additional difficulties pointed out are the fact that sometimes you get occlusion of normal vessels, and it has actually been stated that perhaps that is at the root of most of the complications you see with treating AVMs with PVA.

Recanalization rates can be high. They can be as high as 30 percent. That is acknowledged in the literature. That may be less of an issue if the patient goes on to a definitive surgical procedure within 4 weeks, for example.

It can be technically difficult to determine when

the nidus is filled. You want to fill it, but if you overfill it that can be problematic, and from a technical point of view some of the interventionalists acknowledge that it is difficult to determine that end point, and then of course, there is always the problem of migration of particles into the pulmonary vasculature.

Next slide?

Very limited information here, it is PVA to treat fistulae, just two studies dealing with its use in dural AVFs which can be very complicated lesions that pose a very significant challenge to the surgeon. So, it may be used with those prior to surgery, and here, too, it is hardly ever just used as the only device. It is used with other devices in combination.

There were two studies, one 21 patients and PVA, liquid adhesive or balloon was used and the complete occlusion was 43 percent.

In another study six patients, and there they actually combined the PVA with the coils and the liquid adhesives and a cure, in quotes, was 67 percent.

You have the complications there but really cannot make much out of this because we are talking about such few numbers.

In the discussion sections on this application you will see that some consider maybe this is best for the less

complicated dural AVFs, the Type I AVFs.

Next slide?

To conclude, there really was a limited number of articles for the specific device indications off that matrix. The literature that was there had a number of limitations, and a lot of that goes back to the fact that some of the literature was rather old and dated, and some of that is getting better.

The other thing that was really obvious to me anyway was that you are not going to find these neat little studies where one device is the sole device used on one specific lesion for one specific indication. You really have a given lesion treated with more than one device, and that is especially true with the AVMs and it gets really complicated when you realize that AVMs are a tangle of vessels that within the AVM you can have an aneurysm. You can have fistulae. You have a whole lot of things going on there. So, the neuro-interventionalist ends up using a number of different devices.

Another thing is that I am finding that more and more the field is viewing endovascular embolization and surgery as complementary. So, more recent studies especially outside this country they are talking about lesions where embolization may be followed by surgery, and the two are working in combination.

As far as complications go, I think it is recognized in the field that you have to recognize clinician skill is an important factor there, but with improved training and experience that is getting better, and then finally, we have a couple of charges to the Panel, questions to be considered.

Can special controls provide for adequate control of risks associated with these embolization devices for specified indications? So, that is really the issue here, can special controls control for those risks, and if so, what are those controls?

Can these same controls be applied to all embolization devices under consideration today or are there indications and/or devices which will require different controls? So, can they all be lumped or do we have to split them and consider them individually, and overall really the task here is to consider the appropriate device class based on what we know about these embolization devices and the controls that apply?

I am going to turn this back to Mr. Foy.

LCMD FOY: With regard to the questions that Dr. Glass mentioned, we have six Panel questions that I would like to read off before we have the industry presentation.

If you would refer to your supplemental data sheet, Question No. 4, that relates to the first two Panel

questions.

First is please discuss the proposed classifications. For the different artificial embolization devices, i.e., coils, balloons and PVA particles what other descriptive information should be added to the present classification identification?

The second, again, referring to Question 4 on the supplemental data sheet, based on the literature and device registries for each of the artificial embolization devices for which patient population or populations should the artificial embolization devices be indicated?

The third question referring to Question 5 on the supplemental data sheet, based on the information presented in the 515(i) submissions, please discuss the intended uses and specific risks to health related to the artificial embolization devices? Please discuss whether these can be assigned to all devices or should be addressed separately.

No. 4, again on Question 5, supplemental data sheet, from the literature device registries and MDRs, please discuss the risks to health for artificial embolization devices, and what are the additional risks that should be described that have not been addressed by the information presented?

Please refer to the general device classification questionnaire, No. 7. For that page please discuss whether

the current clinical testing, such as biocompatibility testing, mechanical and chemical properties testing, etc., are adequate to control the identified risks to health? What additional preclinical tests should be used to control the risks to health.

Again, on Question 7 of the general device classification, when and under what circumstances, for example, a new device or a new indication for use is it appropriate to require clinical data as a special control for a new artificial embolization device undergoing marketing clearance? And either the industry representative or whatever.

DR. CANADY: We can certainly use these questions, I think to guide our deliberations later this afternoon.

What we would like to do now is are there any questions for Dr. Glass or Lieutenant Commander Foy?

Okay, I would like to, if we could, go on to the industry presentation, planning for lunch at one, and in the after lunch session it will all be the deliberative portion. Is that acceptable to the Panel?

Okay, then we would like to have the coordinated industry presentation by representatives of the three manufacturers who submitted 515(i) information to FDA to help the agency determine whether reclassification of the arterial embolization device is supportable.

The three companies are Cook, Incorporated, Cordis, Incorporated and Target Therapeutics, Incorporated.

I would ask that each speaker introduce him or herself, tell the nature of their financial interests. I believe Ms. Valenti of Cordis will give the introductory portion.

MS. VALENTI: Exactly, yes, thank you.

We are passing out the latest update in regard to the presentation for the Panel members, and I am Marlene Valenti. I am the Director of Regulatory Affairs for Cordis Corporation, and I will be presenting on behalf of industry for those people who submitted the 515 submissions.

Next slide, please?

As stated, Cook, Incorporated, Target Therapeutics and Cordis Corporation submitted 515 submissions. I would like to acknowledge these individuals who contributed to the presentation today and who are, also, in the audience in the event that you have specific questions for them.

The agenda for today is just a brief introduction, and then we will go into the recommendation on behalf of industry and really stress the primary reasons for that recommendation, and Mr. Foy did an excellent job in regard to reviewing the medical device report. So, we will probably skip through that very quickly, and then get into the device descriptions and discuss the long-term and short-term risks

associated with that, and then I will turn it over to Dr. Tomsick from the University of Cincinnati who will present the clinical use for these devices.

We do appreciate the opportunity to discuss the reclassification of these devices with the Panel today. These are devices that present a significant medical need for the medical community.

In some cases there are not many alternatives for these patients, and in some cases, especially for non-surgical patients they are life saving.

In terms of reduction of surgical risks we have seen that after embolization that can decrease the time to resect the AVMs, ease of resection of those AVMs and minimize the blood loss associated with it.

So, for all of these reasons, we feel that it is in the best interests of the medical community to continue to bring these products to the market in a timely manner.

Industry recommendation is to put these into Class II, utilizing the genuine special controls that have been utilized for the past 20 years, classifying all of the devices together, both the PVA coils and detachable balloons, and the primary reason for this recommendation is the fact that these devices have been marketed via the 510(k) process very successfully over the last 20 years and there has been nothing to indicate that there is any need to

regulate them as Class III devices.

The device performances are very well known. The risks and benefits associated with these devices are adequately characterized in the literature and, also, the device labeling.

We, also, feel that there is valid scientific information in the literature and this information is much more realistic than what would be obtained in a clinical study and really is reflective of how they are utilized, and I think Dr. Glass did an excellent job in regard to emphasizing that part.

Again, these are the general and special controls that industry has been utilizing over the last 20 years successfully for these devices, and they include labeling in terms of precautionary statements and warnings, sterilization, biocompatibility and good manufacturing practices which are now referred to as QSR compliance with special emphasis on design control activities and medical device reporting.

Mr. Foy did an excellent job in regard to the medical device reports, and you will see a difference in terms of the number. I think he had 95, and we have 82. We did our medical device search on the database search using the class code HCG from 1984 through 1997.

If we estimate which I think is a low estimation

in regard to how many procedures were performed for the neurovascular during this time, we estimated approximately 200,000. This would equate to a less than .05 percent incident rate of MDRs for these types of devices.

Again, Mr. Foy went through the types of events that have been associated with MDRs. So, I am not going to reiterate that, other than to bring up the fact that it is a low incidence rate in regard to MDR reportable events and in particular with a patient population that is very sick.

Let us very briefly go through the history of each type of device starting with PVA. There is over 25 years of clinical experience with these devices primarily in AVMs and other vascular malformations, and we estimate approximately 15,000 procedures performed with PVA for the neurovascular system in the US.

This is a brief description of the PVA devices that were included in the 515 submissions. As you can see the intended uses are very similar, and the characteristics of the devices are virtually identical.

Next, history of coil embolization, again, there is over 25 years of clinical experience with these types of devices, primarily using aneurysms, AVMs, AVFs and other malformations and approximately 15,000 procedures performed annually in the US with coils.

The devices that were included in the 515

submissions, I will start with the target therapeutic devices. They have two general types of devices, pushable coils and GDC coils.

The GDC coils are mechanically detachable systems. The primary difference here is in regard to the intended use. The GDC is for non-surgical aneurysms whereas the pushable coil similar to the Cordis and the Cook coils are for AVMs and AVFs and other malformations.

