DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

PUBLIC HEARING ON:

FDA REGULATION OF COMBINATION PRODUCTS

Monday, November 25, 2002

9:00 a.m.

DoubleTree Hotel
1750 Rockville Pike
Rockville, Maryland

Panel Members

Mark Barnett, Moderator
Dr. Murray Lumpkin
Linda Skladany
Dr. David Feigal
Dr. Kathy Zoon
Jim Morrison
Ann Wion
Mark Kramer

C O N T E N T S

P R O C E E D I N G S

MR. BARNETT: Okay, folks, I think it is time to get the meeting underway. I want to welcome you to this public hearing on FDA's Regulation of Combination Products. I am Mark Barnett of the FDA and I will be serving as your moderator today.

With me on the panel are: Dr. Murray Lumpkin, FDA's Principal Associate Commissioner; Linda Skladany, FDA's Associate Commissioner for External Relations, will be joining us in just a few minutes; Dr. David Feigal, Director of FDA Center for Devices and Radiological Health; Dr. Kathy Zoon, Director of FDA Center for Biologics Evaluation and Research; Jim Morrison, the Ombudsman at FDA Center for Drug Evaluation and Research; Ann Wion, FDA's Deputy Chief Counsel; and Mark Kramer, who is Director of the Combination Products Program within the FDA's Ombudsman's Office.

Let me first briefly describe the issue we are going to be talking about today and then let you know something about the format for this meeting.

Basically, we are here to listen to your

views about how FDA should regulate combination products, that is, those that contain a combination of drugs, devices, or biologics. More specifically, we want your views on how FDA should decide on which FDA center should be assigned these products, how this choice should be made, what kind of premarket applications are most appropriate, and what approach should be used regarding manufacturing regulations and adverse event reporting.

Both the FDA and the regulated industries have focused a lot of attention on the issue of assignment, that is, which FDA component should have regulatory responsibility for various types of combination products, and that is not an easy question to answer.

The law requires that the decision rest on the primary mode of action of the combination products in question, but for many products, this may not be an easy question to answer and it may not be clear.

This isn't the first public meeting we have had on this topic. Many of you know that in June of this year, we convened a meeting to discuss one particular type of combination product, those

that contain living human cells in combination with a device matrix, and those products are used for wound healing.

The key issue there, of course, was whether these products ought to be regulated by the Center for Biologics Evaluation and Research or the Center for Devices and Radiological Health, in other words, as biologics or medical devices.

Now, with this meeting, we are expanding the discussion to include any and all combination products and the discussion topics are broader in scope, but as before, we are interested in getting the views of as wide a variety of stakeholders as we can. We are thinking about researchers, clinicians, professional groups, trade groups, manufacturers, consumers, and to be sure we get these views in a consistent and comprehensive way, the Federal Register document that announces public hearings laid out seven specific questions for you to consider.

I assume you all have copies of that, so I won't repeat the questions, but let me quickly summarize what they are. The first question addressed the types of guiding principles FDA should use as it revises the existing Intercenter

Agreements on which centers regulate various combination products.

The second question addressed what factors FDA should consider in determining the primary mode of action of a combination product, and where that is not certain, what other factors should be used.

The third question addressed how the FDA should determine which premarket review mechanisms are most appropriate for various combination products.

The fourth question addressed how FDA should determine whether a single application or separate applications would be most appropriate for a given combination product.

The fifth question addressed which manufacturing regulations are most applicable for a combination product.

The sixth question addressed how FDA should decide which adverse event reporting system is most appropriate.

The seventh question asked for other comments applicable to combination products.

Eleven people have signed up today to speak in this room and to help answer these questions, and we are going to hear from them

first.

If you are signed up to speak, remember you have got to leave two copies of your presentation at the registration desk. By the way, some of the scheduled speakers have brought extra copies of their presentations or slides, and if so, you will find those out at the registration desk.

When the scheduled speakers are done, we are going to open the floor to anyone else in the room who may wish to address these questions. You will notice I said "these questions," and that leads me to the first of two limitations we are going to impose today.

The first is that we are going to address only combination products. That is the purpose of this hearing, so we are not going to allow questions about other topics or other kinds of products.

The second limitation concerns time. The time for each speaker, as shown on your agenda, is the time that the speaker requested, in other words, we didn't cut anybody's time. So, I am going to ask the scheduled speakers to stick to the times shown on the agenda, so that everybody can get a chance to speak and so that we can adjourn on

schedule.

I know that some people have told us that they want to leave here on time this afternoon, so in order to keep us on time, I am going to give you a gentle warning when you have two minutes left to speak, and then I will ask you to stop when your assigned time is up.

One more piece of housekeeping. We are providing audioconferencing for people who couldn't attend this meeting in person, and as a result, we estimate that well over 100 people are listening in to us this morning. For technical reasons, these folks can't make oral presentations or ask questions, but they can, like everybody else, submit comments or questions electronically or in writing up until January the 24th, and that is explained in the Federal Register document.

Also, we are going to provide a transcript of this meeting on the web address that is shown in the Federal Register announcement.

This is our game plan for today's meeting. I want to stress again that if you are in the audience today and you aren't going to speak or if you are listening in, please do submit comments to us in writing. That docket will be open until

January. We really do want to hear from you.

Before we call on our first speaker, let me ask Dr. Lumpkin if he has a preliminary comment to make.

DR. LUMPKIN: Thank you, Mark, and I thank all of you for being here today. On behalf of Dr. McClellan, who is in Texas, and Dr. Crawford, who is in Europe, and the entire senior leadership team at FDA, we really would like to thank you for taking time out of your schedules, particularly this holiday week, for joining us here to give us your perspective on these very challenging issues regarding the regulation of combination products.

As those of you in the audience know perhaps better than anyone, combination products, by their very nature, are some of the most innovative and some of the most promising new medical therapies that we have, and yet they have also historically been some of the most challenging when it comes to figuring out what is the best way to oversee them from a medical perspective, from a patient access perspective, and from a legal perspective.

As many of you know, the agency has struggled with this for a long time. In fact, it

was interesting this morning I was talking with Jerry Halperin from FDLI, and he was reminding me of some of his experiences here when he was at the agency back at the time of the Medical Device Amendments, and talking about the discussions they had on whether a band-aid that had mercurochrome on it was a drug or a device.

I think that perhaps a quarter of a century later, if you asked three people, they would probably still give you three different answers. That is about where we are with this issue as most of you know.

One of the things that we have tried in the past year to help make the issue of policy development perhaps a little easier, a little more efficient, and a little more transparent is the creation of what is called the Combination Products Program in February of 2002, which at this point in time is part of our Ombudsman's Office.

But as all of you know, too, we have had a great deal of congressional interest in this particular topic. In the latter part of this year, there was specific reference made to combination products in the new Medical Device User Fee legislation that Congress enacted and the President

signed recently.

One of the things that is in that particular piece of legislation is the requirement that the agency establish within the Office of the Commissioner, an Office of Combination Products, and the dealing for establishing that is Christmas Day.

We, at the agency, obviously are working extremely hard to meet that particular deadline for getting that office established and then even more than that, obviously, getting it up and running and doing the things that Congress has told that it needs to do.

For those of you that are not familiar with that particular piece of legislation, there really are six specific duties that Congress has assigned to this new office. One is to assign the center that will be reviewing the product and overseeing the product once a determination is made that, indeed, the product is a combination product.

Secondly, is ensuring the timely and effective premarket review by overseeing the timeliness and coordinating reviews involving more than one agency center, but let me make it clear this office is not going to be doing the reviews.

The reviews are going to continue to be done in the centers where the technical expertise resides. This will be more of a coordinating function as far as this office is concerned.

Number 3 is ensuring the consistency and appropriateness of postmarketing regulation.

Number 4 is dispute resolution.

Number 5 is reviewing and updating agreements, guidance, or practices specific to the assignment of combination products.

Number 6 is issuing required reports to Congress on the impact of this office.

As you can see, obviously, the timing of this meeting is very critical to the establishment of this office. Many of the ideas that we hoped to hear from you today, we also believe are going to be critical for this office being able to fulfill the mission that Congress has given it.

So, for many reasons, this is a very timely meeting for us in the Office of the Commissioner and within the various components of FDA. Again, on behalf of Drs. McClellan and Crawford, I would like to thank you again for being here and sharing your time and ideas with us. We look forward to hearing from you.

Thanks very much.

MR. BARNETT: Thank you, Dr. Lumpkin.

Let's get in now to our discussion and our first speaker is Dr. Barbara Boyan of the American Academy of Orthopaedic Surgeons.

Dr. Boyan.

American Academy of Orthopaedic Surgeons

Barbara D. Boyan, Ph.D.

DR. BOYAN: Thank you very much for giving us this opportunity to speak with you. I represent the American Academy of Orthopaedic Surgeons. I am also a professor at Georgia Tech in Atlanta, and I am Deputy Director for Research for the Georgia Tech Emory Center for the Engineering of Living Tissues.

[Slide.

The Academy would like to make it clear that we are highly committed to quality care in patient safety initiatives, but we do have some suggestions that we would like to make to you about the regulation of combination products.

It is important in our mind that there be a decrease in the regulatory burden to bring these products to market and in the context of everything being safe, we would like to put these ideas

forward to you.

[Slide.]

These products obviously I think we are all in agreement they provide unique challenges to the FDA and under the current scheme, it is going to be difficult to get products to market in a timely manner.

One of the problems in our field has been that the large startup capital is in short capital, and these companies have to make their regulatory path clear to them early on in their development of the product, so that they can get there in the fastest possible way.

When they do get the products to market, their market potential is much smaller than would be experienced in the drug industry, and the possible exception right now would be cartilage substitute, but then there it is not clear just what the market is going to bear, and there are certainly issues related to third party payments that will make the ability to put these products on the market much more difficult.

It is of incredible importance to our industry right now that we face these problems in a timely way, because two tissue engineering

companies just in the last month have filed for bankruptcy. Part of the reason why they did so is because the regulatory path changed midstream and they were set up under one regulatory set of guidelines and discovered that they were dealing with another regulatory set of guidelines.

Now, we are not trying to put the blame on FDA because certainly there are other reasons why these companies filed for bankruptcy, but the reality of life is the products have to get into the market, they have to get there in a way that is economically viable for the industry.

So, this is what we would like to propose to you. One thing that we think is critical, and I think you certainly are on the team with this, is that there be a team approach to getting these products reviewed, but we are asking for this to go one step further than it presently goes - that all of the combination products be reviewed in a multidisciplinary way, that there be material scientists, biologist, clinicians, and engineers all working as a team, not independently, first one review, then another review, a consult here, a consult there, but that the team be established when the product is assigned and that team work

together and function as a team, and also that this team function together in the form of homework, which I will get to in just a minute.

We would suggest that the reviewers be kept to an odd number, so that we can get a clearer view of whatever the team has determined is the correct approach to the take to the regulation of a product, and also that when a homework assignment is made, that the sponsor have an opportunity to provide additional information within the FDA packet that goes out to the outside reviewers.

[Slide.]

We suggest right now for these kind of products that we focus on safety rather than effectiveness. For many of the products in orthopedics, effectiveness is going to take 10 to 20 years to establish that new age product is, in fact, going to be better than or worse than a device that might now be in practice that would remove tissue rather than try to reconstruct or repair or regenerate tissue.

We again stress that there be a single and consistent regulatory pathway over time. Our feeling right now is that in many ways, the device agency or the device center would be the

appropriate place for many products in orthopedics because the surgeons use them as surgical devices.

The law says mode of action, and we would like you to remember that many of these products are used as devices even though their mode of action may include a biologic component that acts in some ways like a drug.

[Slide.]

So, for many of our products, the mode of action then falls into one of three categories. One is that these products promote osteogenesis, which we define as the cellular elements that either come from the host or from the tissue engineering product, which survive transplantation and synthesize new bone at a recipient site. This could also be applied to cartilage or ligament.

[Slide.]

The concept of osteoinduction is that there be new bone that is derived because of some active recruitment of cells due to something in the combination product that causes cells to do something they wouldn't have otherwise done. Maybe they become osteoblasts or they undergo something that is embryonic-like in its formation like new bone formation.

This is facilitated by the presence of growth factors and things like the bone morphogenic proteins, which is a combination product, but one that while it may act as the drug, the BMP may act as the drug, in some ways the primary way that this product would be used is as a device.

Also, we have many products that would fall under the category of osteoconduction, and these are where something in the combination device allows for bone to form on a pre-existing scaffold that is part of the device.

