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FOOD AND DRUG ADMINISTRATION

**Gastroenterology and Urology
Devices Panel of the Medical
Devices Advisory Committee**

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P R O C E E D I N G S

[9:50 a.m.]

DR. MELMAN: I would like to remind everyone in attendance at this meeting you are requested to sign in on the attendance sheets that are available at the doors.

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

I would like each member to introduce him or herself and designate their specialty, position title, institution and status on the panel, whether voting member or consultant. And I would like to start on my far right.

MS. YOUNG: I am Diony Young. I am from Geneseo, New York, which is just south of Rochester. I am editorial of the journal "Birth: Issues in Perinatal Care," which is a peer-reviewed quarterly journal. I am a consumer member on the panel and I am cannot vote.

DR. VERTUNO: Leonard Vertuno, nephrologist and professor of medicine, chief of staff, associate dean for professional affairs at Loyola University School of Medicine in Chicago, Illinois. I am a voting member.

DR. BENNETT: I am Alan Bennett. I am a urologist and I am vice president of medical affairs for C.R. Bard. I am the industry representative and I am a non-voting member.

DR. SADLER: I am John Sadler. I am a nephrologist from Baltimore, from the University of

Maryland. I am a consultant and will be a voting member for this meeting.

DR. MULCAHY: John Mulcahy, professor of urology, Indiana University. I am a consultant and a voting member.

DR. HAWES: My name is Rob Hawes. I am from the Medical University of South Carolina in Charleston. I am a professor of medicine and am in the Division of Gastroenterology in the Center for Digestive Diseases at MUSC. I am, I think, currently a consultant and a voting member.

DR. YIN: I am Lillian Yin, a member of the Center for Devices and Radiological Health, FDA.

DR. STEINBACH: Joseph Steinbach, University of California and the VA Medical Center in San Diego. I work in the Division of Gastroenterology. I am an engineer and a biostatistician.

DR. LEWIN: I am Peter Lewin. I am with Drexel University in Philadelphia. I am professor electrical engineering and bioengineering and I am also professor of radiology at Thomas Jefferson Medical School in Philadelphia.

DR. AGODOA: I am Larry Agodoa. I am a nephrologist, director of the End Stage Renal Disease at the National Institutes of Health. I am a voting member.

DR. MELMAN: I am Arnold Melman. I am professor

and chairman of the Department of Urology at Albert Einstein College of Medicine and I am the chairman of this panel.

MS. CORNELIUS: I am Mary Cornelius. I am a nurse consultant in the Urology and Lithotripsy Devices Branch and executive secretary of this panel.

DR. DONATUCCI: Craig Donatucci from the Division of Urology, Duke University. I am a voting panel member and I will be moderating the process here.

DR. MELMAN: I will now turn the meeting back to Mary Cornelius, who will read the Executive Secretary statement.

MS. CORNELIUS: Good morning. Before we begin our discussion of the issues of reclassification of Extracorporeal Shock Wave Lithotripters indicated for the fragmentation of kidney and ureteral calculi, I would like to ask you to make sure that everyone fills out their lunch slip. That is our priority first.

I would now like to read for the record the conflict of interest statement.

This announcement addresses conflict of interest issues associated with this meeting and is part of the record to preclude even the appearance of impropriety.

To determine if any conflict existed, the Agency reviewed the submitted agenda and all financial interests reported by committee participants. The Conflict of

Interest Statutes prohibit special government employees from participating in matters that could affect their or their employers' financial interests. However, the Agency has determined that participation of certain members and consultants, the need for whose services outweigh the potential conflict of interest involved, is in the best interest of the government.

The Agency took into consideration matters relating to Drs. John Mulcahy, Jenelle Foote, Peter Lewin and Robert Hawes. These individuals reported financial interests in firms at issue but in matters not related to the topics discussed by the panel. The Agency has determined, therefore, that they may participate fully in today's deliberations.

In the event that discussions involve any other products or firms not already on the agenda for which the FDA participant has a financial interest, the participants should exclude themselves from such involvement and their exclusion will be noted for the record.

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

I also would like to read for the record a

statement concerning appointments to temporary voting status. Pursuant to the authority granted under the Medical Devices Advisory Committee Charter, dated October 27, 1990, as amended April 20, 1995, Drs. Jenelle Foote, Robert Hawes, Peter Lewin, John J. Mulcahy, John Sadler and Joseph Steinbach have been appointed as temporary voting members by Dr. Bruce Burlington, director for the Center of Devices and Radiological Health for the July 30, 1998 panel meeting of the Gastroenterology and Urology Devices Panel.

For the record, these people are special government employees and are consultants to this panel under the Medical Devices Advisory Committee. They have undergone the customary conflict of interest review and they have reviewed the material to be considered.

DR. MELMAN: Dr. Foote, would you like to introduce yourself?

DR. FOOTE: Sure. I am Dr. Jenelle Foote. I practice in private practice in Atlanta with clinical appointments at Emory and Morehouse. I practice general urology with a subspecialty practice in female urology and voiding dysfunction.