Then in regard to the characteristics you will see they are very similar between the Target, Cook and Cordis.

Here are the Cook coils and Cordis coils, intended use in AVMs and other vascular malformations and again, the materials, configurations and size ranges are very similar between all three types of devices.

Last is the detachable balloons. There is over 20 years of clinical experience with these devices primarily for CC fistula, carotid cavernous fistulae and parent artery occlusion, and we estimate that there are fewer than 500 of these procedures performed annually with the detachable balloons.

Again, the indication in regard to the parent artery occlusion in CC fistulae, it is a silicone balloon, and these are the size ranges and release ranges that are offered for that device.

Now, Dr. Glass did an excellent job in regard to

listing out the adverse events that are associated with these types of devices. So, I am not going to get into detail in regard to that. What we tried to do here though is list out the adverse event, identify whether or not we felt there was a short-term risk which we indicated would be less than 30 days or a long-term risk and then specified the special control that has been used for the past 20 years to minimize these risks associated with these types of devices.

Can you hold that one for a second?

In regard to just pointing out a few of the items, foreign body reaction which we considered a short-term risk, that we felt has been controlled through utilizing the FDA and ISO guidance document in regard to biocompatibility, infections utilizing the FDA guidance document in regard to sterilization.

Then labeling, what we are talking about here is the warnings and precautions statements that are included in the instructions for use which include such statements as proper sizing of these devices, proper placement, that these procedures should only be performed by trained physicians and in particular in regard to the damage to the vessels, the vessel spasm or perforation to make sure that you never advance the catheter when resistance is encountered.

Other adverse events, listing out the short term and long term, again, the special controls, and one other

item the design controls, what we are talking about here is making sure that we are offering to the physician different types of configurations.

As I indicated before, a lot of these malformations are very different between patients and they need different sizes and different configurations in order to be able to occlude the malformation properly.

Finally, the adverse events listed here, I think the other point to make here is in regard to the hematoma and the clot formation. There are warning and precautions statements in the instructions for use for proper management of the patients including flushing of the catheter and heparinization.

Now, death is obviously a short-term and a long-term risk associated with these types of devices, and that can result in regard to any of the adverse events that have been listed previously.

I think if you look at the literature, a lot of the deaths that have been published in the literature are really associated with the underlying disease.

So, in conclusion, it is important to remember that these devices are used by neurospecialists. They are very highly trained. There are very few physicians who are performing these types of procedures, we estimate around 500 in the US. There are approximately 35,000 procedures

performed annually.

These malformations vary significantly, and as a result of that they require different types of devices in different combinations while they are treating them.

For all of these reasons we feel that it is important to continue to be allowed to market these products utilizing the 510(k) process as we have been for the last 20 years to be able to bring these products to the market in a timely manner.

With that I would like to thank the Panel for giving us the opportunity to speak and turn it over to Dr. Tomsick who will be discussing the clinical use of these devices.

DR. TOMSICK: Thank you. Good afternoon. I am Tom Tomsick, professor of radiology, adjunct professor of neurosurgery at the University of Cincinnati where I have been since 1976, and I have worked with the same neurosurgeon since that time. So, we have kind of a mature relationship in choosing treatment of disease processes.

For instance, on the diagram up there we have listed five diseases, AVM --

DR. CANADY: Excuse me for one second? We have our rules. We need to know if you have any financial interest?

DR. TOMSICK: Excuse me. I have been an

investigator for a variety of the industry companies, Cordis Corporation, Target Therapeutics, MicroIntervention Systems over the years with research support. I have, also, had physician-sponsored IDEs of my own for latex detachable balloons from 1979 to 1986, for NBCA from the Ithacon(?) Corporation, my own physician sponsored from 1980 to 1985. I have a physician sponsored IDE for PVA versus NBCA at Tripoint(?) Corporation. That was 1985 or 1986. Excuse me. That is inactive from 1992, in addition to participating in a number of company-sponsored investigational devices through the years.

DR. CANADY: Thank you very much.

DR. TOMSICK: So, going to the disease processes, for instance AVMs of the brain at the University of Cincinnati, perhaps only one-quarter of AVMs are treated with some form of interventional procedure. The other three-quarters may be small enough, safe enough to surgically resect alone or treat with radiotherapy.

Aneurysms, approximately 10 percent are treated by one of the methods that we are going to talk today at our center. It may be higher elsewhere but in our mature treatment center it is 10 percent currently.

Arteriovenous fistulae, most will be subjected to an interventional procedure, interventional navigation procedure using one of the agents described.

Carotid cavernous fistulae or direct communications between the carotid artery and the cavernous sinus are exclusively treated by an interventional method currently and only when they fail would surgery be contemplated and parent artery occlusion for one of the processes obviously is an interventional purpose.

So, let us look at the individual diseases and the treatment modalities. Coils in the treatment of AVM although Dr. Glass had that box blank on her slide, I believe, I do think there is a place for coils in the treatment of AVMs. I show the descriptor.

Here we have a chart of an AVM with a number of small vessels and a number of large vessels. Well, any of the particulate agents, sponge, for instance, PVA may go through the large vessels and may block the small ones. So, coils may be necessary as a large embolic agent to block larger arteries associated with brain AVMs, and this may be as a temporary measure prior to surgery or in cases that are not surgically removable in hope for somewhat permanent resolution of the problem.

Right on the line often AVM detachable balloons have been used in the past to block the larger arteries leading to brain VM or the arteries within, but again, I think coil has predominantly taken over that place in the management of AVMs in detachable balloons, both as

preoperative or permanent measures.

PVA sponge in relation to AVMs, again, once again because blood vessels may be of the 50, 100 micron size, PVA sponge may be expected to lodge within, block it as a permanent agent over time or as a temporizing measure prior to surgical removal.

Sponge, obviously will not work when there are larger communications present and some other adjunct material will be required, and that is why Dr. Glass referred to multiple modalities, multiple agents being used with some of these disease processes.

There is no perfect agent, no one disease process that lends itself. AVMs do not lend themselves well to treatment with a single agent.

Let us go on to aneurysms. Aneurysms, outpouchings, if you will of the wall, the deficient portion of the wall of an artery can be treated with coils. The Goliomi(?) detachable coil approved by the FDA in 1996, of course, is approved for non-surgical aneurysms where coils can be placed into aneurysms as a permanent measure, we hope although we do realize that the long-term permanence of GDC coil treatment over more than 5 years is certainly not yet proven.

It may be used as a temporizing or pre-operative measure in a patient with a subarachnoid hemorrhage,

occlusion of the aneurysm in the short term to prevent rehemorrhage while the patient recovers from the neurologic effects of the hemorrhage and perhaps to allow surgical treatment at a later date as a reasonable option. So, it can be used as both permanent and pre-operative measures.

Detachable balloons although Dr. Glass didn't dwell on detachable balloons for treatment of aneurysms and even for placing in aneurysms, there is very little enthusiasm on the part of the neuro-interventional community anymore for putting balloons in aneurysms for all the reasons and drawbacks and deficiencies that she mentioned.

So, in point of fact, detachable balloons in aneurysms are pretty much a thing of the past. However, detachable balloon occlusion of the parent vessel, the artery from which the aneurysm arises is still a very useful technique particularly as she suggested in the internal carotid artery, particularly for those that are not surgically accessible in the cavernous sinus region, petrous bone, upper cervical internal carotid artery. Detachable balloons are useful for parent vessel occlusion.

PVA sponge has little to play in the treatment of aneurysms except perhaps pseudo-aneurysms arising from arteries going to AVMs or some other lesion.

Next?

We will talk about arteriovenous fistulae. We

happen to show here a number of different arteriovenous fistulae of the cavernous sinus regions. Some would call them carotid cavernous fistulae of a dural or meningeal type. We are just using it as an example of a arteriovenous fistula here. We are in small arteries.

Type A is a large communication between the carotid artery and the cavernous sinus. Types B, C and D are small vessel connections. Types B, C and D are more of the arteriovenous fistulae type, and again, arteriovenous fistulae can be treated with polyvinyl alcohol sponge through arteries by putting catheters inside the small arteries leading to an arteriovenous fistula and blocking them as totally as is accessible. So, it is both useful as a pre-operative measure if surgery is contemplated and in some cases it is a permanent and curative measure.

Detachable balloons have a place in carotid cavernous fistulae of the direct type which we will talk about subsequently. Coils can be used in arteriovenous fistulae treatment as well.

So, with Type B, C and D there we have blood flow into the cavernous sinus from small arteries, but currently the primary mode of treatment of this particular lesion is to catheterize the veins and come retrograde and pack the cavernous sinus in with coils. So, there is a primary use of coils in treatment of fistulae particularly on the venous

side.

Next?