Again, there will be a component of the product that would be drug or biologic or something that might fall into the biologic category through its mode of action, but is definitely treated by the surgeon as a device, managed by the surgeon as a device.

[Slide.]

So, we ask again now that I have covered that issue and you are clear on where we stand on that, I would like to turn to a little bit of more global view, and that is that we ask that CBER and all of the centers at FDA work with the standards organizations in an active way.

CDRH has been very proactive in working in

this format and we ask that CBER take an active role in this format, as well. These are the standards that are going to determine how these devices are produced in industry and that if we can incorporate these standards into the regulatory process, it would facilitate everything all the way around, one set of standards that all of us can use.

[Slide.]

We ask that you create an advisory panel, and I think that is what we are here for right now, that is panel have both device and biological expertise and that they work side by side in the review process, not independently, but side by side, that they teach each other each other's language.

Finally, that we consider the method of use, as well as the primary mode of action, in determining where these devices are regulated. We remind you that the tissue-engineered medical products are not the same as drugs or biologics. They are something new and different.

[Slide.]

We are definitely supporting a patient safety movement, and we support the legislation

that was introduced in Congress that will help encourage nonpunitive approach reporting, and we encourage the finalization of the donor suitability and good tissue practice regulations.

[Slide.]

Many of you can read what is here, but for the people that are listening, we suggest that the FDA work with experienced clinicians to define the term "adverse event" for this kind of product, that we feel strongly that the FDA's interpretations of adverse events is too broad, and that for combination products, users are not going to readily understand the regulatory class.

The user doesn't know and is not educated to know that it is important that these things get reported properly, so there needs to be an education component in what the FDA does.

Finally, we feel that the FDA mechanism that is presently in place is not interactive, and we would ask that you consider ways of improving that.

[Slide.]

Our general principles are that the combination products, the regulatory path should be consistent, it should be predictable. There should

be FDA accountability. We ask again that the rules not change midstream. It is very difficult for these companies, many of which are small companies, to change midstream.

They set up their company on a regulatory path and they need to have some sense that it will stay that way while they go through the regulatory process, and we promote the idea that there be one application, not two, and that for many of our products be managed through CDRH and ultimately we would hope through an agency at the FDA that is now developed to handle combination products in a global way.

[Slide.]

We look forward to working with the FDA on bringing new products to marked and ensuring patient safety. We appreciate the chance to speak with you in this open public meeting and I would like to thank you.

MR. BARNETT: Thank you, Dr. Boyan.

Our next speaker is Dr. Paul Goldfarb of Genetronics.

Genetronics, Inc.

Paul Goldfarb, M.D.

DR. GOLDFARB: I would like to thank the

panel for allowing me to speak.

I am a surgical oncologist in private practice in San Diego. I am on the full clinical faculty at UC/SD as a full professor, a teacher at the Navy Hospital. I have ben president of the Cancer Society of both California and San Diego and on the National Board.

I have worked for the last several years with several small biotech companies and medical device companies and when the opportunity came up to present, I wanted to take the opportunity because of some of the problems and frustrations that we have had both as a clinician using these products and working with the company in trying to develop them.

[Slide.]

As a sign of my age, I thought I felt safer using overheads than trusting myself to a computer, but I was able to put them up upsidedown.

Our impression, my impression I guess as a surgical oncologist using these devices is that right now the way it works is the product comes in, specifically, I work with a company right now, Genetronics, but I will try to keep it more generalized, focusing on management of surgical

patients, the mode of action is defined by the agency which, as I understand it, the mode of action is what is the active part of the product.

It then goes to the FDA center that is considered appropriate for that, and then based on demonstration of a clinical benefit, the product then gets approval.

[Slide.]

I think that there is a disconnect in some way to how we, as clinicians, look at these phrases, and I think how people at the agency look at it, and that has been part of the problem.

So, certainly from the agency's perspective--and I apologize to the people on this side, because I don't know if you can see this--but currently, the mode of action is determined by the principal active agent.

It is my simple approach as a surgical oncologist that the way we ought to think about it is the mode of action ought to be looked at from the patient's perspective, and not the device's perspective.

So, if we think of what do these drug-device combinations do to people, then, everything either could be broken up that has a local effect,

a regional effect, or a systemic effect.

So, specifically, with Genetronics' device, we have a device that puts bleomycin into a tumor cell, it destroys the tumor cell, and has no other effect on the body than that, so that is truly a local effect that is no different than radiofrequency ablation.

There are products out there now that carry drugs to the liver, and we put drugs into the liver, they have no systemic distribution, it only works in the liver, it only works in the single organ.

You could then take the same technology that Genetronics has and you could put a gene into a muscle and i would then create a protein that would circulate through the body, so would have a systemic effect, but I think in my world, this is the logical way of how things actually work.

I think if we were more cognizant of that, it would be more easy to create a strategy for how to then evaluate products.

[Slide.]

I think what we need as clinicians for the agency to do is to assess the therapeutic effect of the products we use and, in a sense, this speaks to

what we heard from the people in the Orthopaedic Society.

The therapeutic effect needs to be assessed on a mode consistent with what the action is. If it is a local effect, then, we need to look for a local effect that we measure. It should be assessed in relationship to other technologies that have a similar action regardless of whether those other technologies are devices or drugs.

So, for instance, if this Genetronics device goes through as a drug, but its effect is to destroy tissue locally, then, its effect really is much more analogous to radiofrequency ablation than it is to cisplatinum that treats head and neck cancer, so I think cognizance of that has to be taken into account.

[Slide.]

This is where the talk sort of drifts open to more personal views. I think when I have been at a meeting with the agency and when I have discussed it, it seems that the issue of clinical benefit comes up in all of the discussions.

As a surgeon, I would say the clinical benefit is an idiosyncratic experience. It is the patient and the physician deciding what is in the

patient's best interest in that individual setting, and that I believe that it is difficult to universalize that.

I think much of the problem that we have had in defining the clinical benefit of new technologies is because it is hard to define even in clinical practice what is a clinical benefit that extends over large populations of patients.

I think what we can't define is effectiveness. By that, I would mean if a product comes to me for me to use as a surgeon, I need to know that what the company says that product does, is what that product does. So, we look to the agency to validate and confirm that if a company says something does something, that that product really does it, and then based on that information, I use that information to help the patient decide whether that is in their best interest. That would be the distinction that I draw.

[Slide.]

The other issue that I would bring up is in the review process right now, I think there is not sufficient attention paid to the fact products should be looked at by a group of physicians who are going to be using that product in their

practice, so again specifically, if we have a product that does a local ablation of a tumor, that is going to be something that is going to be done by surgeons more likely than not.

So, to have a product like that reviewed by medical oncologists, the benefit that would be apparent to a surgeon may not be apparent to a medical oncologist, and I apologize to any medical oncologists who are here, but it is just a difference in perspective and a difference in view, and I think that that flows over into how we use these products.

At the current time, I believe there are no surgeons who sit on Oncology Drug Advisory Committee, and this is not to be perceived as an offer or a request to take that position.

[Laughter.]

DR. GOLDFARB: Actually, I was waiting for the person to say are you now or have you ever been. I guess you have to be of a certain age to appreciate that.

[Slide.]

I think that the way I see the review process and the way I would see a change over time is that the mode of action is what you need to

decide which center this product goes to, and I have no problem with that, but I think at that time we then make a second assessment of mode of action from the patient's perspective.

Then, once we decide that this is a local effect, a regional effect, or a systemic effect, then, the demonstration of effectiveness that we want would be consistent with that view regardless of which center was doing the final evaluation.

I think to my mind as a surgeon, this would be the more logical approach and I think has to take into account, and I think many of the problems that we have had, have been this confusion.

I want to thank you for allowing me to speak. It has been an education for me and I have certainly enjoyed it, and I certainly look at this as a first step as an ongoing process.

Thank you very much.

MR. BARNETT: Thank you, Dr. Goldfarb.

Our next speaker is Dr. Guy Chamberland with Angiogene, Inc.

Angiogene, Inc.

Guy Chamberland, Ph.D.

DR. CHAMBERLAND: Good afternoon, ladies

and gentlemen. My name is Guy Chamberland. I am the Vice President of Regulatory Affairs and Drug Development at Angiogene, Inc. Angiogene develops unique drug-device combination products that increase the success rate of vascular interventions.

[Slide.]

The topics I wish to address today are the premarket review mechanisms that a mixed and regulatory approach should be applied and orphan designations.

[Slide.]

Just to give you a bit of background and the experience Angiogene has, I refer to them as Product 1 and Product 2. Product 1 is an unapproved stent combined with an unapproved drug, and there is also a device to manufacture the combination product on site at the hospitals.

They are sold as separate items and combined on site. The primary function was designated as that of the device and therefore is regulated as a PMA.

Product 2 is a preamendment device normally regulated as a 510(k), combined with an unapproved drug, becomes a combination product

since the primary function is that of a device.

[Slide.]

I will begin basically by responding to several of the FDA questions raised in the Notice for Public Hearing and then continue on to discuss premarket regulatory authorities and benefits.

[Slide.]

The first question I wish to address is Question No. 3 - what are the general scientific and policy principles that should be followed in selecting the premarket regulatory authorities to be applied to combination products?

The second part of that question - Is one premarket review mechanism more suitable than another for regulating combination products?

[Slide.]

In fact, I guess the answer to my question will also address part of Question 1 that was raised in the notice. Currently, the agency will give the primary jurisdiction based on the primary mode of action of a product.

We all recognize that the combination of two components, such as a drug and a device, bring new development issues, such as drug release from a polymer coating, local safety issues of drug and

polymer, new drug stability issues, and drug-device interactions.

[Slide.]

The criteria that should be followed in selecting the premarket regulatory authorities should be based on assuring safety to patients, and not one purely based on the primary mode of action.

FDA should determine through a designation process what are the issues that suggest potential risk to patients.

For example, the product should be given to CDER for primary review if the risks of the drug outweigh the risks of the device, and to CDRH if the risk of the device outweigh the risks of the drug.

The division with the most experience with primary safety issue would have the primary review responsibility. We don't believe that this should impact development since good science should dictate the types of nonclinical studies, device and drug manufacturing requirements, and clinical trials required.

[Slide.]

For example, some drug-eluting stents may have drugs that represent more safety issues for

patients than the device. An approved stent coated with an unapproved drug from a new pharmacological class, based on the current regulations, the stent would be declared the primary mode of action and CDRH would obtain the primary review responsibility.

However, the stent on its own should not have any unique or potentially complicated issues, however, a new class of drugs could represent unique safety issues including systemic toxicity. In addition, the molecule could have complex stability and chemistry manufacturing issues that raise safety concerns.

If FDA develops scientific and policy principles based on potential safety concerns, this type of combination product would be regulated as a drug.

[Slide.]

A single file should be applied for combination products even when one or both of the components are not approved. An FDA review team must review the application from the point of view that safety and efficacy is entirely dependent on the combination of the two components.

Irrespective of the premarket review

mechanism, a drug-device combination product application would consist of preclinical studies, nonclinical safety data, biocompatibility testing, physical testing, chemistry manufacturing and controls, submission of an IND or IDE, clinical data, and then eventually submission of an NDA or a PMA.

[Slide.]

The most efficient method for review is the creation of a review team that is composed of scientists and regulatory personnel from more than one division. The file must be assessed from the point of view of what will be commercialized and administered to patients. How the two components interact is often pivotal in the assessment of safety.

[Slide.]

FDA should develop a combination products general guidance. Consistency is required between divisions if safety is to be assured to patients. For example, acceptable preclinical standards, such as GLP, for in vivo studies used to demonstrate safety and efficacy in animals.

For medical devices, local safety is often assessed in a model of efficacy. Current FDA CDRH

guidance documents do not emphasize compliance with GLPs. A lot of studies are conducted in university facilities, and the degree of compliance to GLP varies within these facilities.

[Slide.]

The development phase of a device is regulated, for example, design input, design control. FDA should provide a definition description of when the development phase of a combination product should begin. Companies currently may be beginning development phases too late.

[Slide.]

Question 4. Recognizing the need to ensure product safety and effectiveness, what criteria should FDA use to determine whether a single application or separate applications for the individual components would be most appropriate for regulation of a combination product?

[Slide.]

FDA should not impose a separate application. It is crucial that the FDA review a combination product in a joint effort. The drug alone has issues, but the drug-device combination also has issues, and these must not be

underestimated because of separate applications.