MS. CORNELIUS: I have one other thing to add to this appointments to temporary voting status. I neglected to add Dr. Lawrence Agodoa, who has also been granted temporary voting status for this meeting.

Agenda Item: Open Public Hearing

DR. MELMAN: We will now proceed with the open public hearing session of the meeting. I would ask at this time that all persons addressing the panel come forward to the microphone and speak clearly as the transcriptionist is dependent on this means of providing an accurate transcription of the proceedings of the meeting.

Before making your presentation to the panel, state your name and affiliation and the nature of your financial interest in that company. Let me remind you that the definition of financial interest in the sponsor company may include: compensation for time and services of clinical investigators, their assistants and staff in conducting the study and in appearing at the panel meeting on behalf of the applicant.

The first speaker listed on the agenda is Marie Marlow, who is vice president for clinical and regulatory affairs of HealthTronics, Inc.

MS. MARLOW: Good morning. Dr. Melman, members of the panel and consultants, Dr. Yin, Mr. St. Pierre, other FDA staff members, my name is Marie E. Marlow. I am a registered nurse. I am vice president of clinical and regulatory affairs of HealthTronics, Inc. So, I have a strong financial interest in that company.

My company is a PMA sponsor and a distributor of

extracorporeal shock wave lithotripters.

Thank you for the opportunity to share our company's extensive clinical experience regarding use of these devices and to support the Agency's reclassification of ESW lithotripsy systems from Class III to Class II.

I would like to begin my discussion by very briefly summarizing the regulatory history with regard to extracorporeal shock wave lithotripsy systems, which from now on I am going to refer to as ESW lithotripters.

Next, I will briefly describe the overall device characteristics and I will then discuss some of the principal potential risks that have been identified in the clinical studies performed to support PMAs for ESW lithotripters, in the published literature and by FDA via labeling requirements.

Finally, I will focus my comments on how the principal potential risks associated with ESW lithotripters can be addressed by special controls recommended by HealthTronics for each of these risks.

Regarding the regulatory history and reclassification process, you probably all know that the first ESW lithotripter, which was a spark gap system, was granted PMA approval by FDA in December of 1984. Since that first approval, approximately nine other original PMAs and more than 100 PMA supplements have also been approved for

ESW lithotripters, including spark gap, electromagnetic and piezoelectric systems. Therefore, over the past 15 years, these devices have seen extensive clinical experience.

In 1990, the Safe Medical Devices Act amended the medical device provisions of the Federal Food, Drug and Cosmetic Act and expanded FDA's authority to regulate life-sustaining or life-supporting devices as Class II devices. The Safe Medical Devices Act introduced "Special Controls" as a tool used by FDA to reasonably assure the safety and effectiveness of devices classified in Class II.

The new statutory and regulatory framework of the 1990 act anticipated the reclassification of a number of Class III devices into Class II. Based on the extensive clinical experience with the ESW lithotripter and the fact that each of the risks can be addressed by special controls, the device is precisely the type of medical device for which such reclassification was intended.

Significantly, intracorporeal electrohydraulic lithotripters, as identified in 21 CFR Section 876.4480, are preamendment Class III devices for which as we understand FDA is planning on proposing reclassification. FDA indicated in an August 1995 Federal Register notice that these devices, which have the same intended use as ESW lithotripters but do so invasively as opposed to extracorporeally, have a high potential for

reclassification. We believe that given the probable reclassification of these intracorporeal lithotripters, reclassification of extracorporeal lithotripters is similarly warranted, given the safety and effectiveness record and extensive clinical experience with these devices.

With your permission, I would like to quickly review the general device characteristics common to all ESW lithotripters, so that then we can discuss the principal risks in terms of these characteristics. Every ESW lithotripsy system, whether it is spark gap, electromagnetic or piezoelectric, is characterized by similar basic primary components; that is, the shock wave generator, along with its delivery system and the imaging system.

The overwhelming majority of ESW lithotripters in clinical use in the United States today generate shock waves either electrohydraulically, that is through spark gap, or electromagnetically, which I am going to refer to by the acronym EMSE from here on in. Generally speaking, the EMSE devices do not produce as great power as the spark gap system. Excessive generator power obviously may result in an increased risk of collateral damage to tissue surrounding the targeted calculus or to tissue in the shock wave "blast path." Inadequate or unreliable generator power may translate to a high failure rate or retreatment rate for

patients treated with such a device.

The generators in spark gap devices work in conjunction with an ellipsoid, such that the electrical charges produced by the generator and applied to an electrode result in shock waves that are deflected by the ellipsoid to form a focal zone or treatment focus. Generators in EMSE devices similarly work in conjunction with a focusing bowl, in which the electrical charge vibrates to form the focal zone or treatment focus.

The focal zone in an EMSE device is characteristically very narrow, forming a needle shape. The focal zone in a spark gap device is commonly wider and forms an oval shape. Too small a therapy focus can increase the difficulty of reliably hitting the targeted calculus every time, especially when the procedure is performed with only sedo-analgesia or with no anesthesia.