Carotid cavernous fistulae, now, this is the Type A or direct from that last chart. Type A or direct, and again, this is a fairly uncommon lesion in a major center like our own although 10 years ago we treated 12 a year, right now we treat two or three a year because of the nature of referral practice and wider availability of techniques. We are in a small microcatheter where the balloon can be passed through the carotid artery through the rent, the tear in the carotid artery, inflated in the vein space of the cavernous sinus, detached and as Dr. Glass suggested with approximately 70, 80 percent likelihood occlude the fistula and leave the carotid artery patent.

Coils are useful in this decision process as well. If the hole is small one can work through the carotid artery. One can work through the veins in a retrograde fashion to overlay the ostium of the fistula with coils.

I would suggest, however, that some holes are too big for coils. Some holes are going to be too big for balloons, and the only way to treat it is to block the parent artery as Dr. Glass suggested.

There is no place for polyvinyl alcohol sponge or any small particulate agent in fistulae such as this.

Next?

We just alluded to parent artery occlusion with aneurysms, and carotid cavernous fistulae. For instance, if you have an outpouching of an artery with continuous flow through it, a fusiform aneurysm you might choose to use parent vessel occlusion for aneurysms of that type or any other surgically inaccessible aneurysm.

In conclusion it is a brief description of what the indications for treatment might be, and I would only say that none of these devices are perfect for the disease processes, that the greatest risk is related to the nature of the disease processes themselves, and once again to the person who by virtue of hopefully adequate experience and training is doing the treatment, namely, the operator.

Thank you.

DR. CANADY: Thank you very much, Dr. Tomsick.

Do the panelists have any questions at this time for Ms. Valenti or Dr. Tomsick?

None?

Then I propose we adjourn for lunch and meet back quite promptly at quarter to two.

(Thereupon, at 12:46 p.m., a recess was taken until 1:45 p.m., the same day.)

AFTERNOON SESSION

1:45 PM

DR. CANADY: I would like to call the Panel back into open session.

We are going to begin our deliberative process in the normal way in which we have a lead investigator from the Panel. This time it is Dr. Andrew Ku who will give a presentation from a panelist's perspective of the data that he has received.

DR. KU: Thank you, Madame Chairman. Fellow participants and guests, I thank you for this opportunity to review this reclassification petition for particulate embolic devices.

As has already been presented, there is a large body of studies reporting the usefulness of embolic devices in the treatment of a variety of vascular lesions and hypervascular tumors.

There are certainly limitations in the literature due to lack of randomized controls. This, I think is in part due to several factors, one, the generally high-risk of the underlying diseases that are being treated by embolic therapy; two, the wide variety of vascular lesions and neoplasms which are being treated with embolic therapy and the rapid evolution of endovascular techniques which were practiced by a few pioneers to a more widely based therapy in the continued evolution of delivery devices and delivery

techniques.

There are certain ethical limitations in performing randomized studies because in several areas embolic therapy has become accepted as a primary treatment of choice which makes randomization more difficult, and due to the fact that very often combinations of embolic devices are used in treatments of complex vascular malformations.

I think it is important to recognize that many embolic devices as has been noted have been in existence for 20 to 30 years and that operator skill and judgment may be one of the major determinants in determining how safely these devices are used.

A major factor as has been noted is that the improvement in safety of many of these embolic devices is secondary to improved delivery devices and due to improved operator training over the last 10 or 15 years.

It may be possible that the number of actual device failures may be small when compared to the number of cases where the operator exceeds the design specifications of some of the devices as to whether they are used in areas or territories where they were not designed to be used or where clinical factors are not taken into appropriate consideration.

I think the Panel should consider the long-term evaluation of some of these embolic devices in that a

significant number of patients were treated with so-called "pre-operative embolization" may wind up having partial resection of their lesions or no surgery at all if the final result or cure is achieved primarily through embolization or if there is adjuvant use of radiation therapy in achieving the successful treatment of the lesions.

This, I think, should be tempered with the fact that there is a long history of use of many of these embolic agents and the number of reports of delayed complications associated with these retained devices such as PVA has been relatively low or almost non-existent.

I think some of the questions that are going to be important will be the long-term follow-up of some of these agents because they are implanted devices, and maybe they are longer than originally labeled and, also, the question of what types of labeling may be helpful in order to improve or restrict the availability of the devices to people who are well-trained in this particular area.

DR. CANADY: Thank you very much.

What I would like to do now is kind of a general discussion, and I would really like to go around the Panel and have everyone give what their general thoughts might be or as we begin to create really a structure for a general discussion. One of the issues I would like you to specifically address is your sense as to whether or not we

should divide and split the various embolic devices or consider them more as a group.

I am going to ask you to start, if you would, Dr. Hurst.

DR. HURST: Thank you. I think that these are pretty clearly a very generic group of devices at least to me. They have very small uses and indications, and I think if we focus on the major uses and indications for which these devices are manufactured and sold, that is the occlusion of vascular structures, one can see that from a lot of data that has been presented here and even more that we were given prior to this time that there are 20 or maybe even 30 years of experience backing up to the conclusion that these devices can be used safely in terms of benefit exceeding risk and secondly, that they are effective, and I think that given that and the fact that they are, also, generic devices under the same category, my inclination would be to feel that special controls are probably adequate to monitor these devices.

DR. CANADY: Dr. Walker?

DR. WALKER: Dr. Ku's point that the ethical difficulties of randomized trials and any request that we would make to do that would really be a two-edged sword is a very good one that bears repetition. I, also, agree with him that probably the physician skill is more important than

the minor differences in design.

This is a design that is stable. It has been shown by the marketplace to be safe and efficacious over the past 25 years, and probably those market forces have said more and louder than we could say as a group here today.

I agree that only special controls are needed. I cannot see a reason why specific PMAs are needed, but I am very concerned about the long-term effects of ionizing radiation on particularly the polyvinyl alcohols in patients who are prescribed a dose of radiation therapy far away from the injection of the polyvinyl alcohol, and while biomaterials is not my specific area, maybe I am completely wrong.

Maybe this is one of those rare polymers that is not affected by ionizing radiation, but I am hoping that maybe later in the discussion we could hear from some of the industry representatives about the long-term effects of high-dose ionizing radiation on this material.

DR. CANADY: We could ask them now. Would anyone from industry like to comment on that?

Come to the microphone for us and identify yourself.

DR. TOMSICK: Once again, Tom Tomsick from University of Cincinnati. I am unaware of the biological effects per se at the cellular level, animal studies of PVA

and radiation.

There is no question in my mind, however that radiation to AVMs is going to cause other tumors over time. We are going to see that happen in humans. Probably it may be unrelated to the PVA itself.

In clinical studies, however, there is one center at the University of Pittsburgh that has both performed PVA embolization with radiation and has reported on their data, most recently last month in Neurosurgery in their most recent follow-up of patients treated over the years with no untoward clinical effects in the observed periods.

Yes, they have the 15 percent recanalizations of PVA and AVMs with radiation, but considering the alternatives even to them that is an acceptable result and perhaps radiation, again, can be meted out, but the specific biological effects I don't think we have very good --

DR. WALKER: I am thinking more of the chemical effects of the breakdown of the PVA under ionizing radiation and until that is known it should be contraindicated.

DR. TOMSICK: The short-term effects of a brain AVM, the deleterious effects of the short-term natural history I think probably obviate and outweigh long-term biologic effects in most patients in whom that treatment is being administered. I would raise that argument.

DR. CANADY: One other comment from industry, if

you would identify yourself and what your role may be?

MR. DE FORD: My name is John DeFord with Cook.
Obviously there is a conflict there.

DR. CANADY: No conflict, just an interest.
(Laughter.)

MR. DE FORD: A strong interest. PVA is, we sterilize it with gamma. So, it is sterilized. We have done some significant studies to determine the effects of that ionizing radiation on it, and we have not found significant degradation of the material over time.

DR. CANADY: It stays PVA even with that breakdown?

MR. DE FORD: Yes.

DR. CANADY: Okay, thank you.

Ms. Wojner?

MS. WOJNER: From a consumer's standpoint I feel very comfortable with the safety and efficacy of these devices. I, also, do not see a need to separate them into three different subclassifications. These are very heterogeneous patients. It is a very small sample size involved in any type of study.

I feel like the findings that we have thus far are ones that I take comfort in though, and clearly we are providing patients with alternatives that they didn't have in the past.

So, I am quite comfortable with where we stand right now.

DR. CANADY: Ms. Maher?

MS. MAHER: I think from an industry standpoint these products have been marketed, on the market through a similar, the same classification for 20 plus years, and I just don't see any need to break them out into separate classifications now. I don't see what benefit that would bring to anybody.

DR. CANADY: Dr. Roberts?

DR. ROBERTS: I don't know that I have much to add from what everybody else has said. I would certainly agree that I think that the use of these agents over certainly my lifetime as an interventional radiologist, I think that there is no doubt that these devices work. They work well. There is no question that it is operator dependent, and you can foul up these devices if you are not careful about how you are using them, but that is true with anything, whether it be a scalpel or even a needle.