For example, the safety of an approved drug for intravenous administration may be well established. The delivery of the drug locally in the coronary artery raises new safety issues since the local drug concentration may exceed that achieved by the intravenous product. Therefore, safety must be assessed from this new route of administration and this requires understanding how the drug is released from the device.

[Slide.]

FDA should develop a mixed regulatory process and determine what elements of different regulatory authorities are required during the designation process. Regulations should permit FDA to modify these elements if data submitted during the review process suggests or demonstrates a potential safety issue.

The guiding criteria must be safety of patients. Potential to lose efficacy should also be a criteria. FDA must not develop a strict policy but instead establish criteria to determine the elements.

Question 5. What scientific and policy principles should be followed in determining the

appropriate manufacturing and quality system regulatory authorities applicable to combination products?

[Slide.]

Both GMPs and QSR regulations were developed with the same philosophy, basically to control manufacturing and quality in order to minimize risks to patients.

In the early phases of development, QSR is more demanding on companies since it regulates design control. This includes design and development planning, design input and design output.

FDA should develop a combination product QSR regulation that includes parts of 21 CFR 211, that would be required for the drug component prior to the merging of both components. QSR requires that the merge of the drug with the device be part of the design control. In fact, the development of the combination product begins after the merge.

[Slide.]

Both QSR and GMP require that companies hire qualified employees, provide training, document the training, and require documentation of the manufacturing process through SOPs and a batch

record.

The combination product QSR regulations should include a section that cross-references to GMP sections that require documentation, in-process and raw materials control, specifications, validation, et cetera, to assure the safety, quality, and potency of the drug component.

[Slide.]

Now, to address the premarket regulatory authorities and benefits. The advantage of orphan status to the drug component of a drug-device combination product.

[Slide.]

We all recognize the complexity of developing a drug-device combination product. Let's take, for example, addition of a drug to a preamendment device. If the primary function is associated with that of the preamendment device, it would be regulated as a device.

Obviously, the addition of the drug would render a decision of Substantially Not Equivalent, and this is normal since the drug introduces new development issues, such as manufacturing and safety of the drug component, drug-device interactions, elution/release of the drug from the

device or other unique issues, therefore, this product would be regulated through a PMA process.

[Slide.]

Recently seen on October 22nd at the advisory panel where Johnson & Johnson presented the CYPHER Sirolimus-eluting Stent, tremendous therapeutic advantage of a drug in a device function. This product was given to CDRH as the primary review center since the primary mode of action was that of a device.

Sirolimus was added to the stent to augment the performance of the stent. The therapeutic action of the drug was short term.

Clinical trials demonstrated superior effectiveness to bare stents. I think the medical community recognized that this product was a breakthrough.

[Slide.]

Drug companies are encouraged to develop products for rare diseases through the FDA's Orphan Drug Act. Companies are now beginning to develop drug-device combination products for the treatment of rare diseases.

[Slide.]

For combination products regulated through

the PMA process where primary function is associated to the device, drugs are added to the device to provide additional therapeutic or preventive properties.

These drugs don't act necessarily in combination with the device, but they act actually independently of the device, and the role of the drug should be recognized by the FDA. The drug should be entitled to the Orphan Status even when the premarket regulatory authority is through the PMA.

[Slide.]

Orphan Status would encourage the development of promising drug-device combination products for the treatment of rare diseases, just like the CYPHER Sirolimus-eluting Stent has brought to the field of interventional cardiology.

[Slide.]

Angiogene would like to thank the FDA for allowing us to communicate our experience with drug-device combination products and how the modification of current regulations could continue to assure the safety and efficacy of these new technologies.

Thank you.

MR. BARNETT: Thank you, Dr. Chamberland.

Our next speaker is Dr. Owen Fields with Wyeth Pharmaceuticals.

Wyeth Pharmaceuticals, Inc.

F. Owen Fields, Ph.D.

DR. FIELDS: Good morning. I am Owen Fields. I am in Regulatory Affairs at Wyeth Pharmaceuticals.

[Slide.]

I should begin my talk by saying that if I yell out during the talk, it is due to the muscle spasms in my back. I am not doing it for effect.

[Slide.]

By way of overview, I will provide comments on Question 1, Revisions to the Intercenter Agreements; Question 2, Assigning the Primary Mode of Action; Question 3, Is One Procedure Better than Others; Question 4, Combination Products; and Question 4 and Question 5.

[Slide.]

By way of a preface, my comments this morning are based on experience with at least one combination product. My suggestions do not imply that FDA is not already generally conduction

combination product reviews appropriately, at least in my experience. Of course, my experience, like everybody else in the room, is limited to one or two products, and for that reason my experience may not be typical.

In many cases, we suggest that FDA continue current practices, but we suggest that they standardize procedures in order to increase predictability and transparency.

[Slide.]

Concerning Question 1, Revisions to the Intercenter Agreements. What principles should FDA use in revisions to the existing Intercenter Agreements?

We believe that the roles and responsibilities of the different reviewing centers should be defined clearly, early, and often. This would begin immediately following a jurisdictional ruling, at which time we suggest that FDA devise, and its sponsors be provided with, a review plan identifying the roles and responsibilities of the centers.

This wouldn't be a lengthy document, it would simply be a letter, a paragraph in a letter. This would address the need for certainty among

sponsors as to which center will be involved and which standard should be applied to the product.

[Slide.]

Concerning Question 2, Determining the Primary Mode of Action. I will go over a few scenarios in the next few slides.

If one component clearly serves only as a delivery vehicle for a biologically active component, we believe it is fairly straightforward in that situation to assign the primary mechanism of action to the biologically active component. In that case, a delivery component should be considered as an excipient or as a container closure system.

[Slide.]

Things get a bit more complicated when there are two components, each of which possesses biological and/or structural activity. In this case, we believe the agency should consider which of the components contributes the primary or determinative activity and which contributes the secondary or enabling activity.

You may argue that this is one of those things that you know when you see, but in order to see it, I think you need to consider the intended

therapeutic clinical effect. In other words, you need to consider which component provides the primary activity will determined by the clinical purpose and the clinical indication intended for the product.

[Slide.]

In the very complicated situation in which the primary mode of action can't be assigned with any certainty, we have listed some additional criteria that could be applied, and I do point out that these are placed in order of importance.

First of all, it should be considered which component presents the greatest safety risk, and it should be considered which center has the greatest experience managing that risk.

Second, the center's experience with clinical, preclinical, and manufacturing aspects of the product should be considered. Precedence is, of course, important, that is, how related products were handled that will lead towards even treatment.

Last, and certainly least in my mind, are practical concerns such as agency resources, review timelines, procedural simplicity and flexibility, and also the sponsor's familiarity with a given procedure. I think we all agree that practical

concerns like this for products which present public health implications probably should come at the bottom of the list.

[Slide.]

Question 3 concerning Regulatory Authority and Procedure. We believe there is no fundamental scientific difference between the NDA, BLA, and PMA mechanisms, so we believe that the procedure most familiar to the lead center is probably advisable.

There are obviously differences in history and culture among the centers and that does affect the questions that are asked and the concerns that are raised, but we don't believe that the actual procedure contributes to that.

[Slide.]

There are, however, differences in documentation formats which are triggered by differences in the application type, and we think this should be considered due to practical considerations.

Because all combination products will contain either a drug or a biological component, we believe that the ICH common technical document should be a permitted format even in those

situations in which the product is under CDRH's primary jurisdiction.

This is especially useful in the case of those device combination products in the U.S. which are considered drugs in the EU, and there are a few of these because of subtle differences in the definitions between the U.S. and the European Union.

We believe that the common technical document format, because it is designed to allow independent review of individual sections, is well suited for use of combination products.

[Slide.]

Question 4. Which criteria should FDA use to determine whether single or separate applications for the component should be required?

We believe that separate applications are not generally advisable. This does not mean that if all three parties agree, they should not be permitted. It simply means that the agency should not generally force two applications on a sponsor without the sponsor's agreement.

The rationale for this statement is fairly simple to express. For any given combination product, a single approval decision and a single

set of conditions of approval are ultimately required, and we believe that a single decision is best reached through a single application.

Further, there are some practical issues with two applications, and I will address these on the next slide.

[Slide.]

To make two applications generally practical, FDA would need to develop internal procedures which counterbalance the tendency of the centers to work in isolation from each other.

Isolation in this situation is clearly highly undesirable, and that is because the CMC or manufacturing preclinical and clinical data necessary to support the approval of a medical product are highly related to each other.

As you know, the appropriate CMC specifications can only be assigned once the clinical use is determined. The appropriate preclinical studies to be done can only be assigned once the preclinical use is considered, et cetera.

Dual applications would usually be procedurally complicated for sponsors. You wouldn't know who to call with a question in many cases. In addition, the various centers have

different review clocks, and two different review clocks would be involved, and harmonizing two different review clocks especially when the review clocks are set by statute could prove complicated, if not impossible.

In addition, policies and the applicability of user fees would be needed. This is especially going to get complicated once medical device user fees are also in place.

[Slide.]

So, I have told you that we don't generally suggest two applications in those situations in which the components of a review could be split out from each other, so what do we suggest?

Our overall proposal is as follows. In those cases in which the various major components of the application are not cleanly separable from one another, that is clearly not the kind of situation you would think about two applications anyway.

We believe the involved center should follow the procedures in the July 2002 SOP. In those cases in which components of the application are cleanly separable from one another, we believe

that the intercenter process should be standardized, and I will give you some concepts we believe should be applied in that case.

[Slide.]

In the case of what I call separable intercenter review, we believe that the agency should establish clear primary and secondary roles and responsibilities. This serves the purpose of eliminating duplicative reviews, which is a drain on agency resources and also on sponsor resources.

We believe that the secondary center should, however, take ownership of the review of the relevant section of the application, that is, they should not do it in isolation, but they should essentially administer that review.

We believe--this is a familiar recommendation already this morning--we believe that an intercenter scientific review team should be set up in such cases and that it should have a consistent structure and charter.

At regular intervals, the intercenter review team would need to consolidate and discuss the meaningfulness and applicability of various questions and issues. So, the kind of questions that they would be asking each other would be,

number one, why do we care about this issue, or, number two, why don't we care about this issue.

If there were an intercenter review team and sponsor interactions, and if the secondary center had sort of ownership of one component, during sponsor interactions, we believe that the involvement of the project manager or lead reviewer from the lead center should be required at all times to ensure procedural consistency.

[Slide.]

In addition, we believe it should be clearly defined who has final decisionmaking authority regarding each section, and most importantly for the overall application. We believe a common technical document format should be encouraged because of its modularity.

Clearly, the agency would have to establish an integrated policy to assure an assistant administrative record. There are still differences in the administrative record procedures used amongst the centers, so there would need to be some consistent system set up.

This would lead to probably a much more procedural simplicity than having two applications because under such a system, the review clock, user

fees, and other procedural details associated with a lead center would continue to apply, so you wouldn't have to deal with any issues of that nature.

We also believe that the agency should eventually establish compatibility. I am not saying uniformity, I realize that is a very expensive undertaking, but at least we think the centers should have compatibility in their IT systems. In other words, they should be able to view documents on each other's IT systems, and in some cases that is not possible now.

[Slide.]

Turning to the quality system to be applied, and here I am using "quality system" with a little q and a little s as a generic term, our basic feeling is that the quality systems for devices and pharmaceuticals are different from each other, however, they are both adequate within their scope.

So, given that, our comments are mostly of a practical nature because we don't believe there is anything fundamentally different about the two that makes one unsuited for a certain type of product.

First of all, from a practical perspective, it is difficult and confusing to apply two conceptually similar but administratively different quality systems, for example, the device quality systems regs and pharmaceutical GMPs within the same manufacturing facility, and we feel they should be avoided if at all possible.

[Slide.]

Other considerations to keep in mind. In the absence of scientific need, components of combination products should normally be controlled by the quality system already established by their manufacturer. This is obviously the most practical way of doing things.

Once a component enters the control of a combination product sponsor, then, the quality system already in place at that facility should normally apply to the product.

If the component is an existing approved medical device, the quality system established by its manufacturer should normally apply at least until it joins with the other component of the combination product.

If the component is an existing approved pharmaceutical or biological, the quality system

established by its manufacturer again should normally apply until that product is combined with the other component of the combination product.

Of course, additional specifications or requirements may apply based on scientific considerations to assure that the component is appropriate for the intended clinical use.