This may require a maximum or excessive number of shocks to be delivered for an effective outcome or may also result in an increased retreatment rate or it may increase the risk of renal or perirenal hematoma. This is additionally significant because the published literature suggests that there may be a relationship between multiple ESW lithotripsy treatments and transient post-lithotripsy hypertension and between renal trauma and transient post-lithotripsy hypertension.

Too large a therapy focus may increase the possibility of unintentional delivery of shock waves to surrounding tissue. This is of particular concern in the treatment of renal stones because of the increased risk of renal or perirenal hematoma, trauma to the renal artery and of particular concern in the treatment of ureteral stones in women of childbearing age because of the proximity of the uterine arteries, the ovaries and the Fallopian tubes.

As regards the x-ray system, a dedicated x-ray or fluoroscopy system is part of every ESW lithotripter and ultrasound capabilities are also available with some systems. The imaging system for any ESW device must be compatible with the shock wave generator and the delivery system, not only in terms of mechanical, electrical and electromagnetic compatibility but also in terms of ease of positioning and imaging during the lithotripsy procedure. The imaging system must be capable of supporting the labeling claims for the ESW lithotripter; for example, if the device is labeled for use in the treatment of middle and lower ureteral stones, the imaging system must be capable of providing adequate visualization of stones during procedures in these locations.

Of course, the radiography or ultrasound device should comply with any or all current FDA standards and guidances for these types of devices, things like maximum

radiation exposure suitable for the procedure, diagnostic ultrasound capabilities and so on.

Moving to principal risks and the special controls that apply, as the FDA panel and FDA staff know very well, part of the PMA approval process for every ESW lithotripter includes development of labeling that discloses the potential risks or complications and adverse events that may be associated with use of the device. For purpose of examples here, I am going to use the principal potential risks that are described in the labeling for the HealthTronics device, but all of the ESW lithotripters bear very similar labeling, which seems to be additional proof that the risks associated with these devices are well-known and well-characterized.

Each of the principal risks, which I am about to discuss is addressed by a special control, which I will also briefly summarize.

For purpose of review, "Special Controls" is a term used to describe a variety of features, which guard against potential risks arising out of device design, manufacturing or use. Special Controls allow each potential risk to be addressed to reasonably assure the safety and effectiveness of the device. A variety of special controls may be used. General categories of controls include FDA Guidelines, data requirements for 510(k) submissions,

labeling requirements, enforced via FDA's misbranding authority, performance standards and "other appropriate actions."

Each potential risk associated with the ESW lithotripter has been matched with one or more special controls, which provide sufficient regulatory assurance of safety and effectiveness.

I have provided copies of three overheads that I am going to use now. Probably the most clinically significant risk to any lithotripsy procedure is treatment failure or other procedure or ESW lithotripsy retreatment required following the primary procedure. Of course, for any of these risks, there is a certain amount of association with the proficiency of the physician or the technician participating in the procedure. But, nonetheless, many of the risks also have causes that are under the control of the manufacturer.

I am going to stick to those, but every once in awhile I will acknowledge the fact that possible causes can be technique related. For example, possible causes of treatment failure can include a stone location or size outside of the device capabilities and labeling recommendations; stones that are excessively large or in areas that for mechanical reasons the shock head can't reach or the imaging system can't reach.

The size of the focal zone and the depth of penetration may be inadequate, especially in heavier patients. This could be associated with a design flaw in the device or claims made by a company for a device that hasn't been proven effective for subindication for use.

The reason that a treatment may fail or a retreatment rate may be high is because the shock wave delivery is erratic. This could be because the generator misfires, that the water has poor conductivity or a number of other reasons that are under the control of the manufacturer.

As I said before, inadequate or unreliable imaging may lead to an inability for the operator and the physician to adequately target the stone.

There are a number of special controls where these possible causes can be addressed. One of the things we do now under the PMA requirements is to provide shock wave characterization testing. HealthTronics would recommend that the characterization testing methods be reviewed and perhaps more modern or current techniques and measurement tools can be used.

I won't embarrass myself by discussing that further in Dr. Lewin's presence.

Test data can be submitted to show the device capabilities for stone disintegration. Now, certainly some

of this can be done in bench testing, but this also may require clinical data to reliably demonstrate the performance of the device in its actual clinical setting.

The same thing applies for test data to ensure the shock wave is accurately and appropriately focused to disintegrate stones. A lot of bench testing we can do beforehand to test the device's performance characteristics, but ultimately that is probably going to require some clinical data.

Another 510(k) requirement under special controls for the company to submit test data to show that the imaging device supplied with lithotripsy system has sufficient has sufficient diagnostic quality to detect and localize renal and/or ureteral calculi greater or equal to 4 millimeter or to meet any other requirement that corresponds to a labeling claim.

Again, this may require some clinical data to demonstrate safety and effectiveness.