So, I think that they are safe. They are effective, and I think that basically with some special controls I don't see any reason not to make them Class II.

DR. CANADY: Dr. Edmonston?

DR. EDMONSTON: I guess I am going to be the maverick to some extent in that I probably want to separate

out detachable balloons for two concerns, namely, with regard to long-term safety issues, we are dealing with a small population of patients annually that receive balloon embolization, but the materials used to do that namely latex and silicone raises long-term safety issues.

In regard to latex we know that some folks have had really pretty serious allergic reactivity to it, and in contrast to operating on someone repeatedly with latex gloves or whatever this is an implanted device, and it is intrascular, and so, there is an interface with lymphocytes and other arms of the immune system that may be provocative over time to cause chronic allergies or even more serious allergic reactivity that we just don't know, because if you don't look, you don't see.

So, that is one query. The other query with regard to silicone is that of course this has been a charged issue in other devices as we know, but with regard to immune reactivity we seem to attach to the notion of classic rheumatologic diseases and autoimmune diseases when this issue comes up, namely, rheumatoid arthritis and lupus and all of the classic textbook autoimmune disease, but if you take the stance that there may be a new type of autoimmune process, and the ruling is not completely solidly black and white completely settled, then my issue is that again since this is intravascular we have the opportunity to look at

various silicone products over years.

We know that for example, shunts, there have been no major problems at all with them, and shunts have been used, but we have to bear in mind that the brain in that setting is really immunologically privileged whereas an intravascular type of site bears more general systemic exposure and the immune system is more reactive in that setting.

So, again, if we don't look, we don't see, and so, my concern would be design of some sort of study to look at autoimmune reactivity in this population of patients who have had balloons in, whether singly as the only agent, embolizing agent or in combination with others to see what the incidence of autoimmune disease is or not even in the classic sense but how many have various non-specific general connective tissue disease-like complaints?

DR. CANADY: I guess my personal concern is just the size of the exposure in this case and the size of the balloons we are talking about as compared to a large exposure with breast or even shunt, much smaller.

DR. TOMSICK: Again, regarding latex I would just like to point out that the silica compounds --

DR. CANADY: You have to identify yourself.

DR. TOMSICK: Tomsick again from the University of Cincinnati. The silicon balloon is the only approved

balloon for investigation at this time, recently approved for marketing actually.

Historically though I mentioned I had the IDE for the latex balloons from 1980 to 1987, where we treated 65 patients with latex detachable balloons, and did a follow-up of those patients published in Neurosurgery in 1995, I think where we had 95 percent follow-up of those patients with no unusual allergic histories, autoimmune disorders discovered.

Now, the skin testing was not done or any such, but there is literature on long-term follow-up of such patients.

DR. EDMONSTON: With regard to the dictum if you don't look you don't see, my query would be with regard to several different symptomatology, the questionnaire regarding chronic fatigue symptoms, polyarthralgias, incidence of cardiolipin antibody syndrome or maybe even just serology looking for serological signs where there may be some immune activation, autoantibody studies, for example.

DR. TOMSICK: Certainly it would be possible at the level that you are interested, but there were no unusual medical disorders, some low-back pain but no unusual medical disorders described.

DR. CANADY: Dr. Rousseau?

DR. ROSSEAU: I would just echo what the majority

of the rest of the Panel has said in that I believe there is a very long history of proven, both safety and efficacy of these devices, and speaking as a neurosurgeon they offer treatments for patients that as our consumer representative said were heretofore unavailable.

So, I would recommend that they be continued to be used and in a Class II status.

DR. CANADY: Dr. Gatsonis?

DR. GATSONIS: I hope I don't sound too doctrinaire in the way I will approach this, and I, also, want to preface my comments with the following statement, that very often something may be an advantageous device or drug or procedure, but the evidence for it may not be there.

The two issues are separate, whether there is evidence for something and whether the thing actually works. So, with that kind of dichotomy I will talk about the nature of the evidence that we have for these devices. It seems to me that just listening to the reviews, for instance, this morning and what everybody has put together in these nicely compiled documents, if there was strong substantial evidence for efficacy that was gathered according to the usual rules that we use in other parts of medicine, namely, the rules of prospective, well-designed, well-thought-out studies, this evidence would have been summarized for this Panel in the form, for instance of a systematic review or a meta

analysis.

I don't see any of that being attempted and for the right reasons, and most of the reasons were the kind of reasons that Dr. Glass pointed out in her presentation, that a lot of the studies, as a matter of fact, the vast majority of the studies that form the evidence here are case series retrospective studies, convenient samples and so on with very little evidence of any design and very little evidence of attention to the usual rules of gathering and interpreting evidence.

So, from that point of view I am not personally convinced at all that the evidence is here in terms of the rules for gathering and interpreting evidence, but the evidence is here that these devices are effective, and if I was, for instance, a payer for such a device I may require the kinds of studies that may seem difficult to do, and it seems to me that if we are going to move the whole field of devices forward we have to start thinking about it, and I am talking about well-designed prospective studies. Very little of that is here. As a matter of fact, I spotted one study of this kind.

So, that is my overall impression about the quality of the evidence about the effectiveness of these procedures. I will defer to all the clinical colleagues obviously who have seen these things work in the laboratory,

sorry, in the hospital, but you would have to, also, take into account that there are plenty of situations in which things that were always thought to be very effective, by the time you put them in the context of a rigorous clinical trial, for instance, they fell flat on their faces. So, I will not be very surprised if the efficacy of these, if the effectiveness of some of these devices if you put them into rigorous prospective testing will disappear.

So, that is my general comment. Beyond that then in terms of specifics I think the long-term outcome for these devices has not been studied to any appreciable degree, and this makes me nervous especially when I hear statements that these are effective.

They may be effective, for instance, for a particular situation for particular time intervals, but the long-term is not there, and what concerns me actually more than that is the issue of operator dependence.

We have said that these are operator dependent. What are the data for that? Did any of the studies present data? For instance, how did this device work in the hands of this surgeon; how did it work in the hands of that surgeon? Did we have any quantification of this dependence? Did we have any plans for what kind of education or training or what have you or redesigning of the features that will minimize that dependence?

I did not see anything in the presentation and I think that to the extent that the operator dependence is a big issue, and we see, for instance, the same thing in radiology, in diagnostic radiology, we need A, the data for it, and B, we need the plans for ameliorating that type of dependence.

So, with all this in mind in terms of the classification of the devices I think whether you put them into Class B, in the second class and you ask several of these controls, in particular these prospective studies to be done, and whether you still leave them in Class III to me it is an even call.

DR. CANADY: Other comments?

Dr. Roberts?

DR. ROBERTS: I am going to take a lot of issue with the last statements that were made. I think that there is a lot of problems with the data. There is no question about that, but you know, part of that is that there is a very small patient population that we are dealing with.

No center has seen very large numbers of these, and as a matter of fact, the numbers, anybody who has a relatively large number, it is over a number of years that the data have been collected because you don't do one of these a week or one a month.

They tend to be relatively rare types of things,

and I think that a lot of the changes in the effectiveness of these devices have come across in the last 10 years with the changes in microcatheters and that kind of thing.

So, I agree. I am not disagreeing with the fact that the data aren't good, but to say that the data don't show that these are effective I think is not correct.

I think that actually it depends on how you define it, I suppose, but if you are looking at it which is the way that I define it is that this is an embolization material that the idea behind it is or the proof of it is that it blocks the blood vessel, it does that, and I think it is not really that clear.

I mean I think you would be very hard pressed to say that the study showed that it doesn't block the blood vessels.

Now, whether you say that it cures the disease process of the AVM or that you know, further therapy is needed or whatever, no. I don't know that you can actually make that point, but I think that in terms of stopping blood flow to an area these devices do that, and so, I think that they are effective in doing that and by and large I think that they are safe in doing that.

DR. CANADY: Other comments?

Dr. Hurst?

DR. HURST: I would say pretty much the same

thing. I think that we are talking about such a heterogeneous group of patients, of disorders, of treatments, of prognoses, for example. An unruptured aneurysm maybe can be treated with a combined mortality and morbidity of less than 5 percent. After rupture it is 65 percent.

So, you are always dealing with humans. There are very few or no animal models to do these kinds of studies. In many cases you are dealing with people who are very, very sick, and I think that the basic data that need to be collected or evaluated in terms of this is just what has been mentioned already.

Does this effectively occlude a blood vessel or not?

When we start to get into other questions regarding treatment, then we have to be talking about the judgment of the physician involved and really trying to practice medicine on cases that we are trying to predict all the specifics of.

So, I think that really we have to focus on whether or not it occludes the blood vessel. I think these studies would be very, very hard to do.

DR. KU: I feel that these agents should be lumped as one particular group, and I think that they probably would be beneficial to qualify for a Group II category.

I do agree with Dr. Gatsonis in that the literature is not the best, and it is probably pretty poor because there is very little outcome data overall, and in the long run that is the thing that is going to determine whether an insurance company is going to want to pay for it or not.