I would like to thank you for the opportunity to testify.

MR. BARNETT: Thank you, Dr. Fields.

Our next speaker is Dr. Zorina Pitkin of Nephros Therapeutics, Inc.

Nephros Therapeutics, Inc.

Zorina Pitkin, Ph.D.

DR. PITKIN: Good morning. I am Zorina Pitkin, Vice President of Regulatory Affairs and Quality Systems at Nephros Therapeutics.

[Slide.]

I would like to thank the Office of Ombudsman at the FDA and Director of Combination Program Mark Kramer for the opportunity to speak at this hearing.

Today's presentation will focus on one of the approaches to support several initiatives that have been taken by the FDA and the industry to

address regulatory process for combination products.

The presentation is on the risk classification of combination products comprised of biologic and device components.

[Slide.]

I would like to briefly describe the Renal Assist Device as a cell-based biologic-device combination product and then present some of the critical issues in the RAD development.

In the course of addressing these issues at Nephros, we came up with a risk-based classification of combination products which I would like to discuss with you.

[Slide.]

The Renal Assist Device was designed to treat acute renal failure. It is used as an extracorporeal system for a relatively short time. The RAD is a combination product comprised of a biological component, which is a human kidney proximal tubal cells and a device component, a hollow fiber cartridge incorporating a biocompatible membrane.

Regarding the biological component, we use human kidney cells with no modifications. The

cells are isolated from human kidney transplant discards and expended in a culture medium.

The hollow fibers provide support for the cellular system, allow for the transport of essential cell products and nutrients, and prevent the cells from entering the circulatory system. The RAD is incorporated into a conventional venovenous hemofiltration circuit.

[Slide.]

The RAD is currently being regulated as biologic by CBER with CDRH consults and is currently being evaluated under two physician-sponsored INDs. Currently, we are in Phase I/II clinical studies with a targeted population of patients with acute renal failure with a predicted high mortality rate. A total of 10 patients have been treated with the system.

[Slide.]

Moving on to critical issues in the RAD development. The first critical issue in the RAD development of the combination product is the development of quality systems that includes characterization of both product and the system, as well as the assurance of its safety. Also, reproducible and consistent delivery of viable and

functional cells in the system to the patient.

Secondly, there have been some unique biologic device issues that were encountered in the development of this combination product. In particular, a complex interaction between material and cellular processes.

Finally, the applicability of specific regulations to various components of the Renal Assist System is a critical issue. The starting point in addressing the critical issues in the development of Renal Assist Device was an initial risk assessment of this novel combination product.

Several approaches were considered based on different combinations of the risk factors. To date, we propose a simple and transparent risk-based classification which can be applied to the majority, if not all combination products. A uniform classification is important due to current uncertainties in the regulation of newly-developed combination products.

[Slide.]

For example, combination products do not fit adequately into existing statutory definitions for there are issues which are unique to combination products.

Further, it is still unclear which GMP regulations are applicable to the manufacturing of combination products and inspection by the FDA. It is also unclear how the assigned center will handle reported changes in the manufacturing of combination products.

The FDA and the industry have also acknowledged a lack of consistency regarding assigning similar products to the same lead center.

[Slide.]

We would like to propose a risk-based classification of combination products that could be helpful in the development of combination products. The purpose is to identify the component of the combination product that potentially presents the highest risk, create one quality system which will encompass the most appropriate regulation that can be applicable to all the components of a combination product, and to establish a common approach to similar issues.

[Slide.]

The main assumption that we made in the development of our model was that the risk of combination product increases as direct exposure is increased. Factors that contribute to risk

assessment are extracorporeal use versus an implantable system, the presence of a physical barrier like a membrane versus direct contact, and brief contact with the product versus long-term exposure.

[Slide.]

Risk-based classification should encompass multiple factors. As the first step in the development of the model presented today, we propose ruling out some factors that are very critical, but cannot fit in a simplified version of the classification presented today.

We therefore outlined the full implementations. We employed the existing classification of devices, class I through III. Assessment of mode of action was not considered. No distinction was made between novel and off-the-shelf components.

No distinction was made between autologous and allogeneic sources of cells or tissues, and no distinction was made between human and xenogeneic sources of cells or tissues.

[Slide.]

We calculated the combination product risk score as a sum of the risk score for biologics and

the risk score for devices. As we will see in a moment, the biologics risk score ranges from 1 to 12, and the device score ranges from 1 to 3, corresponding to current ranges in device classification. Therefore, the total combination product risk score could be from 2 to 15.

We defined risk classes of combination products based on their risk scores. A risk score from 2 to 5 is combination product risk class I. A risk score from 6 to 10 is a combination product risk class II, and 11 to 15 is a combination product risk class III.

[Slide.]

This slide demonstrates how we would assign risk scores for biological components of combination products. There would be four categories of risks based on use and type of exposure, either implanted with direct contact like cell therapies of cells delivered in biodegradable materials, implanted with barrier. The third is extracorporeal with direct contact, and finally, extracorporeal where contact is performed through a barrier.

Each category is further subdivided based on the duration of exposure, such as short-term,

mid-term, and long-term. We define short-term exposures as being hours to days, mid-term exposure as weeks to months, and long-term exposure as years. Thus, we have 12 scores ranging from 1 to 12.

[Slide.]

This is a classification chart for risk assessment for combination products, which combine risk scores for biologics and risk scores associated with classes of devices. Each element on this chart or cell is the sum of biologics risk scores and device risk scores.

So, for each combination product for which one can identify both a biologic and a device score, this chart will provide a total score which will give us a combination products risk class from I to III, where III is associated with the highest risk.

[Slide.]

In summary, a risk assessment classification for combination products has been proposed based on risk factors associated with both biologics and device components. The classification was developed under the assumption that the risk for a patient and for the public at

large increases with long-term direct exposure of a combination product.

Risk classification might eliminate the ambiguity of combination products regulation, and this classification system might be helpful in the decisionmaking process for the characterization, designation, and regulation of combination products.

Thank you very much for your attention.

MR. BARNETT: Thank you, Dr. Pitkin.

Our next speaker before we take our break is Mark Hamblin of Carnegie Mellon University.

Carnegie Mellon University

Mark Hamblin

MR. HAMBLIN: Good morning, everybody. Again, my name is Mark Hamblin, and I am from Carnegie Mellon University in Pittsburgh, Pennsylvania.

I would first like to thank the FDA for the opportunity to speak here today.

[Slide.]

Specifically, I am coming here as part of a Public Policy project course in which we are investigating the field of tissue engineering. Obviously, this fits very well into combination

products.

Within this class, we are looking into four different areas of tissue engineering; first, looking at the navigation of the FDA approval process, various social and ethical issues of tissue engineering, various financial and marketing issues of tissue engineering, and finally, what I am going to be focusing on today is the jurisdictional determinations for combination products, specifically, the review of the current process, the review of the Intercenter Agreements, and finally, the description of our creation of the web-based decision support tool.

[Slide.]

First, to touch on our thoughts of the current jurisdiction process. The Intercenter Agreements provide rules for classifying combination products, but we feel they are too focused in scope and they really only cover existing technologies. Therefore, the Intercenter Agreements may not apply to new technologies and new innovations.

The jurisdiction determination is then based only on the determination of the primary mode of action of which there is no clear definition.

Therefore, some subjectivity is necessary to reach a decision, yielding a lack of consistency, predictability, and transparency in the process.

[Slide.]

This is where our decision support tool comes into play. The purpose of our support tool is as follows. First, to create a rule-based system that classifies medical products based on product characteristics. Also, to incorporate previously established jurisdiction rules from the Intercenter Agreements. Also, to add additional criteria for determination jurisdiction to fill in the gaps that the Intercenter Agreements do not cover.

The purpose of the tool is to allow for easy adaptability and variability to accommodate current FDA regulatory requirements and trends, and we would like to make the tool widely available, such as web-based system, to allow for greater transparency and predictability in the jurisdiction determination process.

[Slide.]

Now, for some brief technical details of the decision support tool. Each product being reviewed by this tool will have three pools of

points, one for each of the three regulatory centers - CDER, CBER, and CDRH.

Then, there is a list of 88 yes or no questions pertaining to general product characteristics. If a question is answered yes for a specific product, therefore, the characteristic in that question is present in that product, a certain number of points will go to pool 1, a certain number of points will go to pool 2, and a certain number of points will go to pool 3.

Then, each question has a weight from zero to 1 based on how important that question is in the overall classification scheme or how important that product characteristic is in the overall classification scheme.

Then, the points given to each of the three pools will be scaled based on the weight for that question. In the end, the product gets classified into the respective center based on the pool of points that has the most points.

This setup makes it very easy to change the classification scheme just by changing the respective weight for the questions and the point distributions for the three pools.

[Slide.]

Next, to cover how we created the model inputs, first of all, we extracted 67 questions from the jurisdiction rules in the current Intercenter Agreements. We then went on to conduct a survey of tissue engineering experts.

To do this, we sent our survey to 205 members of the Pittsburgh Tissue Engineering Initiative because we had rather easy access to the member database here. In the survey, we proposed 21 different general product characteristics, and we surveyed the experts as to how the presence of these characteristics should affect product classification.

We then went on to create 21 questions for our model based on these 21 product characteristics, and then we assigned points to these questions based on the respective survey responses.

Also, as part of the survey, we gathered responses from the experts about their opinions of the FDA jurisdictional decision process and the current approval process for combination products.

[Slide.]

How does the system help? Well, first of all, the Intercenter Agreements currently form a

precedent-based decision model by looking only at specific characteristics of previously developed products.

It is known that precedent-based decision models typically are not optimal for classifying new types of products because they are too subjective in nature. Our proposed decision support tool is a rule-based model that looks at products of general characteristics and is therefore more applicable to future products and technology while the accessible rule-based decision model will provide a consistent, predictable, and transparent method for classification problems.

It is noted that this tool will fit very well into the current FDA regulatory framework without much additional bureaucracy being created. After saying all this, it is important to say that human decisionmaking would still be necessary along with a multidisciplinary review of combination products/

[Slide.]

As a side note, one of the other groups in our project course is doing some similar interesting work. They are performing an analysis of the FDA approval process focusing specifically

on tissue engineering products and combination products.

They are conducting an in-depth analysis of the approval process, created detailed flow diagrams of this process, and surveyed and interviewed several firms in the area on their prospectus.

They also went on to develop a web-based tool through the analysis of this process and interview feedback and developed the following guidelines. Firms who benefit from a graphical view of the entire process, they would like easier quick access to FDA contact information, and on-line form submission to the FDA is highly requested to expedite the approval steps.

More details on these interviews and the web tool are available in the final project report.

[Slide.]

I can't finish without giving a plug to our final presentation and report. Our final presentation of our research activities is to be given in Washington on Wednesday, December 4th, 2002. Members of our review panel for this presentation include senior management from the FDA, academic and industry researchers, and other

stakeholders in the field of tissue engineering and combination products.

We are publishing our written results and this is expected in January of 2003. You can contact me at the above e-mail address for details about our final presentation and written report if you would like to hear more about those things.

As a reminder, there is a lot more to our research activities than just this decision tool I have presented today.

Thank you.

MR. BARNETT: Thank you, Mr. Hamblin.

Before we go to our break, I would like to see a show of hands. How many people here who are not on the formal agenda would like to speak later during the open microphone session, can I see a show?

Okay, a couple more back there. Just to get a rough idea of how many we have. We are due for a 15-minute break. I have almost 10:25. Why don't we say 20 minutes of 11:00 back here and we will commence.

Thank you.

[Recess.]

MR. BARNETT: Thank you. The more

observant of you will have noticed that we have an additional panelist with us now. She is Linda Skladany, FDA's Associate Commissioner for External Relations.

We are ready to start with our next speaker who is Terry Sweeney of the National Electrical Manufacturers Association.

Mr. Sweeney.

National Electrical Manufacturers Association

Terry Sweeney

MR. SWEENEY: Thank you very much. I appreciate the FDA's opportunity to present information regarding combination drug-device products today.

[Slide.]

My name again is Terry Sweeney. I am Vice President for Quality and Regulatory Affairs for Philips Medical Systems. I am here representing NEMA, the National Electrical Manufacturers Association. This is an organization that represents about 95 percent of the imaging device industry worldwide.

What we are here to talk to you today is looking at the Combination Drug-Device Program is that we believe that combination drug-devices may

be able to be placed in three broad general categories.