Another 510(k) requirement under special controls could be submission of test to demonstrate to demonstrate that the shock waves are reliably delivered at a consistent power level. Bench testing may be able to suffice in most cases here.

There should be data to show that the radiography equipment is compatible with the shock wave generator. Very

simply, can you image throughout the procedure without exposing the patient to excessive radiation. Can both the shock head and the imaging system work together mechanically so that you can image during the procedure.

Manufacturers could also be required to provide data to show conformity, to design performance specifications and voluntary standards, such as IEC-601-2-36.

One of my colleagues this morning said I may have the wrong number there. It may be 602-2.

Then finally under FDA misbranding authority, the labeling requirements for each individual lithotripter should address such issues as the device applicability for renal, as well as upper, middle and lower ureteral stones, ECG-gated versus non-gated use, appropriate instructions for users based on the technical capabilities of each device, so on and so forth.

So, as we go on down the list of risks, it becomes apparent that certain special controls are common to all these risks and their possible causes. Bleeding and hemorrhage after a procedure is a common complication; causes, trauma to soft tissue structures, disruption of blood vessels. It could also be due to trauma from instrumentation from required secondary procedures or from the stones passing through the urinary tract.

A lot of the same special controls are going to apply to control this with: shock wave characterization testing to make sure that the blast path is appropriate for treatment of urinary tract calculi in the locations that are clean; accurate and appropriate shock wave focus. Again, that is the issue of do you have depth of penetration sufficiently narrow, sufficiently wide treatment focus.

It would probably be appropriate for test data to be submitted to show the imaging capabilities, to show the generator reliability, to show the compatibility of the radiography equipment with the shock wave generator delivery system and, again, to conform to any performance specifications developed by the company, as well as voluntary standards that may exist.

The same thing again here with labeling requirements, under FDA's misbranding authority, each company should be able to or should be required to develop labeling based on the test data that they have supplied as far as indications for use, appropriate instructions for users and so on.

Urinary tract obstruction or Steinstrasse, again, many of the same special controls can apply to control this risk. The possible causes of this risk are inadequate destruction of a calculi, inadequate visualization of stone fragments or edema and clot formation, post treatment, which

may be associated to trauma from the lithotripter but maybe due to other causes also.

I should also mention that sometimes urinary tract obstruction is really caused by inadequate stenting or other physician and technique dependent causes. But the things that the manufacturer can control, as far as this risk, some of the same items that we have talked about before under special controls -- and, again, the same thing, under FDA's misbranding authority, labeling requirements should be that each company disclose honestly what the capabilities of their devices are for treating large stones, heavier patients, what the maximum stone size and stone volume is and so forth.

The final overhead talks about two last risks that we can cover here today; one, being excessive -- I am sorry -- ecchymosis, petechiae and other localized reactions at the treatment site, again, we are getting common possible causes, as well as common special controls: an excessive number of shock waves delivered in a single treatment can be associated with localized reaction, where the shock wave enters the body or an excessively high power setting can be associated with this complication.

The same special controls apply: appropriate characterization of the shock waves, appropriate test data to show how each device behaves in a clinical setting can

help minimize this risk.

Excessive radiation exposure, this probably is more under the manufacturer's control than some of these other procedures. If we know that imaging throughout the procedure is required, then the performance standard for any imaging system selected to work a lithotripsy system should allow sufficient imaging to be conducted throughout the procedure without exposing the patient to excessive radiation. There are good FDA guidances in place as to appropriate controls for radiation devices. Those can be incorporated here.

The labeling requirements for each company should have an honest disclosure about the typical average radiation exposure that is expected during a procedure with that device.

Finally, there is the potential for electrical or mechanical injury to the patient or user. I think that design flaws and manufacturing flaws can in a large part be controlled by manufacturers complying with voluntary standards, ANSI/AAMI standards, with the UL and IEC standards. And also that under FDA's misbranding authority that we fully disclose potential capabilities of the device, as well as putting in procedures to minimize the risk to the patient and the user.

And I would just like to very quickly make some

additional comments and recommendations for special controls.

The FDA's Draft Guidance Document "Suggested Information for Reporting Extracorporeal Shock Wave Lithotripsy Device Shock Wave Measurements" should be reviewed and updated to reflect the current state of the art measurement methods and techniques, as I said before.

And as far as labeling requirements enforced via FDA's misbranding authority to prohibit false and misleading labeling, in addition to the labeling requirements previously discussed, HealthTronics recommends that labeling requirements should be used to address off label or unapproved use of lithotripsy devices. For example, there is only one ESW lithotripter right now that has been approved for use in treating cholelithiasis and this is in conjunction with a pharmaceutical agent. And I note that this indication for use has not been included in our discussions today. I think that is appropriate that ESW lithotripters indicated for uses other than the treatment of renal and upper ureteral calculi and renal calculi should remain in Class III.