It would certainly be very helpful to do some outcome studies. The question is who is going to finance those studies because they are technically not easy to do, and I don't know if that is the appropriate forum for us to consider.

As far as devices I agree with what Dr. Roberts said that these devices are effective in doing what they are designed to do which is to block the flow of blood. What you do with that blockage of blood and what the risks are in doing that procedure are things that we will have to look at in the long run to determine whether the overall effectiveness of embolization is worth the risk of the procedure.

DR. CANADY: Dr. Rousseau?

DR. ROSSEAU: Yes, in response to Dr. Gatsonis's request for information regarding what is the plan of the professionals who are actually placing these devices in patients, I can say that I know that the professional association of neurosurgery in concert with the professional

associations of radiology and neuroradiology are in the process of or maybe already have published guidelines for the training of individuals who will be able to be recognized as expert in the delivery of these devices.

So, perhaps the interventional neuroradiologist could comment on the specifics of that, but I know that the societies have already responded to that request for expert administration of these materials.

DR. KU: I mean that may be something that could be addressed in the labeling of these devices because most of the practice standards or recommendations as far as training have come out within the last year or 18 months or thereabouts.

DR. CANADY: Other comments?

At this time, we are going to go over the FDA questions. I think the consensus is clearly that we can deal with them as one group. So, we are going to deal with them as one group.

Lieutenant Commander Foy has the overheads for us as we address the questions.

LCMD FOY: I will just review these again. Again, Question 4 of the supplemental data sheet for Questions 1 and 2, please discuss the proposed classifications? For the different embolization devices, i.e., coils, balloons and PVA particles, what other descriptive information should be

added to the present classification identification?

DR. CANADY: Okay, I think having had a general conversation I think there are several issues. One, the sense is that we should deal with this as one group. I think we can dispense with that, but the second one would be the issues raised about silicone and the issue raised about outcome.

DR. KU: My own personal opinion on the risks of allergic reaction either short term or long term to these devices is that you have to consider the patient population that you are dealing with. Many of these patients have a risk of permanent morbidity or death in the range of 10 percent or larger over a 1-year period.

The likelihood that they will have a severe allergic reaction either on the short term or long term is probably a fraction of a percent, so that as far as the risk/benefit ratio it would not come to me as a serious consideration overall.

DR. WALKER: Perhaps we can bifurcate the silicone and the latex because as I appreciate it and maybe one of the industry reps can correct me, the silicone that is used is simply Silastic sheet material which has been used for 30 years for pacemaker leads with no adverse effects whatsoever, whereas the latex perhaps does not to be considered separately because there is some documentation of

immunological challenges from latex.

DR. CANADY: I heard, am I correct that there is no latex balloon available now? So, we are not considering latex balloons at all, only silicone balloons?

MS. VALENTI: That is correct.

DR. CANADY: That is a safe material.

DR. EDMONSTON: May I ask if the silicone is truly high-molecular weight or is it really a mixture? Is it really Silastic or is it really a mixture with some low-molecular weight material?

DR. CANADY: Instead of interrupting you, I will remind you to please identify yourself and your affiliations?

MS. BAXTER: I am Roxanne Baxter with Target Therapeutics, Boston Scientific, and I don't know the particular answer to that question, but I can certainly find out and let people know.

DR. CANADY: Is there anything in terms of the addition of other descriptive information that the panelists would like added under this first question? Otherwise I think we have resolved this one.

Question 2?

LCMD FOY: Question 2 for Question 4 of the supplemental data sheet. Based on the literature and device registries for each of the artificial embolization devices

for which patient populations should the artificial embolization devices be indicated?

DR. CANADY: Comment from panelists? Do we want to again be lumpers or splitters?

Dr. Hurst?

DR. HURST: I would say that I am probably a lumper in this case, also, and I would say that they should be indicated for basically the indications that Dr. Tomsick had on his slide. I think the only one that I would say is not indicated is the use of PVA for aneurysms.

DR. CANADY: And probably for CC fistulae.

DR. HURST: And probably for CC fistulae.

DR. CANADY: The question I would ask just as a clarification was we discussed and referred to the use of these material for hypervascular tumors but on none of these sheets has that appeared. What is the sense of the Panel relative to -- are we being asked that question, I guess would be the first question to the FDA?

It is a usage we have discussed throughout the meetings and throughout the materials but is not on the summary sheets.

LCMD FOY: The previous studies and indications for use did have hypervascular lesions. That is your question?

DR. CANADY: That is correct, and so all of the

summary sheets --

LCMD FOY: Do you want to exclude it?

DR. CANADY: No, we do not, but it has not been included in the materials we have reviewed today. So, we should add that and make sure, at least make sure that it is included.

Other questions? Comments?

DR. WALKER: Dr. Canady, do we want to comment or ask why we have two supposedly almost identical products, and one is listed only for presurgical use, and the other manufacturer's product says nothing about presurgical only?

DR. CANADY: Sure, if you would like to ask, we will ask.

MS. VALENTI: Marlene Valenti, with Cordis Corporation. I believe you are talking about the Cordis PVA material in regard to the difference between that and the Cook and the Target, and the only reason why we went with pre-operative at that point was because we did not have long-term biocompatibility data to submit with our 510(k). That was the only reason. We could do it now at this point. We have done those studies. We just haven't gone after that indication as yet.

DR. WALKER: So, what would they have to do in order to be like their competitors, resubmit?

MS. VALENTI: Yes, we would resubmit with long-

term biocompatibility data.

DR. WALKER: So, there is no difference. You just hadn't done the work yet?

MS. VALENTI: Exactly.

DR. CANADY: You brought this up before.

Okay, No. 3.

LCDR FOY: Refer to Question No. 5 of the supplemental data sheet. Based on the information presented in the 595(i) submissions please discuss the intended use or uses and specific risks to health related to the artificial embolization devices. Please discuss whether these can be assigned to all devices or should be addressed separately?

DR. CANADY: Comments from panelists?

Yes?

DR. HURST: I would address them all together. I think that the types of risks associated with these devices are pretty much the same for all of them as are the indications, and I would suggest that we should lump them.

DR. CANADY: I would state that the specific risks as presented earlier by the FDA I think fell into the risk. There was not much disagreement on that.

Other comments?

No. 4?

LCDR FOY: Referring to Question 5 on the supplemental data sheet, from the literature, device

registries and MDRs, please discuss the risks to health for artificial embolization devices? What are the additional risks that should be described that have not been addressed by the information presented?

DR. CANADY: I don't see a lot of difference between this question and Question 4. Am I missing it?

LCDR FOY: That is Question 4.

DR. CANADY: I mean Question 3.

DR. WITTEN: It is just are there any other risks that weren't presented here that you think we should identify?

DR. CANADY: Panelists?

DR. GATSONIS: Do you need to say anything about long term or is that listed already, namely, the long-term risks or the long-term implications may have not been.

DR. CANADY: We mentioned dislodgement, recanalization which are long-term complications. I guess the only one we haven't mentioned is some immune response. So, I guess we could if the Panel wishes include that as a consideration not known.

DR. WALKER: If it is high molecular weight Silastic it is probably not worth mentioning. If it is a low molecular weight I agree with Dr. Edmonston that it ought to be.

DR. CANADY: Fine, can we put that in with that

caveat then for purposes of our recommendation?

DR. ROSSEAU: I have a question. What about the issue raised by Dr. Tomsick that we don't know about the long-term effects of combined use of PVA and focused beam stereotactic radiosurgery? We are just now starting to treat AVMs with those combined modalities, and are we going to find a lot of patients 10 and 15 years down the line who prematurely have sarcomas or other unknown tumors because of long-term toxicities with that?

DR. CANADY: From my perspective we are clearly going to find people down the road with tumors. I mean all of the literature suggests that based on low-dose radiotherapy.

DR. ROSSEAU: Are we going to find an increase or an excess incidence I should say?

DR. CANADY: Perhaps we want to phrase that that the combination of these two therapies over a long term is unclear and I think that would be a reasonable thing to do.

DR. ROSSEAU: Yes.

DR. CANADY: So, we would comment about the combined modalities with radiotherapy and their impact, and if it is low-molecular weight silicone concerns about immune responses down the road as well. Does that meet the Panel's wishes?

(There was a chorus of agreement.)

DR. CANADY: Okay, No. 5.

LCDR FOY: Referring to Question 7 on the general device classification questionnaire, please discuss whether the current preclinical testing, such as biocompatibility testing, mechanical and chemical properties testing, etc., are adequate to control the identified risks to health? What additional preclinical tests could be used to control the risks to health?

DR. CANADY: I am going to take the prerogative of the Chair to start on this one. I think that clearly the current reporting is not adequate because the MDR numbers are inadequate to my own personal experience, and I am not even a neuroradiologist.

So, I think there are a number of complications that are not being identified, and perhaps we can think about how better to identify them.