There may be other categories, but one of the drug delivery devices, such as insulin infusion pumps, those devices that administer drugs, drug-eluting devices, such as coronary stents that have coatings on them to prevent occlusions, and also, in our case, looking at drug viewing devices.

In our situation, we actually just look at a drug, we don't interact with the drug, we are just viewing that drug, and that is what I am here to speak about today is that interaction and the declaration of that being a combination drug-device.

[Slide.]

We are going to be addressing Questions 2 through 7 today. The first one deals with the safety and effectiveness. We believe these combination drug-devices should be evaluated by the FDA on a case-by-case basis, on a component basis, separately from each other.

In certain cases, as recognized earlier by some of the previous speakers, where the drug and device interact together, it may be appropriate to have a single submission.

In the case of these device-drug

combinations where there are imaging contrast agents involved, where you are looking at them with, say, a magnetic resonance system or an ultrasound system, it may be more appropriate for the consideration of the devices to be two different submissions rather than one combined submission.

So, in looking at imaging contrast agents devices, it may be appropriate to split them apart and look at the effectiveness separately of each, should be delegated, we believe, to a primary function for that area.

So, if you are looking at a drug, for instance, an imaging contrast drug, it may be appropriate for the CDER to look at that drug, its safety and its efficacy, as a general application of statement of claims. If a specific claim is being made for that drug, then, the drug manufacturer would submit those claims.

We believe that on the other side, for the medical device arena, it would be more appropriate for the device company to look at the applications of the drug and see where that may be applicable.

[Slide.]

The Center with the appropriate expertise

again should be the primary functional group to be the lead reviewer for that, so if a drug is being applied for the first time where there has been no demonstrated safety or effectiveness of the drug, obviously, an NDA application would be appropriate and follow the normal procedures and processes for that type of drug.

The CDRH lead reviewer, we believe, though, would be appropriate for imaging systems modalities that look at these drugs with the contrast agents having already been approved for their safety and efficacy, that the CDRH then should be the lead reviewer for additional clinical applications of that drug as it would be used for viewing of different parts of the patient.

[Slide.]

So, the review process under Question No. 3, we think it is appropriate that the agency division that deals with the component do the evaluation of that component, so the contrast agent, the drug safety side should be done via CDER for a new drug or if there is like a revised dosing program based on perhaps a new application that has been developed.

On the imaging device side, we believe

imaging efficacy should be evaluated by the CDRH, which has expertise in looking at all other imaging modalities and efficacy of those modalities for viewing a patient anatomy, so they would be looking at new indications for use that may be developed by researchers with a combination of the drug and the devices and also any expanded indications for use.

[Slide.]

Question No. 4, we believe the use application appropriate for the component should be those that are called forward for the evaluation of the drug or the device, so again, the typical NDA, aNDA process for the drug or the contrast agent in our case and for the imaging device, the modality is applicable that the 510(k) or PMA routes be appropriate for the evaluation of the product.

[Slide.]

The quality systems again, there has been some discussion earlier this morning, but in our case, since the drug and the device are never interrelated, they are never connected, they never touch each other, we believe it is more clear-cut that for the contrast agent, that the CGMPs for drugs apply and that for imaging devices, the

quality system regulations that are used by device manufacturers would be the appropriate regulatory scheme to follow in those cases.

[Slide.]

Question 6 deals with the adverse event reporting, the same thing like with the quality system requirements, it would be appropriate that for the contrast agent, if the adverse advice experience reports would be the methodology for reporting of those incidents, and that for imaging devices, the medical device report system would be appropriate.

We believe that it is going to be kind of confusing at times which device or drug is involved in an actual incident with a patient, and we believe that at least in the initial phase for the reporting cycle, that the physician that is involved with the incident would report what he believes was the cause, whether it be the drug, maybe had a drug reaction or whether the device caused some type of incident injury potential with the patient. That would help us understand where to route the application for the incident, whether it be to the drug company or to the device company for appropriate reporting.

[Slide.]

For Question No. 7, we are looking at the need for the cross labeling requirements, and this is one that has caused a burden in our industry for both the drug and device side for contrast agents.

The cross labeling requirements presently link us to have the same claims for use and intended uses for these contrast agents and for the devices that image them. This presents a problem because the cycle times and the types of reviews that are done for the drug and the device are quite separate.

At this point in time, the device manufacturers of imaging devices like MR and ultrasound systems are not able to make any type of regulatory applications to the agency for extending the use of these contrast agents, and that has stopped the development and the utilization in the United States of these agents which are increasing the effectiveness of our devices and the sensitivity of our devices to be able to image patients.

So, therefore, we propose that the FDA consider as it presently exists under the CDRH scheme for regulation that they use the least

burdensome system and the provisions set forth there to set the appropriate regulatory controls and determination of what information needs to be required for the applications.

We believe that applications both by the drug manufacturer and by the device manufacturer are appropriate in this case and that we not be limited to only let the drug manufacturers make the claim for use.

We think that the Center for Devices and Radiological Health should be able to evaluate either a 510(k) or a PMA, if appropriate, the types of claims that could be made for extending the uses of these drugs.

The intended use statements should be distinctly based upon the safety and the risk analysis. We had some discussions earlier today about how to do a risk assessment of the drug-device combination. I think that is very appropriate to be done in these cases.

Where contraindications develop based on that risk analysis, they may apply either to the drug or the device, or perhaps to both components, and the labeling may not be the same between the two. I think based on that risk assessment,

however, you would do cross references of the risks and the labeling of both products.

We think it is possible to decouple the components specific issues, for example, effectiveness between the drug and the device. We are faced right now with trying to determine clinical endpoints based on a historical CDER approach for evaluation of drugs that may not be appropriate for additional clinical applications of contrast agents.

In the case of imaging devices, clinical endpoints usually are not defined. The physician or the radiologist makes an evaluation of an image and makes a determination as to what the diagnosis is.

The system does not diagnose the patient, the system does not treat or provide any therapy to the patient, so in the case of the drugs that are used in this situation, the drug has no bioeffect or pharmacokinetic effect on the patient, and the imaging device also has no effect on that patient, so we are looking at it may be possible to decouple each of these components from each other, evaluate the obvious bioeffects and safety of the drug with the patient under the NDA process and then on to

CDRH side with the 510(k), look at whether it can effectively image those drugs is what we are suggesting.

I appreciate your listening to us today and receiving our comments, and we are open for any questions that the panel may have of us.

MR. BARNETT: Before we go any further, several people asked during the break whether they could get copies of the presentations, and you can do that. The easiest way is as follows. We are going to scan those and put them on the docket web site where you can pull them down.

So, I am going to tell you how to do that. The web site is www.fda.gov and then when you get there, search under--and I am going to ask Mark Kramer to make sure that I have got this right--search under 02N-0445, and that is the docket number, and then you will pull up all the information about this issue including the presentations.

Let's go on now then and we will hear from Alan Kirschenbaum, who is with the Medical Imaging Contrast Agent Association.

Medical Imaging Contrast Agent Association

Alan Kirschenbaum, Esq.

MR. KIRSCHENBAUM: Thank you. I thank the panel for this opportunity to address these issues today on behalf of the Medical Imaging Contrast Agent Association, or MICAA, as we like to call it.

[Slide.]

My name is Alan Kirschenbaum. I am with the law firm of Hyman, Phelps & McNamara, and I will be presenting just a brief statement on behalf of MICAA this morning.

[Slide.]

There are two points I would like to make. The first has to do with the scope of combination product regulation, and the second is a brief point having to do with the requirement in the new device user fee legislation for timely and effective premarket review of combination products.

[Slide.]

Turning to the first point, this is really a definitional issue. It is not explicitly identified in any of the questions listed in the Federal Register Notice, but it is implicit really in all of them because it has to do with which products are combination products in the first place.

The point is essentially this, that

products that are used together concomitantly are not necessarily combination products. One of the definitions in the regulatory definition of a combination product is a drug, a device, or biological product packaged separately that according to its proposed labeling is intended for use only with an approved, individually specified drug, device, or biological product where both are required to achieve the intended use and where upon approval the marketed product's labeling will have to be changed.

You will see I have underscored the words "individually specified" because even if you have a drug that is going to be used together with an approved device or vice versa, and even if you need both to achieve the intended use, that is still not a combination product unless the other product is individually specified in the proposed labeling.

FDA has recognized that many concomitant use products are not combination products in the preamble to the Combination Product regulation. FDA stated that the definition of combination product excludes most concomitant use of drugs, devices, and biological products.

One example of products that are used

together, but are not combination products, is contrast agents and diagnostic radiopharmaceuticals that are used with imaging devices. The drug labeling typically refers to a type of procedure or general type of equipment, but it does not individually specify a particular device.

In the past, devices and drug have historically been regulated by FDA as independent products rather than as combination products, and we are not aware of any particular safety or efficacy issues that have arisen because of the independent regulatory treatment, and under the principle that "If it ain't broke, don't fix it," we think that this ought to continue. These products that are used together ought to continue to be treated independently, not as combination products.

Of course, it is possible that you could have a combination product involving an imaging device and a contrast agent if the requirement of the regulation is met, in other words, if the labeling individually specifies the device that is to be used with the agent.

[Slide.]

Turning to the second point, again, this

would fall under the Other Comments category.

[Slide.]

In the recent medical device user fee legislation, Section 204, as you know, pertains to combination products, and it is clear from that section that Congress' clear intent is that combination products be reviewed in a timely and effective manner. The word "timeliness" or "timely" appears six times in this relatively brief section.

[Slide.]

Where you do have a combination product involving medical imaging device and a drug--well, any combination product involving a medical imaging technology will most likely involve a drug, and therefore, timely and effective premarket review of combination products obviously will require timely review of the safety and effectiveness of the drug component.

MICAA would like to make the point that we think that Section 204 adds urgency to the need for FDA to ensure timely review by, number one, reducing times to approval for new medical imaging drugs and new indications of approved drugs, and, secondly, by issuing a medical imaging drug

guidance.

The guidance would help companies streamline their development by giving guidance on what FDA's expectations are for safety and effectiveness data, how to design their studies and their image readings, and whether they could perhaps reduce their safety data set as described in the draft guidance.

Of course, MICAA is in favor of reducing times to approval and quickly issuing the guidance for all drugs, for all medical imaging drugs, not just combination products, but the device legislation I think adds some urgency to these needs.

That concludes my statement. Again, thank you very much for giving me the opportunity to make this statement for MICAA.

MR. BARNETT: Thank you, Mr. Kirschenbaum.

The next speaker is David Fox from Hogan & Hartson.

Hogan & Hartson, LLP

David Fox, Esq.

MR. FOX: Thank you for providing me the opportunity to speak this morning. As you said, I am David Fox from Hogan & Hartson. I am not here

on behalf of any one client or group of clients, I am not here to advocate a position. I came simply to share some thoughts based on my experience as FDA counsel previously on a number of combination product matters, and now as outside counsel to a number of sponsors who have focused on this challenging issue.

Listening to the presentations this morning, I was reminded of an event a couple years ago in which a world champion chess player, whose name escapes me, was locked in a match with an IBM computer. I think it was an 11-game match and the champion chess player lost the match. At the end, he complained bitterly that each night the computer programmers changed the algorithm in the computer, and he kept on saying "Too much human intervention, too much human intervention, not fair."

I think human intervention is a good thing. I think this issue is inherently a management issue for the agency, inherently a human issue, I don't think it's susceptible to algorithm, to flow chart, and I think that is a theme that is beginning to emerge throughout this presentation.

[Slide.]

With that, I would like to try to run

through four general topics. Classification or designation, is the product a drug, device, or biologic, a single entity product, or is a combination? As the previous speaker alluded to, that is a threshold question that is not squarely addressed in the Notice, but I think it is critical in terms of defining and developing the mandate of the new Office of Combination Products.

Then, I will touch upon jurisdiction or assignment, where within the agency will lead responsibility for the review of the product go, which center. Regulation, I don't have any breakthrough comments on this one, but how exactly will the combination product be regulated, will it be regulated solely, for example, as a device, solely as a drug, solely as a biologic, will there be two or in some cases you could have the trifecta, three tracks.

Then, a brief word or two about process and the recurring them in the Notice about the need for transparency.

[Slide.]

In terms of classification, I think the most important conceptual breakthrough came probably in 1997 with FDAMA, which if there was any

uncertainty about it, the so-called fourth category, as a stand-alone category, combination products was recognized in Section 563 of the Act, and now it is even more present in Section 503(g). That is now a separate regulatable category and doesn't require the agency to force a product into one of the other three therapeutic categories.