Along similar lines, the safety and effectiveness of extracorporeal shock wave treatment is currently being studied for some orthopedic indications. It is important that not only labeling requirements but also special

controls for the design and performance of ESW lithotripsy devices address the potential for unapproved or off-label use of these devices.

A potential risk inherent in design changes to an ESW lithotripter is that certain modifications of the devices, such as changes to the configuration of the ellipsoid or changes to the patient interface or imaging capabilities may imply an intended but unapproved use for orthopedic indications. Unfortunately, some of these modifications not only can make the device more useful for orthopedic indications but also can potentially affect the safety and effectiveness of the lithotripter for treatment of urinary tract calculi.

The current approved uses of ESW lithotripters for treatment of renal pelvis, renal calyx and upper ureteral calculi dictate certain design and performance criteria that are well-known and have been well-established over the past 15 years of clinical use.

In order to address the potential use of an ESW lithotripter for orthopedic or unapproved indications and to address the risk of device changes to accommodate unapproved use, it is suggested that a provision in the recently enacted FDA Modernization Act can be implemented as a special control.

Specifically, Section 205 of the act states that

generally FDA's 510(k) review is limited to the uses contained in the proposed labeling. However, the law provides that if FDA believes that a reasonable likelihood exists that a device will be used off label for a use that could cause harm and not identified in the proposed labeling, FDA may request a contraindication in the labeling. Thus, a special control is suggested by the new law for the risk of a design that implies a new unapproved use of the device. FDA has statutory authority to require contraindications in the labeling.

HealthTronics believes that these special controls will provide FDA with the regulatory oversight necessary to reasonably assure the safety and effectiveness of the ESW lithotripter and further demonstrate a Class II designation for these devices is appropriate.

Thank you very much for your attention and your consideration of the issues associated with reclassification of this device.

DR. MELMAN: Any questions for this -- I would like to ask you a question.

What is the company's obligation, your company or other companies, to assuring that the device is working in the way it is supposed to after it has been used x number of times?

MS. MARLOW: Right now, the first thing that comes

to my mind are the GMP requirements for us to have a well thought-out and well-implemented complaint handling system.

DR. MELMAN: That is only if the person knows there is something wrong, but how do you know that there is something -- I don't do lithotripsy, but how do you know, like an airplane engine, after x number of miles, it is required to be brought into the shop to make sure it is working.

MS. MARLOW: Dr. Melman, with your permission, our president is here and my technical knowledge is minuscule compared to what he knows about how we service the devices and how we do complaint handling.

May I have him answer that for you?

DR. MELMAN: Sure.

Mr. Brown: Good morning, panel.

My name is Roy Brown. I am the president of HealthTronics.

If I may just address that question, HealthTronics, like I think every single device manufacturer in lithotripsy, has a preventive maintenance plan with each and every device that they deliver into the market. That is to say, generally speaking, there are today probably two or three preventive maintenance visits each year to ensure that the device is working in a proper manner.

But over and above that, on a daily basis -- and I

believe, Marie, I am speaking correctly, that it is written into the FDA law that F2, which is the key, is checked every morning. Is that not correct?

MS. MARLOW: I know it is in our labeling.

Mr. Brown: Yes, in our labeling. So, every morning before the first lithotripsy treatment takes place, there is a check that takes place to make sure that the focal zone has not drifted, been knocked off or something of that nature. So, there are requirements in place in the FDA labeling on that score.

Does that adequately answer your question, sir?

DR. MELMAN: Yes.

MS. YOUNG: Can I follow up --

Mr. Brown: Yes, ma'am.

MS. YOUNG: What is the life expectancy of the device?

Mr. Brown: Well, I guess the best answer to that is the original lithotripsy, which was approved in 1984, 1985, in that time frame, was the HM3 device and I believe there was something like 200 of these devices delivered into the U.S. marketplace, of which probably 50 or 60 are still in use. So, between -- certainly up to the 15 years would seem to be a realistic time frame regarding the mechanical capabilities.

Now, obviously, they are sort of a little bit like

automobiles. As they get older, the spare parts get a little bit more difficult to get from various sub-suppliers, but, by and large, certainly ten years would seem to be a reasonable number with which you could work.

DR. HAWES: What regulatory controls are there for the person operating the machine? Can anybody who wants to operate your machine?

Mr. Brown: Marie, why don't you -- could you sketch in the details of the stuff that I am not totally familiar with. That is your bailiwick.

MS. MARLOW: Again, during part of our PMA approval process, we worked out labeling and training requirements with FDA appropriate for our device. I am sure that because FDA has greater experience with all the devices, they can answer in general terms, but I will be glad to tell you what our experience is at HealthTronics.

Would you state the question again?

DR. HAWES: What requirements are there for credentialing to use your machine?

MS. MARLOW: Every new user of our device has to go through a set training program that we developed along with FDA and the institution buying our device or using our device is responsible for then credentialing that person based on our training.

Users that are familiar with lithotripsy go to an

abbreviated part of that training and, again, to my understanding, every institution is responsible for actually credentialing their staff members, but we provide the training and we provide the training and we provide the institution with a copy of our syllabus.