I mean we had for one device there were two complications, and I have seen two with that. So, the reporting mechanism is clearly inadequate.

So, we might, I am not sure how to best split that up. Maybe, Sally, you might have some help for us since you know the ins and outs.

MS. MAHER: I have some thoughts. I mean the MDR requirements are for when manufacturers are told about problems by the users of the products. That is when they

get reported.

I think what this question is looking at is are the devices the way they are being tested now before they go into the marketplace, is the testing that is done adequate to demonstrate the safety of them or are there new tests that need to be done, and I guess if that is what the question is, we have got 25 years' experience or 20 plus years with most of these products with the testing that they have been using in submitting their 510(k)s and it seems that they have been adequate to control the risks to public health because we can already discuss why we think the risks are pretty well controlled.

If we are looking at though are there other risks out there that we haven't heard of because people haven't written about them or told the manufacturers I don't know how best to get at that, and I guess it depends on what the FDA is getting at with this question here.

DR. ROBERTS: Maybe it is actually Question 4 where we should sort of think about we haven't really perhaps, we think we have identified what the risks are. We just don't know what the rate of the risks is, and maybe it is really in No. 4 where we want to look at the MDRs.

DR. CANADY: Certainly in the medical literature in general if you have a terrible result you tend not to publish it, and we have an MDR system that is inadequate,

not by intent but perhaps by design, and so, then the two mechanisms which we are relying on to assess are both fraught with some major holes.

MS. MAHER: It may not be, this is Sally, again, that the MDR as it is designed is ineffective. It is when the users of these products see a problem with them. Is it a problem that is related to the device, in which case they would report it to the manufacturer or is it a problem that they actually just expect to see because of the nature of the disease that they are treating, and that is the issue.

I mean I am sure everybody if they see a problem with the device itself reports it to the manufacturer.

(There was a chorus of no's.)

DR. CANADY: I think that is a nice idea.

Other comments?

DR. ROBERTS: This is a general one that I would just make to the FDA just in general and that is that I have actually reported a number of device failures. I believe I sent them to the FDA. I never heard anything back as to whether or not they got those and the fact that yes, thank you very much for sending us your problem so that at least I felt like somebody had seen it.

I know that there have been some initiatives here in terms of trying to improve the MDR, and I would just encourage that to continue.

the embolization material itself.

We are not looking at the device that is used to deliver the embolization material, but I would again make a plea to the manufacturers that they have good consistency when they say that something is one size or another size, that in fact, you know, when you put it through a catheter that says that it is going to deliver that size of a coil or particle or whatever that it really do that because I think there is no question that sometimes some of the complications that result because there is a discrepancy, and it is a very, very small discrepancy, but it is enough of a discrepancy that when you go to deliver these things they don't behave the way they are supposed to because they don't really fit, and so, again, quality control in terms of those issues.

DR. CANADY: Other comments?

The final question?

LCDR FOY: The last question, refer to Question 7 on the general device classification questionnaire. When and under what circumstances, for example, a new device or a new indication for use, is it appropriate to require clinical data, as a special control, for a new artificial embolization device undergoing marketing clearance?

DR. CANADY: Panelists? That is a big one.

DR. WALKER: It is, also, an impossible question

to answer. I am glad you didn't write that question.

DR. CANADY: Thank you very much. I wish I would have written it. Then I wouldn't have to answer it.

DR. GATSONIS: May I pose a question for the FDA? What would be a circumstance in which you wouldn't require clinical data if a new device or a new indication came through?

MR. DILLARD: Jim Dillard, FDA. There are two parts, I think to this question. The first part was depending on what your answer was as to whether or not we should be lumpers or splitters under this circumstance. If we were splitters which ones of those indications that might not be recommended for a particular type of device would you think we would need some clinical data and perhaps we have gotten through that with your discussions, since it appears that they can be lumped.

So, I think that was really that question was directed. However, I think Dr. Gatsonis, your question of if they are all lumped together, and your recommendation has been to look at really pretty much the indications that are in the clinical literature is what I heard as being reasonable indications, barring a few under some specific circumstances, then any new indication beyond those, if it was any of these devices that a manufacturer came in with an application and asked us for clearance for a completely new

indication that has never been used, even under a 510(k) situation there is a fairly good chance that we would ask for clinical data under that circumstance.

So, specifically to your question, you are right. A brand new indication for a device generally requires clinical data no matter what kind of application we get.

That was really not where this question was directly focused. It was more if you were going to be splitters then which of those circumstances that we might ought to require clinical data. So, it is not as appropriate I think now at this point.

DR. CANADY: And as long as we are talking about embolization, it really is a mechanical --

DR. KU: There might be one area that really hasn't been addressed in this particular forum, but most of the way that these embolic agents work is they occlude a vessel. There has been talk of making some of these solid particle materials partially bioreactive either by coatings or other agents to deliver chemotherapeutic agents.

I think in that type of situation they should certainly be reviewed separately.

DR. CANADY: And so we could say perhaps when the embolization's intent is other than mechanical obstruction.

DR. ROBERTS: I guess I am not sure whether this would be, I would think this would turn, let us say, I can

see like, for example if someone develops a coil that is very similar to a coil that is out there. I mean you may want to just get data in terms of what it is made out of and how it responds in the lab without having to get clinical data on that.

On the other hand, if you were to get something that has a unique let us say release mechanism or something that is very different than what is out there, because I think one of the big questions always when you are doing embolization is is something going to respond in the blood vessel the way that it does on the bench, and is the operator going to be able to let us say get that thing into position and then release it by whatever the sort of new mechanism of release is that is different than anything that there has been before.

That to me probably should have some kind of clinical data to show not that it cures the disease but in fact that you can put it up. You can release it. It releases the way that it is intended to release, and then it blocks the flow, let us say.

That to me would be sufficient. I don't think you have to say that it cures the AVM or whatever, just that it blocks off the flow, and you can release it without causing damage.

MR. DILLARD: Dr. Canady, could I ask the response

question to that because I think it is a crucial issue for us which is that point as to under that circumstance that you just described would you think a human clinical trial would be appropriate and/or necessary or could some of that information be done in an animal model if an animal model were appropriate, and if you think that might be the case, I would love to hear a recommendation of what that animal model might be.

DR. ROBERTS: If you can find an animal model that is appropriate, I think that would be fine. I don't know what you are going to use. Again, I am not saying that there have to be large numbers of cases, but I think that you need to have some kind of assurance that in fact it can be used and used safely, and I think it, also, gives you an idea which gets back to the training issue, it gives you an idea of what do people need to know about how this device works so that they can, you know, until you really use it in some kind of a real situation you are not going to know what all the problems are, and I think that this kind of gets back to some of the issues in terms of training and complications.

You know, things like coils and particularly the older coils and the PVA have been around for a long time, and so people have sort of trained other people how to use these, and whether the first person was trained well depends

on whether the next person was trained well.

Certainly with the newer devices, the GDC coil there is a much more extensive training component to that so that people who are using it, hopefully, are using it well, and I think that that is the way that medicine has gone, and I think that is appropriate, and I would think you would want the same thing for any new, unique device that came along.

DR. CANADY: Dr. Edmonston?

DR. EDMONSTON: Thank you. I am still locked into this idea of a new device, and for example, if you have a new release mechanism whether that by virtue of being in essence a new product, be a Class III automatically and go through some sort of clinical study or at least some data collection. I would feel uncomfortable, honestly, just lumping that under this Class II category.

DR. CANADY: I don't think we are dealing with release mechanisms today.

DR. ROBERTS: Let me just clarify because I think maybe or maybe I shouldn't clarify. You should clarify, but it seemed to me that just because we are putting it in Class II does not mean that there won't be the requirement in appropriate circumstances for it to basically go through 510(k) and that, also, it may require a clinical trial in order to get approval, just because it is not a PMA. It

doesn't have to go through a PMA. It still will need clinical data.

MR. DILLARD: Dr. Canady, I would make just one comment to that which is pretty much exactly what you are talking about, and the concerns that you have are exactly what we do every day in the 510(k) program which is, I mean if this helps alleviate any of your fears, but any even small device modification that could affect the safety or effectiveness and to that extent it might be a modification to the physical structure, and it might be a modification to the indications for use, but as soon as it sort of trips the button of could affect the safety or effectiveness of the product even as a Class II device the manufacturer will be submitting a 510(k) to us, and that pretty much is what we do with 510(k) as we look through it, and we see whether or not bench data alone, for example, or bench data plus animal data really demonstrates equivalence to the product that currently exists, and if some of the questions are clinical questions that can only be answered with a clinical, and maybe that is a limited clinical study, then many times we will have clinical information in a 510(k) because that is what we need to make that equivalence determination. So, that is actually built into the program and part of what we do for 510(k) if that helps.

DR. CANADY: Thank you, Mr. Dillard.

Dr. Walker?