[Slide.]

As Dr. Lumpkin reviewed earlier, the new Office of Combination Products has a vast management mandate, timely and effective reviews, ensuring consistent standards both pre- and postmarket, for like products dispute resolution, and then it has a periodic reporting requirement to Congress.

Interestingly enough, it also is required by statute the consult with another office, if I read this correctly, within the Office of the Commissioner on whether a product is a combination, which may retain many of the functions that are currently covered by the Ombudsman's Office.

[Slide.]

So, what is a combination product? Again, that is a crucial threshold question as you develop the new Office of Combination Products.

Section 503(g), which has always been the focus of this issue, doesn't really say much, products that constitute a combination of a drug, a device, or a biologic. Several people have alluded to there is a regulation that has stood the test of time so far, but may actually need some adjustment as you move ahead, products that are either physically or chemically combined, packaged together or intended to be used together.

Then, of course, there is the Intercenter Agreements that identify certain categories or products as combinations or not.

[Slide.]

Examples of products that or could be considered combinations, the age-old prefilled syringe Dr. Lumpkin alluded to, the medicated bandage, kind of the then dilemma of combination products, is it a drug, is it a device. Fortunately, the answer is now we know it is a combination to the extent nomenclature matters.

Albuterol dose inhalers, transdermal patches, other pharmaceuticals with novel delivery systems, laser-activated drugs, coated stents and catheters, dental products, and then, of course, my personal favorite, tobacco products.

There is not a lot written on the conceptual issue of what is a combination product, but I think that the ground zero for that issue was in the tobacco rulemaking proceeding and subsequent litigation, and I would encourage you go to and seek out the briefing that was done at the litigation stage on that issue.

All of the briefs are consolidated nicely on the Solicitor General's web site and also a separate web site within the Department of Justice, and you will see in there a bitter dispute over what is a combination product.

FDA, of course, asserted that both cigarettes and even a tobacco leaf represented a combination product insofar as you could look at the product, divide it up, and find within it a delivery system that met the definition of a device and a drug, it met the definition of a drug.

MR. BARNETT: I noticed before you leave that slide that you left a judicious space between tobacco and all the rest of them. That was very tactful.

MR. FOX: Just to point out, I agree that tobacco is a anomaly in many ways, but the discussion on combination products in there, which

was never actually ruled upon by the Supreme Court, is a fairly high-level discussion, and it raises conceptual issues which I will address in a moment, because it does get to a very fundamental point about what is a combination product.

[Slide.]

Just for the sake of completeness, there are also a number of products that look and feel like they could be combinations, but which, based on my recollection, FDA has at one time or another said were actual single entity products, one of the more interesting ones being gas-filled microspheres as ultrasound contrast agents, implantable membranes with cells, and so on, catheter filtration systems to locally or regionally deliver a drug, lots of interesting precedents out there that suggest that there are some limiting features to the definition of what is a combination product, because without limiting features, it is possible that the new Office of Combination Products, as the tobacco industry argued, could regulate everything in a therapeutic category.

Almost everything has built into it some form of delivery and some form of active ingredient, and if you parse the product and treat

it as its individual parts, each of those can meet the respective definitions in most cases, of course, the big limiter being the definition of a device, which excludes those things that rely on chemical or metabolic activity.

But again, if you put the product under enough of a microscope, most delivery systems can be attributed to physical phenomena, at least for the primary way in which they act.

[Slide.]

So, there are at least, by my count, 300 requests for designation precedence that represent formal decisions of the agency issued since the program got going in 1990-1991. My recollection, about 28 per year come in, and again you are the holders of the data, but my sense was about 1 in 3, the agency made the decision the product was, in fact, a combination.

So, I think it is very important as the Office moves forward, to first do a retrospective analysis and look at those decisions, look at the ones in which the agency decided that something was either a single entity product or a combination, tease out the factors that the agency relied upon, and then build from there.

There may be factors you want to do away with, there may be factors that seem to have stood the test of time. It is very important to build on that rich body of precedent.

[Slide.]

The previous speaker alluded to an interesting issue. Again, just in determining whether something is a combination, to what extent does labeling create a combination? I think that is an issue that needs a lot more work. Just to what extent in the case of a drug delivery system does the drug labeling have to change to trigger a product being a combination?

The issue of dosage form versus delivery systems, if each dosage form does represent a delivery system, then, the mandate of that office is enormous, and it even ostensibly would have responsibility for the timely review of generic versions of combination products.

What was raised in tobacco, which was interesting, is whether you look at the product as a whole for definitional purposes or whether you look at its parts, and what the tobacco industry argued is that when you look at the whole, if there is any chemical or metabolic activity associated

with the primary use of the product, then that product is excluded from being thought of as a device or as incorporating a device, and therefore, it is a single entity product.

FDA said no, you look at the product and you break it up into its constituent parts, and you hold up each part to the definition, a very fundamental Gordian knot type dispute which the Court did not reach, but which FDA probably is going to have to think about one more time, again, as it defines the scope of this office.

Then, you have the last interesting area of what I call unitary or single function products. Those are products that bring together components that you could trace back to one of the three centers, an albumin sphere, a gas that is used in contrast agents that are typically regulated as drugs, and you put them together, but the product does not have a dual function.

Those components work together to provide a single function, and I would argue that there is strong precedent for treating those as single entity, noncombination products.

Again, I think it is a good idea to try to look anew at the definition of combinations and

look for limiting factors, so that the Office can be focused on those products that are in greatest need of very strong management.

[Slide.]

Once you cross the threshold issue of whether you have a combination, the next is assignment, and that is that issue of which center has primary jurisdiction, and it is based on the primary mode of action of the product, which article within the combination is responsible for the primary mode of action.

FDA unfortunately is forced to pick one mode of action. Again, we have the issue, do you look at the whole or do you look at the relative contribution of each part. I am not going to say one way or the other.

For delivery systems, I will say that FDA's focus tends to be on the therapeutic, and we heard that several times this morning, what is the final decisive action of the product, and usually, with complex delivery systems, the agency generally says it is the therapeutic, at the end of the day, that is what matters, that is where the rubber meets the road, that is where all the action is.

I would suggest that there is actually an

equally plausible view, and that is that improved drug delivery can just as easily be primary for a given product. I think it is a completely circular issue, it's relativistic, as Dr. Lumpkin said, ask three people how they would treat a given product, you get three different answers.

I was accused always of treating everything as a drug because I was a counsel to the Center for Drugs. My device colleagues, they want to treat everything as a device. I think it is just something you have to just make a cut on.

[Slide.]

Again, I don't think it can be resolved through a flow chart. I think your best bet is to start with 100-plus precedents or so that you have already looked at on primary mode of action. Go back and look at those, try to articulate, try to mind that data and articulate the principles that drove those decisions and build from there.

I will rise to the bait in the Notice and try to come up with a hierarchy of how I would weigh the factors. I think the most important is actually the gross determination, just look at the product on a macro basis, where are like products regulated. You are likely to find the greatest

concentration of expertise, the greatest ability to compare similar products if you go with that.

Then, look at what is the innovation, what is the driver, what is the sponsor thinking, what is their expertise and what are they trying to add to medical technology.

Look at the point of view, as somebody mentioned very early this morning, at the point of view, what feature of the product will predominate. I actually ended putting what raises the most significant safety and efficacy issues lower down because I am of the view that through virtually any of the three centers and any of the application processes, you can obtain the data you need to assure safety and effectiveness.

Then, what is likely to be changed postmarket, where is the most interaction going to be after the product is already on the market. Again, we are only talking about assignment, we are not talking about how the product is regulated. It is who you are going to interact with.

It is in this order I think you start to get to what is going to set the best communication between the sponsor and the center, because again, I sound like a broken record, but I think it is a

management issue.

[Slide.]

I tried this thought experiment. Don't try this at home. But if you went with the idea in close cases let the sponsor decide. There is actually some statutory support for that. Section 563 recognizes that the sponsor is going to try to make a recommendation, and if the agency doesn't rule within 60 days, that sponsor's recommendation will become binding.

The Part 3 regulations have the same concept, it has always been there. Again, assignment is only where, not how, and it is becoming less significant in light of the new legislation. Again, the more balance there is between the centers on user fees and time frames and the scope of an application, and the standards of safety and effectiveness, the less important the "where" becomes.

I will leave it to present agency counsel to advise on this, but you might even come up with better defenses for the agency if you go with let the sponsor decide.

Now, the reason I called it a thought experiment is I think if you run through this, and

think of what the world would be like if on hard questions on primary mode of action you let the sponsor decide, you might reject the concept, but I think the reasons you come up for rejecting it will tell you a lot about the factors you would want to impose as to where to direct things.

When I ran through it, I kept on coming back to the area of expertise. If we let sponsors decide, we will have the same product spread over potentially three centers, will dilute our expertise.

But that is just, as I said, something that might help you break this Gordian knot.

MR. BARNETT: Two minutes.

MR. FOX: Thank you.

[Slide.]

As I said, I don't have a lot of great answers on regulation. These are just examples of single applications, two applications in hybrids.

[Slide.]

My own view is that multiple applications are becoming less of a concern as reviews are better coordinated. I think that has been one of the most important reasons why people have resisted multiple applications is the need to have to go

through two tracks as if they are independent, but if they are coordinated, I think it is less of an issue.

We have advised clients to use a lead application and a pull-out, stand-along application. There are many sponsors, particularly small device companies that actually want that second application, they want their clearance as an asset from CDRH.

With that said, I think, as I said, in most instances, all the necessary data can be obtained under one of the umbrella applications, PMA, NDA, or BLA, and if I am pushing one point this morning, it is the last one. It's for drug delivery technologies, consider using the PMA as the lead application.

Right now again, in almost every instance, primary jurisdiction goes to CDER because it's the therapy inside the body that tends to be the driver, but I think as you get towards very active delivery systems, nanotechnology and things I have been exposed to over the last two years, I think it is very clear that the device issues predominate and all the incremental data you would need to address the drug labeling could be accumulated

through the PMA and may even allow the device sponsor to walk away with labeling that answers the incremental drug questions.

[Slide.]

On lack of transparency, I will make this brief. I think the key is to share all the precedents inside the agency. I was stuck by the survey of employees where employees complain that they didn't know what the agency's prior precedents had been. I think that is just a recipe for disaster.

I think all the classification assignment decisions need a written record of decision. I would urge you to implement Section 563, which was introduced under FDAMA. I think the issue about standards for mixed regulation, if you are going to mix and match, I think that is a very difficult area and I think that you need rulemaking on.

[Slide.]

My discussion wouldn't be complete if I didn't remind you of what I experienced firsthand litigation the ultrasound contrast case in which we had products running through Devices, and products running through Drugs, CDER and CDRH, in which we showed up in court with no administrative record to

explain how we had reached that disparate position.

In the end, in the citizen petition response, we explained exactly how we got there, but we didn't have that going on. It is very, very important that you overcompensate in the beginning by articulating very, very clearly why you are doing what you are doing and memorializing that in writing. That is the only way I think that you will keep your precedents straight.

All of this is, in the end, going to be subject to negotiation on a case-by-case basis, but you need to know and you need to not rely on institutional memory, so to speak, to understand why you negotiated a certain position and why a given sponsor had a given package.

I will take questions. Thanks.

MR. BARNETT: Thank you, Mr. Fox.

Our next speaker is Patricia Shrader from AdvaMed.

AdvaMed

Patricia Shrader, Esq.

MS. SHRADER: Good morning. I would like to thank the FDA for the opportunity to present comments on this very important subject.

My name is Pat Shrader. I am Corporate

Vice President of Regulatory Affairs and Compliance at Becton, Dickinson. Today, I am here as a member company spokesperson on behalf of AdvaMed, which is the largest medical technology association in the world, representing more than 1,000 innovators and manufacturers of medical devices.

One of AdvaMed's principal roles is to support laws and policies that foster innovation and bring safe and effective technologies, including device combination technologies, to market very efficiently.

In its Federal Register Notice, the FDA raised a number of questions to help frame the discussion on steps needed to refine and improve the regulation of combination products. AdvaMed will be submitting written comments on these questions. Today, we just want to summarize recommendations that we have received to date from member companies on these issues.

The first question that FDA asked is for guiding scientific and policy principles that should be factored into the ongoing effort to rewrite the Intercenter Agreements.