DR. HAWES: For mobile lithotripters, does the credentialing come under the guises of the hospital in which it plants itself or -- and what about clinics that are not associated with a hospital, how is credentialing done there?

Mr. Brown: There is no change, per se, in that -- each position, and that is the key issue. The position needs to be trained both in terms of a didactic training procedure that we have worked out and then the number of cases that they must either be present to physically watch a case being treated and then the hands-on treatment. It is not simply, you know, see one, do one, teach one. It is a complete number of --

DR. BENNETT: This was a problem years ago but now in every residency training program, lithotripsy is part of that. So, when someone comes out of the training program there, they usually have their certification in lithotripsy.

DR. HAWES: But what if I want to do lithotripsy?

DR. BENNETT: Well, we couldn't do it.

Mr. Brown: If you want to do lithotripsy on my machine, I would have to have you credentialed and we give a

certificate out to each individual physician who has been credentialed.

DR. HAWES: I think that just in reviewing the classification, I think the instrument is important, but I am wondering what the rules and regulations are in terms of credentialing. These things are mobile units now. They can be parked anywhere, I think. I happen to be a gastroenterologist, but I am interested in lithotripsy for other reasons and I am just wondering what oversight there is in terms of credentialing. What would I have to do to -- do I have to complete a urology residency program? What do I have to do to become credentialed?

MS. MARLOW: I think the short answer to that is there are -- and Dr. Yin can probably say this more eloquently than I can, but just from our experiences in our labeling today and getting our PMA approved, there are provisions in the regulations and there are special controls in the pay regulation that allow FDA to put in requirements for that if the panel feels strongly that there are certain recommendations that should be made.

There are currently, if I am not mistaken, requirements for each company to provide training and, again, I don't think that we want the companies getting into credentialing. That we probably would want to leave for the hospital medical staff.

DR. HAWES: So, Dr. Yin when a company has a lithotripter, are there specific rules sent out from the FDA that tell that company to label the machine in a certain way in terms of training?

DR. YIN: First of all, they must have operating manual to help to start up and like you were asking the same question, how to go -- Dr. Melman's question, how to go to everyday to demonstrate the device is ready for use and that person, whomever that is going to be in charge, should have gone through this training program. And usually for each machine, we work with the company, actually work with the company to come up with that training program.

If it is clinical, we will come and ask the panel if we don't have our in-house physician and if we do have our in-house physician, we will be able to agree with the company. Once that package is done and whomever bought the machine, say like a hospital or a private physician, whomever, then they would go into the contract with the company that has to be done. That is part of the agreement.

MS. MARLOW: Our attorney just passed me a note, which I think is very appropriate. FDA does not regulate the practice of medicine. However, FDA does have control over labeling and appropriate training. That is probably the short answer to that.

DR. DONATUCCI: I have a question about a comment

you make here regarding modifications of the device. I mean, the question you raise is whether modifications to the device, which would allow it to have broader capabilities, will decrease its performance characteristics.

I guess the implication here, of course, is that in order to reach that broader off-label market, modification would be made that would somehow fall below the special control level. Is that what you are saying?

MS. MARLOW: Before I answer, I just want to check and make sure that we can disclose some information that may or may not be proprietary.

All right. For example, HealthTronics has two products. One is a kidney lithotripter, for which we got PMA approval about a year ago. We are currently conducting clinical studies on a modified lithotripter for orthopedic indications. One of the studies that we have going right now is to treat heel pain syndrome, plantar fasciitis. In order to do that, you are treating an area -- you are trying to get the focal zone to hit very close to the skin surface, much closer to the skin surface than you do in kidney lithotripsy.

So, to make this device most appropriate for use in orthopedics, the ellipsoid is going to be different. In Europe, they are using lithotripters for non-unions. So, they use it in conjunction with a C-arm(?). We also have a

small series going right now on a non-union study. You can imagine that the positioning of the patient and the positioning of the C-arm in conjunction with the shock head is very different if you are going to be targeting, you know, midway down the tibia versus if you are targeting a renal stone.

If you try to make the design of the device do all things for all people, you are going to have to sacrifice a little bit of effectiveness here and a little bit there or you should have two dedicated designs.

DR. DONATUCCI: I understand that, but I guess my question is this. As long as the modification, whatever it may be, still meets the specific controls in place in terms of safety and effectiveness, then that is a non-issue. Correct?

MS. MARLOW: Good. So, let's make sure that the special controls are adequate to address that issue.

DR. DONATUCCI: Because otherwise the suggestion that the FDA has to anticipate a potential off-label use that could cause harm, I mean, that is a nightmare.

MS. MARLOW: Right. So, more importantly, make sure that the performance characteristics and the demonstration that the device can, in fact, reliably target and disintegrate a stone fall within certain parameters.

DR. DONATUCCI: Let me just ask the FDA a question

then.

When a modification is made, what is the threshold that requires notification and reevaluation by the FDA?