DR. WALKER: Still on the question of new devices we heard some numbers this morning about 500 balloons per year which seems like it is down on the floor of humanitarian device exemptions. Would that perhaps be a more appropriate mechanism to consider for some devices that may come out?

DR. CANADY: I think certainly that is the option of the manufacturer in terms of their approach.

MS. MAHER: May I respond to that? This is Sally. You are right. The HDE is a method to get some products out onto the market. However, it is not the preferred method for a manufacturer to get a product out on the market because of the constraints that come with it as to how many you can sell in a year.

Let us say that it were to take off all of a sudden and you would need more, and then you would have to go back and do a new marketing application. Also, the constraints on your pricing, you have to make sure that you have all the evidence always there to show that you are not exceeding the cost of your development of it and your cost of getting it on the market, and it is a heavy burden on industry. The HDE is really designed for those circumstances when there is no other way to get the product on the market through the traditional methods.

DR. CANADY: Any other comments on the body of questions?

It not, thank you very much, Mr. Foy.

I would like to open the meeting, again, to public comment.

I see no hands. Would industry like to make any additional comments?

It not, then we will move on to the completion of the reclassification questionnaire.

Ms. Marjorie Shulman from the Office of Device Evaluation, Classification/Reclassification Coordinator will assist us in this form that we know is from the Office of Budget and not the FDA.

It is just like the neurosurgeon saying, "The neurologist really did this one."

For the public you will appreciate why I say this as the form goes up.

I think the first of six questions we can answer fairly quickly. I am going to give a suggestion to the Panel and see if there are any objections. The first question is is the device life saving, and we will say, "Yes." Actually yes for all but question 3. Would you review your forms and see if there is disagreement.

FDA STAFF: Just as a matter of housekeeping everyone please write your name on the top of the forms.

MR. DILLARD: Dr. Canady, if I may, a little bit of a clarification on that. What we would like to have, we would like to make sure that we have each individual Panel member's name on the top of one of these. So, in fact, you participated. So, that would be greatly appreciated, but to the extent of having to fill out, each one of you having to fill it out identically, actually you don't need to do that, but what we would ask is if there is something different for consideration that doesn't make the final form that you would like us to consider but not necessarily be a special control, quote, unquote, an additional kind of control but something you would like us to consider, we would like you to note that on the form, and we would be happy to gather those up.

DR. CANADY: Let me make sure I understand. We are going to do one composite form and then individual forms?

MR. DILLARD: I think, Dr. Canady, you should keep the official form, and then what Margie will try to do is keep consistent with that so that everybody else can be in agreement.

DR. CANADY: Okay, very good.

Dr. Edmonston?

DR. EDMONSTON: If we discuss this, and we are in agreement with various items, can we leave that blank on our forms and just the ones that we --

MR. DILLARD: Yes, you may.

DR. CANADY: All right. Are you going to read them for us?

Question 1, are there any issues, I think some of it we can read ourselves, hopefully at this level. No. 1, the composite I marked as yes. Would that be an accurate reflection?

(There was a chorus of agreement.)

DR. CANADY: No. 2, also, yes. Is that an accurate reflection?

(There was a chorus of agreement.)

DR. CANADY: No. 3 is no.

(There was a chorus of agreement.)

DR. CANADY: No. 4 is yes.

(There was a chorus of agreement.)

DR. CANADY: No. 5 is yes, and No. 6 is yes.

Now, under Question No. 7, I think there will be probably more discussion.

What I have listed is postmarket surveillance. The question of manufacturing quality controls of particle size in particular and monitoring of the combined use of the embolization material with radiotherapy.

Any other comments or things that we would want to add?

MS. MAHER: Dr. Canady, this is Sally. I would

like to question what benefit we get from postmarket surveillance for products that we have already had out on the market for 20-plus years?

DR. CANADY: My sense was that reflecting the concern that there is no good outcome data that is available, even though the general consensus was that it was a good product.

MS. MAHER: You are actually thinking of postmarketing surveillance that we should be asking or recommending that people start looking at collecting outcome data on this?

DR. CANADY: Yes. I am open, this is conversational; this is not --

MS. MAHER: All right.

DR. CANADY: The first ones I thought were clear. These aren't clear, I don't believe.

MS. MAHER: I am just not sure that postmarket surveillance, and Jim, maybe you can explain better what is meant by the FDA when they say, "Postmarket surveillance" there.

DR. CANADY: Let me have someone explain that to you.

Would you come to the microphone please, and identify yourself and your role at the FDA?

MS. SOLOMON: I am Rachel Solomon from the

Postmarket Surveillance Studies Branch.

DR. CANADY: That seems appropriate.

(Laughter.)

MS. SOLOMON: In the Division of Postmarket Studies. First of all, I think if it were determined that we would want to request postmarket surveillance for these devices it would be important to first of all identify what the issues are that are to be addressed and why it was necessary to use postmarket surveillance to address those issues.

It is important to emphasize that postmarket surveillance studies should not be used as a substitute for premarket data. If this were a device that were going to be reviewed under a PMA then a mechanism like a postapproval study would probably be the most appropriate mechanism for collecting postmarket data.

If it is a 510(k) there would be some benefit of postmarket surveillance if we could ensure that the question is targeted to some specific unanswered question that exists that was not answered by the premarket data.

It would, I think be necessary to consider factors that would affect the data that would be collected under postmarket surveillance, how the data would be used, whether it would be feasible to collect postmarket surveillance data and how useful they would be.

So, some of the practicalities of postmarket surveillance data would be important considerations, and there are, in addition there are some other mechanisms that could be used in the postmarket arena that could answer some of these questions. For example, the MDRs that were discussed earlier might be able to provide some of the data that you might be looking for.

Manufacturers as well as user facilities are required to report any incidences of serious illness, injury or death from devices. So, there may be other mechanisms that might be more appropriate for postmarket data collection, and we would need to really consider a very targeted question if we were to call for postmarket surveillance studies.

DR. CANADY: Perhaps you can help guide us in what would be the most effective method. As I understand it the Panel has two concerns. One is the sizing of the particles to make sure that they are consistently at the appropriate size and two, the use of this procedure in combination with particularly stereotactic radiation or gamma knife. How would you suggest that would be best looked at?

MS. SOLOMON: It seems that these are questions that might need to be addressed in the premarket phase, but if there were something that the premarket data could not answer about those issues, then we could --

DR. ROBERTS: Unfortunately, I think we are at a little bit of a disadvantage because this actually isn't premarketing anything. This is a reclassification. So, I think that the time for having done that has come and gone.

I am not sure. I mean I agree I think that there is an issue in terms of the use of radiation in this area. I am not sure of the best way to do that, but I am not sure that -- the particle size I think is a manufacturing --

MS. SOLOMON: That is a quality control issue.

DR. ROBERTS: We don't have to worry about surveillance for that, but --

DR. CANADY: So, then are we confident that the material and information available now is sufficient or do we wish any additional?

DR. KU: What does performance standard apply to? Is that performance standard of the person performing the procedure? Is it operator training or is it something else?

DR. CANADY: It is the device.

DR. KU: Just the device, okay. Are there ways of --

MR. DILLARD: Jim Dillard. Performance standard here in this context, and it is always very confusing really refers back to the kinds of performance standards if you look back to 1976, a product that was designated as Class II

at the time, what a panel was recommending is that a performance standard be developed for the product. What happened was over the last 20 years we have never developed one or gotten pretty close to finishing one, and as you saw earlier 60 percent of those 1700 devices are Class II devices. So, we were not very successful at getting mandated government performance standards together.

So, Congress in 1990, said, "Okay, you ought to keep doing what you are doing." So, we broadened that to special controls, okay? So, that concept of special controls, also, includes consensus and industry standards, but those are not performance standards per se.

If you think a performance standard should be developed by us to control for some risks or all of the risks, and that would be the only thing that would control for the risks, then performance standard would be appropriate, but if the agglomeration of the other standards available really get you there I would say that that is probably a better recommendation at this point, a more reasonable one certainly from the agency's perspective.

DR. CANADY: I would like to go back very briefly to Question 5 where the consensus is going to change it to no because yes would take it automatically to Class I, and I don't have the sense that that is where the Panel would wish it to be.

Okay, so, is the Panel's feeling that no additional information is needed for Question 7? That is my sense of -- Dr. Hurst?

DR. HURST: I think that probably no additional information is needed.

I think that it is certainly a very good question. I think that we do as has been mentioned have a lot of data on this. It sounds like trying to do a postmarket surveillance may not be the best way in terms of the logistics to get that information, and certainly over the time period that is of interest which may be 20 or 30 more years the medical literature is certainly going to probably be sufficient to report these patients and indicate if there is any significant change in the outcome with the combination of therapies.

DR. CANADY: It has been suggested to me that we should list something. It can be something such as labeling. It doesn't have to be a major study.

MS. MAHER: I did hear earlier, this is Sally, again, you were talking about wanting some, you know, that this needs to be used by experienced surgeons.