As you know, in March of this year, AdvaMed, along with Pharma and Bio, authored and

submitted several general guiding principles for combination product reviews. Since that time, there have been a number of significant developments including new amendments to the Food, Drug, and Cosmetic Act, and last summer's Part 15 hearing.

These developments have further directed and refined our understanding and our views on appropriate combination product principles and procedures. We would therefore ask that the March document be referenced only with respect to certain core themes.

For example, the now statutorily recognized need for prompt and efficient review of combinations, the need for combinations involving devices to have full use of the mechanisms provided by FDAMA, and the need for improved and more standardized Intercenter Agreements.

Along with these core themes, other recommendations that reflect these more recent developments should be considered.

FDA's next question relates to primary mode of action and the factors that FDA should consider in determining the primary mode of action for combination products. AdvaMed addressed this

issue in its presentation at the hearing in June on combination products containing live cellular components, and in a follow-up letter to FDA's Chief Counsel on that same issue.

As we have conveyed on prior occasions, we believe interpretive instructions on primary mode of action already exist and are clear from the law itself and from FDA's consistent application of the law over many decades.

Over the last decade, AdvaMed's member companies have come to rely and build their businesses around two fundamental interpretational standards - first, that FDA looks at the combination product, that is, the product as a whole, and not the relative contribution of each constituent component, to assess primary mode of action.

Second, the mode of action would be determined based on the primary intended function of the combined product.

A principal theme of the CDRH-CDER Intercenter Agreements provides that products which have primarily a structural, physical repair or reconstruction purpose should be regulated as devices. From the Intercenter Agreements, from RFD

decisions, and from informal center assignments over the years, there has emerged long and varied lists of combination products granted primary device status based on the intended function of the composite product.

Examples include drug-eluting stents, antibiotic-filled cement and spinal fusion products containing biomaterials. All of these serve primarily a structural function. Condoms with contraceptive agents and dental prophylaxis pastes with drug component, these serve primarily a physical function. Finally, dressings with antimicrobial agents and tissue-engineered wound repair products serve primarily a repair and reconstruction function.

This is just a small representative sampling of the many combinations that have been designated as devices over the last decade based on the assessment of the two essential factors I mentioned, assessment of the primary function of the combined product, and second, an analysis oriented to the composite product rather than a detailed evaluation of the constituents.

These two interpretive factors which have been used very consistently have served both the

agency and the industry well. On the one hand, they fostered innovation, and on the other, they have protected and preserved the public health.

Innovation has been fostered because of the legal and policy initiatives that are uniquely available under the device premarket review structure. From the public health perspective with over a decade of combination assignments to CDRH, there has been, to our knowledge, not a single postmarket safety issue that has arisen as a result of those assignments.

Companies with combination products regulated as devices have oriented their operations around this historical system for classification. Any alteration of product status by virtue of new interpretive factors could potentially change their entire framework for doing business.

Given the substantial and potentially severe consequences AdvaMed believes that formal notice and comment rulemaking is required if FDA is interested in further defining or clarifying the primary mode of action standard.

As a result, we were gratified to hear from the agency last week in an educational forum concerning MDUFAMA, that any proposed modifications

to the primary mode of action standard would, in fact, undergo formal notice and comment rulemaking.

We agree with the agency that these issues are too large and too important not to be debated fully and fairly on the record.

As a related question, FDA has asked what factors should be considered in assigning primary jurisdiction instances where the primary mode of action of a combination cannot easily be determined.

Two factors warrant discussion. First, as AdvaMed has previously stated, one important equitable factor is whether the same product is already approved or cleared by a particular center for different use. Consistency of regulation with respect to product development strategy and premarket development testing programs is important to all companies, large and small.

Development and maintenance of multiple premarket review systems through the same core technology requires a substantial investment of resources, time, and personnel that may hinder future product development for many companies, and could be so burdensome as to destroy core businesses for others.

Second, a theme of fostering technologies and public health advancements should be considered. Many combinations currently regulated as devices represent important improvements in patient care. These products have benefitted from early collaboration meetings, 100-day meetings, and modular reviews, least burdensome review principles and humanitarian device exemption initiatives, all these are unique to the device premarket structure.

Since CDRH jurisdiction over combinations has demonstrated effective review history, in those instances where primary mode of action is otherwise unclear, and companies believe that a device assignment would serve to foster and advance their technologies, deference should be given to this important principle.

Next, on premarket review issues, FDA has asked what scientific and policy principles should be followed in selecting premarket review authorities for combinations. In the preamble leading up to this question, the Notice observes that while the Act requires that primary mode of action must determine the appropriate center for review, it doesn't address which authorities should be used to review combination products.

This statement suggests that there might be flexibility in mixing and matching premarket authorities for combination products. If this is the case, AdvaMed respectfully disagrees for several reasons.

First, Congress has now sent the agency a clear message that use of premarket device authority by other centers must be studied. Under Section 205 of MDUFAMA, Congress recognized the premarket concerns of the device industry and required that the agency prepare a report on the timeliness and effectiveness of device premarket reviews by centers other than CDRH.

Industry concerns with this issue were further reaffirmed recently when, in October, the agency published a self-assessment report on combinations. In that report, the agency offered the following example of other centers perspective on device premarket reviews, and I am quoting now from that report.

"Some CBER and CDER participants mistakenly suggest that CDRH does not require effectiveness data and that the PMA process is only required for the first device of a kind. In other words, the second of a kind could be regulated

under the 510(k) process."

As you can appreciate, these types of comments raise important questions concerning the use of device authorities by centers other than CDRH. Moreover, in contrast to single-entity products, combination laws are very clear on the issue of premarket authority.

The law states that if the primary mode of action is that of a device, the persons charged with premarket review of devices shall have primary jurisdiction. Consequently, if a combination product is deemed a device, such that device premarket authorities apply, it must by law be assigned to CDRH. No flexibility is afforded on this issue.

The agency next asked what criteria should be employed to determine whether a single application or separate applications would be most appropriate for combinations. Our member companies see advantages and disadvantages of separate applications in different ways, at different times, depending on the specific regulatory factual and business circumstances presented by their particular combination.

We believe that these differing views can

be fully reconciled by distinguishing the requirement for separate filings from separate filings that may be at the option of the sponsor.

Several specific recommendations highlight and explain how this could be implemented. First, in order to avoid redundant reviews and excessive regulation, only one filing should be required in the majority of cases. Indeed, we believe that as FDA regularizes and improves its internal processes, and as there is greater accountability for review of combinations, there should be fewer mandated separate applications.

There are certain circumstances, however, when a company might see separate filings as useful for regulatory and business or marketing reasons. You have heard some examples of that already this morning.

These factors include where two different companies, for example, a drug company and a device company are involved in the manufacture of combination components, where the components are expected to have separate distribution and use or reuse patterns and where primary jurisdiction for a combination has been given to a center other than CDRH, and the device component is capable of being

separately reviewed.

Examples include drug delivery devices, infusion catheters, jet injectors, insulin pens, and others. In these circumstances, AdvaMed believes that separate filings may be appropriate, but the key to this recommendation is that it should be at the option of the sponsor.

Related to this topic, FDA has also asked whether the need to apply a mixture of different postmarket approaches should influence the issue of one application or two. We think the answer to this question is much like our proposed general approach to dual submissions, that is, the mixture of postmarket authority should not trigger a requirement for more than one application, but some companies at their option may regard this as an appropriate contributing reason to request dual submissions.

FDA's next series of questions address postmarket controls and asks for the scientific and policy principles that should determine appropriate manufacturing and adverse event reporting requirements for combinations.

As the agency is aware, before science and public principles, policy principles are

considered, legal principles must come to bear. MDUFAMA mandates that the agency ensure consistency and appropriateness of postmarket regulation of like products subject to the same statutory requirements.

In implementing this new law, AdvaMed believes that appropriateness should first and foremost guide postmarket decisions and that consistency of like products should then follow.

We also believe that the concept of like products should be interpreted narrowly to ensure that manufacture and postmarket reporting decisions are appropriate for each and every specific category of combinations.

We believe, for example, that drug-eluting stents and antibiotic filled cement are not like products for purposes of this analysis even though the outcome of the analysis may be the same.

We also believe that delivery systems used to augment specific drug therapies will have many subcategories of like products, each requiring a separate evaluation concerning appropriate postmarket approaches. We are not prepared today to provide specific category-by-category recommendations on these issues. We simply ask

that these issues be reviewed on a narrow like product basis.

In contrast to the statutory constraint for selecting premarket authorities for combinations, there is no similar constraint for selecting postmarket obligations. Consequently, we believe that appropriateness should address, not just product types, but also a variety of other considerations.

For example, the proposed marketing scheme for a combination, that is, whether the two components will be sold by different entities and have different distribution schemes may be considered in assigning postmarket obligations.

Similarly, equitable considerations, such as the quality systems and postmarket reporting reviews already in place at the sponsoring entity should be factored in, perhaps not as the most important determinant, but as one that may help sway when a decision could go in either direction.

Finally, policy issues should come to bear, for example, there are certain legal requirements that are unique to devices, such as design controls and malfunction reporting, and the application of these authorities may be useful in

defining a single or hybrid postmarket regulatory scheme.

The framework for determining appropriateness should be flexible enough to consider all of these factors, but overall, the decision should be based on avoiding redundancy and overregulation.

Finally, the specific rules of the game for quality systems and adverse event reporting, as well as other postmarket issues, such as promotional and compliance systems, need to be made early on in order that companies, both those that have sought requests for determination and those that have pursued more informal center assignments, can begin to build and rely on a defined set of postmarket requirements.

We believe these obligations should be documented, not just for the sponsor, but for agency personnel, as well, to avoid any confusion that companies may experience.

Finally, with respect to your call for other comments, we offer some points on the proposed structure and function of the new Office of Combination Products. As the agency is aware, the concept of enhanced authority was an essential

theme that was advanced by AdvaMed in discussions leading up to the new combination amendments.

We believe as FDA finalizes its plans for establishing this very important office and ensuring its full authority, that it will provide the Office with clear, direct, and regular access to the Commissioner.

We also believe this Office must be well staffed and sufficiently expert to meaningfully review the diverse and complex scientific and clinical issues that so often confront combination technologies.

With those final recommendations, AdvaMed thanks the panel for its time today and for its serious consideration of our comments.

Thank you.

MR. BARNETT: Thank you, Ms. Shrader.

Our final speaker on the agenda this morning is Dr. Michael Gross of Aventis Behring.

Dr. Gross.

Aventis Behring

Michael Gross, Ph.D.

DR. GROSS: Good afternoon. My name is Michael Gross and I work for Aventis Behring as Vice President of Worldwide Compliance. Aventis

Behring is a biologics manufacturer.

I also am the leader of the Parenteral Drug Association's Interest Group on Device-Drug Delivery Systems and have served in that function since its inception about five years ago.

I have worked on various combination products since about 1987, even before I realized I was working on combination products.

[Slide.]

My first overhead lists a few examples or actually lists I guess a resume of experience in combination products just to give some context for my remarks.

Much of what I will present today are my own thoughts. I am not here representing Aventis Behring or PDA, although I have their support in making this presentation. The inputs are mostly my views and the views of a few colleagues who are also experienced in combination products with whom I have discussed this presentation during a recent workshop in Philadelphia on combination products, and I appreciate their inputs.

I am pleased that FDA now recognizes that combination products are a fourth product category in the combination product downstream issues, and I

will explain what I mean by that in a moment, are now getting the attention that they deserve.

When I say "downstream issues," I mean that since 1991, I have been concerned and have been somewhat outspoken about these issues that are a derivative of the jurisdiction and designation process, and these result from differences in regulations that would be applied to these products if they were treated separately, and my next slide has a short list of what my top seven favorites are.

[Slide.]

I list them because not all of them are captured in the Federal Register Notice, so I wanted to get on record by adding a few others.

I believe that the third bullet, manufacturing design changes is a particularly important one. I would like to turn my attention to the questions raised in the Federal Register Notice, and to minimize the word count in my presentation, I have abstracted the questions in the Federal Register Notice.

[Slide.]

In response to the first question, which concerns revisions to the Intercenter Agreements, I

would like to state that I believe that the CDER-CDRH Intercenter Agreement is a useful document and has stood up to over 10 years of use.

It may need some revision now, but I believe that is mainly fine-tuning. Later in my presentation and in response to Question 7, I will mention two examples in the Intercenter Agreement that concern me, however.