DR. YIN: First of all, I think, to answer a very fundamental question is if we say this device is for kidney stone and they are going to use it for orthopedic, if they actually label that. Immediately, there is a new intended use and immediately it will not fit into the category at all. It is a new intended use.

Number two, suppose they say, well, we don't tell anyone. Just put it there. Then FDA's job of doing the substantial equivalent review and we should be able to catch that, maybe sometimes we may be, you know, not able to. If we fail, then it is our problem. So, we should be able to do the substantial equivalent comparison.

DR. DONATUCCI: I guess my question, though, is at what point do you trigger how big a modification has to occur before you trigger a review?

DR. YIN: We do have a list of requirements that they follow and -- FDA follow, but you are right. Sometimes the company just go and introduce and we have to catch them. That is very uncomfortable, but a lot of times is that we have all the regulatory requirements of this for the company to follow and for FDA. We all know what should be it, but the part is that a lot of times we thought why are we having

compliance problem because the company took the very view and said, oh, well, they are little changes.

I know it is not very comforting to you, but we are trying to be, you know, trusting.

DR. MELMAN: This meeting is to modify the classification for lithotripsy, not non-union and not plantar fasciitis.

DR. YIN: No. That is correct. That is new intended use. It is not included --

MR. ST.PIERRE: If it is existent in two different classifications, can it be a Class II for renal lithotripsy and a Class III for, you know, pituitary lithotripsy or something?

DR. YIN: Yes. Definitely, the answer is "yes" and sometimes even I think it has been divided upper stone and lower stone and have different classification. We make that distinction there.

MR. ST.PIERRE: What we will be proposing or discussing today will be all ureteral stones, mid, lower and upper and kidney stones. But if you wanted to do biliary, then that wouldn't fall within this classification. So, same device with a different indication can be two different classifications.

And as I think, to address Dr. Donatucci's concern, that basically if it goes -- if this was

recommended for Class II, then that is a substantial equivalence determination. So, basically what the industry would need to do is say these are the specifications for our device and say these are substantially equivalent to the specifications that are already out there for another device.

So, if they can do that, then they get a marketing clearance for that device. If the specifications are outside of that, then we have to evaluate that and they will need to submit the applications to us and the testing to evaluate that specification if it falls outside the range.

So, to assess that change, maybe that would be done with bench testing, animal testing. Maybe it would require clinical data but, you know, I think any guidance or anything that comes forward, you know, we will address that issue that we are looking at a device with certain specifications. This is what is currently marketed. If you go outside of that, then we need to do our evaluations on those.

DR. YIN: And right now we are going full speed ahead, allowing the company to use the design control and in the design control they will have to demonstrate that the device is reasonably safe and effective also. Even if they believe that they don't require a new 510(k), they still have to meet that requirement even though they do not --

they are not submitting a 510(k).

DR. DONATUCCI: I guess what led me to this in the first place is the implication from what you said to me is that a company would want to make a modification to allow this to be used for orthopedic indications without seeking the indication from the FDA. And at some point that might decrease the ability to meet the requirements for renal stones or urologic stones, so to speak.

But I think -- it seems to me that the safeguards are in place to prevent that.

DR. YIN: Yes. There are safeguard -- number one, if they have a new intended use, but I think what Marie is trying to say is it is off label. Suppose the thing, you know, fits a little bit okay and maybe off -- if I were the physician, I say, oh, well, I am going to try this and there is no way FDA is going to regulate that physician.

DR. DONATUCCI: Right. No, I understand.

DR. YIN: But, however, if the company come out and publish a paper or do training and tell all the professionals that you can do that and immediately then FDA does have authority over them, only the industry. And I would agree with the lawyer out there, we do not regulate medical practices. However, there are ways, other than the labeling and the law requirements, that will limit the use of it.

We never are perfect. Remember that.

MS. MARLOW: There may be an example, if I am not taking up too much time by giving this example, in a cardiology device. Electrophysiology catheters were initially developed to do diagnostic testing and there are circular electrodes on a catheter. When the electrode at the tip of the catheter is large, bigger than 4/6 millimeters, you can do radio frequency ablation with the catheter.

An extremely innovative interventional cardiologist first started doing these procedures and everybody thought he was crazy, firing RF energy into someone's heart, but it was working on arrhythmias. So, it caught on.

Companies started modifying their catheters with a larger tip without making the claim that they could be used for RF ablation, which is absolutely a Class III indication for an EP catheter. When you had one very innovative, very talented, interventional cardiologist doing this procedure, it was not appropriate to intervene.

When you have people going out -- when you had other physicians adapting his techniques, based on their attendance at a yearly symposium, then it was time for FDA to intervene. As they heard that more and more physicians were trying to do this procedure, they required the

companies to show that the catheters could, you know, withstand the heat, could continue to do recordings during a procedure, even though RF energy was being fired through the catheter and so on.