DR. CANADY: Right, that is why I was saying that labeling would be a place for --

MS. MAHER: One of the things that we talked about is that the labeling should specifically call out that this

device should be used by experienced surgeons who have been trained in the use or --

DR. CANADY: More than experienced, specially trained, I think we should say.

Dr. Ku?

DR. KU: I would agree with that very strongly.

DR. CANADY: Okay, biocompatibility for the implants, that is just a routine special control. It is not an additional study, and sterilization controls which are currently routine.

MS. MAHER: So, all of the routine ones?

DR. CANADY: All of the routine ones, plus the labeling regarding trained use.

No. 8, comments?

DR. WALKER: We have said that a regulatory performance standard is not needed. That is where we came down. So, it is a blank.

DR. CANADY: Not applicable, and it is my interpretation that the Panel wishes to reclassify this to Class II?

(There was a chorus of agreement.)

DR. CANADY: We did not divide three. So, we don't need 10. The design controls go with any Class II. So, we will list that, but that would be routine.

No. 11a, if we could review that? Does that

follow from No. 10? The way this looks it refers to that, but it doesn't list that. Oh, I think this is to make it a prescription. We think it should be a prescription device, correct?

(There was a chorus of agreement.)

DR. CANADY: So, it is to be no followed by a practitioner, licensed, with specific training.

Okay, I am going to summarize No. 11 that it should not be a generally available device, that it should be used only with written or oral consent of a practitioner and that person should be specifically trained.

Does that meet the Panel wishes?

(There was a chorus of agreement.)

DR. CANADY: Any other questions or comments?

Now, for another wonderful form, supplemental data sheet.

DR. WITTEN: Dr. Canady, could I just ask the Panel to comment on what kind of special training they would recommend?

DR. ROSSEAU: I will comment on that for neurosurgery, and that is that these guidelines have been developed and published in conjunction with the Society for Interventional Radiology and Neuroradiology after extensive deliberation, and I think there is widespread consensus that they are adequate.

DR. CANADY: We have a little bit of a problem because we have two schools. We have those people who have come into the process prior to the establishment of formal fellowship which I think is one of the requirements, recommendations within the new guidelines, and so, at this point in time the vast number of practitioners may or may not meet those guidelines.

Dr. Roberts?

DR. ROBERTS: Of course, there have been new certification examinations for interventional radiology where most, many anyway practicing interventional radiologists will have had that certification which you know, even if they didn't have a fellowship they have actually gone through, they have gone through and taken the exam. I don't know whether that really helps or not. That is, also, true of neuro.

DR. HURST: Could we say formal training in interventional or neuroradiology? I mean that would probably cover the vast majority of people who are involved.

DR. CANADY: Okay, and I think the guidelines are probably going to be a change in guideline. It is a consortium. So, it is a little difficult to refer to it. So, I think that seems a reasonable way.

DR. ROSSEAU: I think it is appropriate for the professional societies to establish the standard of training

requisite for use of these devices.

DR. KU: Would it be worthwhile for the FDA to work with certain of these organizations?

DR. CANADY: That is where the turf issue comes in. That is why I say that it is a consortium. So far there has been a consortium of the --

DR. KU: Right, to work with the consortium to develop a general guideline.

DR. CANADY: I guess my sense is that there is a recognition now that it shouldn't be a generally available procedure and that those guidelines and those steps and processes are in place.

DR. HURST: They are not formally accomplished yet, I think.

DR. CANADY: But they are in place now. We have people who are moving to make -- and certainly in most institutions now it is a separate set of privileging.

DR. ROBERTS: And I think as new devices come along those will probably have some kind of a training mechanism built into the ones that are more complicated, I suspect.

DR. CANADY: Okay, the supplemental data form. Go ahead, I will let you spearhead this.

Three is yes. So, that would be aneurysm, arteriovenous malformation, AV fistula and hypervascular tumor.

Any other thoughts?

DR. KU: People have used some of these devices for things such as refractory, medically refractory epistaxis and, also for as the main area in the CNS area, I believe used it for other types of things, but that might be a consideration.

DR. CANADY: My thoughts are that since that wasn't presented to us; no data have been reviewed; it wasn't an industry request, that I would be inclined not to include that. What are the Panel's thoughts?

DR. ROBERTS: I think actually there was literature on --

DR. CANADY: It was in the literature but not in the industry request or indications they listed.

Would industry like to comment on that?

DR. ROBERTS: Somebody request it because it does occur. I mean it is in the head and neck area.

DR. CANADY: Nobody wants to comment. Why don't we give the specific indications and other vascular abnormalities?

DR. ROBERTS: Okay, that sounds good.

DR. CANADY: Identification of risk. I think we have done that now in terms of the list that was presented by the FDA actually.

PARTICIPANT: That would be hazards?

DR. CANADY: Yes, I believe so, hazards to health. I think that all is listed within that context. Again, classification would be II.

Priority. I am not sure what the priority means. Could someone clarify that for me?

FDA STAFF: Priority is to class.

DR. CANADY: Medium priority.

FDA STAFF: High, medium or low?

DR. CANADY: Medium.

(There was a chorus of agreement.)

DR. CANADY: Okay, under 7 do we want to explain why we think it should be Class III rather than Class II, thoughts of the panelists?

MS. MAHER: Based on the information provided by the petitioners.

DR. CANADY: I like that, a woman of few words.

Other panel thoughts?

DR. ROBERTS: Length of time that these have been in use and the experience that has been gained with them or the known experience.

DR. CANADY: Okay, and the consensus of clinical efficacy in a difficult population?

DR. HURST: It has been established as safe and efficacious with a lot of data.

DR. CANADY: Good, and we can call back the regs

and say, "Within the special" --

No. 7. Oh, we have done that. No. 8. I think based on the clinical literature and the clinical experience. I know why they don't like this form. It seems somewhat repetitive.

Restrictions, again, would be a trained professional user and a prescription. It is now Class I. So, we can skip No. 10. Again, it is not clear that we need to add anything to 11. Can someone clarify that one for me?

DR. EDMONSTON: It is regarded as subassemblance or these accessories made by other manufacturers or --

DR. CANADY: Mr. Dillard is going to enlighten us.

MR. DILLARD: Thank you, Dr. Canady.

I think 11 what we are asking for there is that if there is either a component or subassembly of the device or the device itself, if you know of a recognized reasonable consensus standard or otherwise that you think would be applicable and/or appropriate to any part of the device or the device as a whole we would enjoy a recommendation here as to whether or not you think it would be appropriate for us to use that as a special control, consider it; where does that factor in in terms of your thinking, if any exist. It doesn't mean that any exist, but it is an open-ended issue.

DR. CANADY: Panelists, I am inclined to say, "No."

DR. HURST: I am not sure. It seems like this

might be designed for the kind of implant like a pacemaker.

DR. CANADY: Sure, yes.

Other comments?

Other questions?

If you take a minute to review your classification sheet and the supplemental data sheet and make sure there are no concerns or any additional thoughts before we actually vote on our recommendation.

The Chair will entertain a motion to accept the classification worksheet as filled out.

MS. MAHER: So moved?

DR. CANADY: Second?

DR. HURST: Second.

DR. CANADY: It has been moved and seconded that the neurovascular embolic devices be classified into Class II.

All in favor?

(There was a chorus of ayes.)

DR. CANADY: Opposed?

(No response.)

DR. CANADY: It is the recommendation of the Panel that these devices be classified into Class II with the routine special controls, design control, labeling, sterilization and biocompatibility.

Any comments?

DR. GATSONIS: I abstain from that. I have a whole bunch of other things that I would add to special controls.

DR. CANADY: Other comments?

DR. KU: Could you mention them?

DR. CANADY: Yes, go ahead.

DR. GATSONIS: I think there should be postmarketing surveillance for untoward effects. I think there should be a standard defined with FDA put on how operators are going to be trained for these types of devices. I think there should be patient registries. I think there should be rigorous studies of efficacy and effectiveness, and I think there should be rigorous studies for long-term outcome. All of these I think should be part of the special controls.

DR. CANADY: Comments from other panelists?

DR. EDMONSTON: I would tend to agree that there should be some form of surveillance with regard to long-term risk.

DR. CANADY: The Chair will entertain an amendment to those issues. Would you like to --

DR. EDMONSTON: I think based on the reaction before we may as well cut to the chase.

DR. CANADY: Okay, we give you every opportunity.

If that is the case, I believe that is the end of the business for this Panel today, and we will entertain a

motion to adjourn.

DR. WITTEN: Before we adjourn I just would like to thank the Panel and in particular your Chair, Dr. Canady and, also, the members of industry and the public and the FDA who participated in this session, and we especially appreciate your hard work. We know you have come from some distance to help us out on these kinds of issues, and I just would like to mention that we appreciate your hard work.

DR. CANADY: Thank you.

(Thereupon, at 3:08 p.m., the meeting was adjourned.)