When FDA revises the Intercenter Agreements, I recommend that there be better inter-agreement consistency in the structure and content between all of the agreements. They should continue to include examples, and when they are reissued, they should be published, I believe, as draft guidances and be subject to comments from the industry.

I believe that the current agreements have created some confusion between combination products and products of unclear designation. The agreement should focus upon jurisdiction and the application of investigational and registration regulations only and the downstream issues should be clarified, but this should be done in a separate guidance, I believe.

The agreement should not state that a

combination product is a drug or a device or a biologic, or that they will be regulated as such. A combination product is a combination product, not a drug or a device or a biologic.

It will be regulated primarily through the application of whatever specific regulations are appropriate for that particular combination. To say anything else, I believe causes confusion in an already confusing area. I think that it is important that FDA policy and the articulations of FDA reviewers are accurate and consistent with the regulations and guidance, and are directed towards minimizing confusion and uncertainty over combination products.

I hope I am clear on that point, but I have actually heard, and I don't raise this as criticism because it is commonly done in this area, but at least on three or four occasions today, in various presentations, I have heard people say it is a drug, it is a device. It is not a drug, it is not even regulated as a drug. It is a combination product that may have drug authorities or device authorities or both applied to it, but the hair raises on the back of my neck when I hear statements like that.

The Intercenter Agreement or, if you will, the combination product jurisdiction guidance, and other future guidances that may address downstream issues, should all contain explanations of the decisionmaking process and should include, where possible, decision tree type diagrams, I believe. I have heard other opinions, differing opinions on that today.

The combination policy issued in July indicates that combination product reviews are to be collaborative and that the Intercenter Agreements--and when they are revised, I think it should be clarified--that these reviews are supposed to be consultative.

The last bullet on this slide refers to virtual combination products, and that is a term that I use for combination products that result from labeling, the third major category of combination products, the others being, according to my terminology, hybrid and co-packaged combinations, the bullet states that I believe that a virtual combination product is only formed when the package inserts or instructions for use specifically mention the use of another product by brand name, requiring mutually conforming labeling.

If the product is mentioned only in a general or a generic way, then, I believe that a virtual combination is not formed.

[Slide.]

The next slide addresses Question 2. I believe the best way to assign primary center jurisdiction is to base the assignment on primary mode of therapeutic action. It must be kept in mind that there are other modes of action in play in combination products, and these can't be ignored.

In those cases where a designation based on primary mode of therapeutic action is not straightforward, then, risk, mode of toxic action, and when all else fails, center expertise and experience should be considered, but whatever the outcome, the legal definitions of a drug, biologic, or device must be respected.

Again, wherever possible, the designation process should be based on considerations that are transparent and therefore a description and a diagram of the decisionmaking process and dispute resolution process should be publicly available.

[Slide.]

Regarding Question 3, it is a good question and one that would require more thinking

than I have needed thus far to apply to such a question, but since you ask, I will respond to FDA's question with a question, which may not please my friends in the medical device industry.

Nonetheless, if we are to consider the suitability of various registration mechanisms that may apply to combination products, since the 510(k) is not a premarket approval mechanism, and substantial equivalence may be more difficult to envision in the context of the intended use of a combination product, we may wish to ponder the appropriateness of placing combination products on the market through involving the 510(k) process.

Finally, although this is only developed in a preliminary sense, we may also wish to ponder the pros and cons of a separate application process for combination products meaning a separate application.

[Slide.]

Regarding Questions 4, 5, and 6, which cover three of the seven downstream issues on my top seven list, these should be addressed in separate guidance containing explanations and decision trees that define the determination and dispute resolution process that lead to

transparency, predictability, and consistency.

With respect to applications, I think it is a matter of establishing conventions that are acceptable to FDA and industry. I do not believe that the format of the submission should in any way control the outcome of any particular downstream issue. FDA is able to draw on whatever regulatory authorities it needs to assure the safety effect and quality of the products it regulates.

Regarding the quality systems downstream issues, I believe the design control process is a useful process in managing quality assurance and change control issues in the development, design, and manufacture of all types of combination products.

In particular, design control can serve as the linkage between separate manufacturers who participate in the development, manufacture, and marketing of either co-packaged or virtual combination products.

With respect to adverse event reporting, again, I believe that we need to establish conventions that make sense to both FDA and industry. What we want to avoid is both falling through the cracks due to underreporting and

overreporting caused by incorrect redundant reporting.

Finally, with respect to other issues I mentioned, that I don't believe that a virtual combination product is formed unless the compound and products are specifically named in each of the instructions for use and package inserts.

I also don't believe that passive transdermal patches or drug-eluting disks, as are cited in the Intercenter Agreement between CDRH and CDER, represent combination products, in particular when the drug-eluting disk is of a uniform composition.

I don't believe they are combination products, I believe they are simply nonconventional dosage forms and should be regulated as drugs.

I appreciate the opportunity to provide these thoughts today and I congratulate FDA for holding this meeting.

Thank you.

MR. BARNETT: Thank you, Dr. Gross.

We are now ready for what the agenda calls the Open Microphone Session. It always reminds me of a comedy club, but that is about as far removed from this meeting as you could possibly imagine,

but if you can do a stand-up routine on combination products, we encourage you to do that.

How many people do we have that would like to speak during this session? Okay. Let's use the microphones that are in the center aisle and let's be sure to identify ourselves when we start. So, come on up and let's say a 10-minute maximum for each presentation.

Open Microphone Session

Dr. Stuart Portnoy

DR. PORTNOY: My name is Stuart Portnoy and I am a physician and a biomedical engineer. I work at PharmaNet in my capacity as a medical device consultant.

I just finished spending eight years at the FDA and I was most recently the Branch Chief of the Interventional Cardiology Devices Branch, so I was involved with the review of drug-eluting stents, which, of course, are combination products, and I was also instrumental in the development of the CDRH-CDER review process for these devices.

I have two comments that I would like to make today. The first is it was interesting for me to hear many companies talk about looking at risk and taking a risk-based approach when you are

trying to make jurisdictional determinations.

I think it is an important factor, but it should be just one of several factors to be considered when determining product jurisdiction. Something that I believe was not mentioned or was not emphasized today was the impact that clinical trial design issues have on the evaluation of any therapy including combination products.

Clinical trial design determinations ultimately dictate how much and what types of safety and effectiveness data will be collected and analyzed to support market approval of a given therapy.

So, when FDA is considering jurisdictional assignments, I believe that it is critical to also examine which FDA center has the best clinical skills and experience to advise a sponsor regarding clinical trial design issues and then to adequately evaluate the clinical results that will be used to support market approval of the combination product.

A good example is the Johnson & Johnson drug-eluting stent, which was just evaluated at an FDA advisory panel meeting on October 22nd, 2002. The sponsor was approved in an IDE study to perform a fairly standard stent trial where patients were

randomly assigned to receive either the drug-eluting stent or the bare uncoated stent, which was the current standard of care.

The patient entry criteria, the study, safety and effectiveness endpoints, sample size, et cetera, they were all typical for a standard stent trial. So, I submit that the Device Group at the FDA was actually the most qualified to work with this company to develop the appropriate clinical trial and that the issues related to the use of the drug agent really did not play a critical role in how the combination product was evaluated.

In other words, it was evaluated as a new type of stent in a standard stent trial, so CDRH rather than CDER was in the best position to lead this review.

So, just to reiterate, it was the clinical trial design issues which were essential in figuring out which group was in the best position to evaluate that combination product.

The second point that I would like to make concerns the structure and function of the new Office of Combination Products. I believe that it is essential for the reviewers of combination products to continue to work from within their

respective centers, and not be pulled out to populate this new office.

In my opinion, the best way for reviewers to remain experts in their respective fields is to work within the current FDA structure. Therefore, I believe that the Office of Combination Products should first develop and articulate FDA policies and procedures and then serve its primary function, which would be to support the individual cross-center review teams in a mostly administrative role.

To reiterate, I do not believe that the office should be reassign FDA reviewers from the various centers to work from within the Office of Combination Products, but rather they should keep the cross-center review teams intact and in their respective centers.

Thanks.

MR. BARNETT: Thank you.

Is there anyone else that would like to come up?

Ron Citron

MR. CITRON: My name is Ron Citron. I am an independent consultant in the medical device area.

I have the what you call the fly in the ointment type of a project I am working on. I took a couple of notes here, which I will do as a submission on-line afterwards, but it says that I am working with a complex mechanical device, and it delivers a drug.

It is a unitary and disposable device, so therefore, because it's a unitary, disposable device, no matter what the complexity of the device is, it was established as an NDA, which is under the current rulings.

Now, the problem is the device has a preamendment predicate, quite of few of them actually. The drug is in a new form. So, what I was advised by the general hospital group, that basically, if the drug form is approved as an NDA, when you have two of those approved as an NDA, you can then have the device separately as a 510(k).

Well, that was likely the true catch-22. So, this is a case where I would definitely say we need two submissions, and one of the problems with this type of a device, and with many of these devices, when it goes as an NDA, you find that CDRH does not really have a say in the matter unless the sponsoring company specifically requests--this is

what I had to finally do--I had to go out there and get the company to make a formal request of CDRH to come in on this project.

When CDRH did come in, they were aware of the fact that they had not been really consulted on this device other than quite peripherally. So, the suggestion is basically that since the device is a very complex mechanical structure, do this as a separate CDRH purview, as 510(k), so the device functions, delivers the drug in the dosages that we declare it is going to be delivered.

Meanwhile, the NDA proceeds on the other side to show that the drug is safe and efficacious. This may sound like a little bit of like an internal conflict, but it is not, because you can prove, if you are saying I might need to deliver a certain dosage level at a certain point of the body to release a certain drug into the system, the device has to perform this function, the device performs a mechanical function of delivering the drug.

In this regard, the device would be much better handled under CDRH and then as the review goes on forward with the drug. So, I don't know how FDA would handle this. This does not mean that

once you approve the device, that therefore the whole thing is now approved. It just means that the people who, as the last speaker just said, the people who have the best experience in this area would be reviewing it.

Drugs really has no experience in determining the safety, efficacy, performance characteristics, and master specifications of a complex mechanical device, and they really should be totally out of that picture. It should be handled strictly through CDRH, and Drugs should be handling whether the drug itself that is being delivered is of an any value.

Now, they may determine that the drug is no good, meanwhile, the device can then be used for another drug, and so on, and so forth. This is where the device gets approved, it does not have to become an appendage to every single new NDA. That is just my comment.

MR. BARNETT: Thank you.

We had someone in the back. Come on up.

Ashley Whitesides

MS. WHITESIDES: Good afternoon. My name is Ashley Whitesides and I am from the law firm of King & Spaulding. We represent various

manufacturers of combination products and would like to briefly respond to two of the questions presented in the Federal Register Notice, Questions 2 and 4.

We submit that FDA must be guided by a combination product's intended use and agency precedent in the regulation of substantially similar products with identical intended uses when determining a combination product's primary mode of action, the assignment of primary jurisdiction, and the requirement of a single versus separate premarket application for the combination product's components.

We suggest that classwide jurisdictional assignments be made whenever possible. In particular, we believe that regulating substantially similar combination products with the same intended use in the same manner would promote much needed consistency in regulatory treatment.

Such consistency is not only desirable because it would result in greater equity, transparency, and certainty in regulation, benefitting both industry and FDA, but it is also legally mandated. In other words, similar products with the same intended uses should be subject to

the same premarket testing and application requirements including requirements for the submission of one premarket application or two.

The same reasoning would hold with regard to the application of postmarket requirements. The need for greater consistency in the regulation of substantially similar products with similar intended uses is called for by the legislative intent articulated in FDAMA.

In particular, in accordance with the least burdensome requirements established by FDAMA, FDA should not require the submission of two premarket applications for a combination product when only one application has been required for substantially similar products.

The more burdensome requirement of a separate application is contrary to congressional intent and existing FDA guidance.

We encourage FDA to revise its regulatory approach to combination products to ensure that the least burdensome pre- and postmarket authorities are applied including imposing consistent requirements for the number and content of premarket applications requested for substantially similar combination products.

Thank you.

MR. BARNETT: Thank you.

Is there anyone else who would like to speak? I will stand up to be sure I can see the hands, and I don't see any.

So, let me say that before we close this meeting, let me ask our panelists or Dr. Lumpkin if anyone has any final thoughts.

Seeing no hands there either, I will say that this meeting is officially closed including the audio teleconferencing portion.

Thank you for coming and we will see you again sometime.

[Whereupon, at 12:05 p.m., the hearing concluded.]

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