So, that is one example that I can think of where, yes, initially you may get one or two people, innovative people, and that is how things happen in our industry, that you have very bright people trying something that no one else would, and then at some point in time you say, okay, it is time to step in and regulate this. This is no longer medical practice. It is public safety.

So, I don't know if that helps at all.

DR. DONATUCCI: It does. I guess the only -- if that catheter still met the original requirements that were in place when it was manufactured, this seems to be a loophole, so to speak --

MS. MARLOW: But there was no requirement that the catheter withstand RF energy being delivered through it. So, there was no requirement that a diagnostic catheter be shown effective to -- for treating arrhythmias.

DR. DONATUCCI: Yes, but that is a major modification with the catheter design --

MS. MARLOW: But it really does seem -- would you catch on that that is a major modification if you saw a 2 millimeter increase in the size of the catheter tip?

DR. DONATUCCI: Only if somebody told me they were hooking it up to a radio frequency.

MS. MARLOW: Yes, then you catch on. But if a company is distributing a catheter with a bigger tip, that is a tough one to catch.

DR. YIN: But we did have a case that, you know, with a biopsy device and then the company make it very big that you could actually remove the whole tumor and they claimed that they didn't make any changes. Obviously, there was a big huge commotion and even Congress was looking at it at that time.

So, I am saying that sometimes it is like 2 millimeter, maybe it is hard for us to catch, but now we are extremely sensitive to those sizes now.

DR. HAWES: But still, is it not based on how the company is acting, though? I mean, even if a hundred doctors were using this catheter to do radio frequency ablation, if the company, in fact, was not labeling it that way, marketing it that way, then it still doesn't fall under the jurisdiction of the FDA. Is that correct? It has to do with the company and their attitude toward it. If they are promoting it, if they are selling it, if they are teaching about it and sales and so forth, then it must be regulated, but if it is just a matter of a hundred doctors doing it,
I --

MS. MARLOW: And to my way of thinking if the company made a special device, a prescription device, as it were, for one and two positions, that is absolutely appropriate. When the company gears up their production line and saying they are for diagnostic use, that is -- it goes beyond disingenuous.

FDA is here to protect the public from things like that, but -- and you know we get into a philosophical issue, are you going to be able to regulate the honesty of any company. So, what you do is you try to put in the special controls and labeling requirements.

The other thing is the industry is pretty competitive.

DR. YIN: But let me ask the question another way. If a hundred physicians are all doing it and only use their product, are we going to call them in and say why? Now, if it is using different people's product, it is harder for FDA to find out, you know, what is really going on.

But it is only one company's product is bigger than all the others and only theirs can do that, it is much easier for FDA to deal with that particular product.

DR. BENNETT: I have a couple of questions.

First, I think, Don and Lillian may be able to answer this -- first, I thought your presentation was quite good and covered almost everything under risks and special

controls.

First we will go back to a concern that I have about down classification that I didn't think about this morning, Lillian, but I am now thinking, after I read the example of current lithotripsy labeling, which was written in the mid-eighties and lithotripsy has changed quite a bit. The 2,000 shocks and the not being able to do bilateral stones is not common practice. People have often used more than 2,000 shocks and they often -- they will do bilateral cases if the stones are small.

So, I have a problem with down classification and using the current labeling as the model for a predicate device. After listening to Marie, I have another problem. One of the major causes of treatment failure is the characteristics of the stone. Dihydrate stones break up better than monohydrate stones. Uric acid stones and cystine stones don't break up as well as calcium oxalate stones.

Stuvite(?) stones may or may not break up, depending upon the characteristics of the stuvite stone. None of this is addressed in any labeling and when you start thinking about off-label uses, some people are going to start treating tendinitis and there are no stones up there. So, once you down classify, you are now bringing up some of the deficiencies in our current labeling, which may never

get addressed at all.

How do you answer that?

DR. YIN: Before we down classify, maybe we need to clean up the labeling again to make it very specific.

DR. BENNETT: Okay. So that can be done.

DR. YIN: Today. And maybe Don already have done some of that. I hope so.

DR. BENNETT: I have never seen any labeling related to the characteristics of the stone. I think retreatments are probably more related to the size and characteristics of the stone than anything else.

Mr. Brown: May I just address that just briefly, your last comment there? I respectfully disagree. I am sure the stone composition has a lot to do with it, but I respectfully disagree because, quite frankly, as a provider of lithotripsy, a maker of lithotripsy and been in it since HM3 days, broadly speaking, I think the lithotripters today have gone down hill instead of up hill as regards to the retreatment rate, which is one of the key issues.

Today, we are getting lithotripters because they comply with the PMA that have retreatment rates in the 20, 30 and 40 percent range. I don't think that is just purely because of the stones. I think it is because of the power of the focal zone and things otherwise.

To a degree, yes, a part of it is due to the stone

composition, but it is not just stone composition.

DR. BENNETT: Well, I think also people have over the -- you know, back in the eighties we were treating everything. Now, you know, the size is important. Reading the x-rays, you can figure out which stones are going to break up better than other stones.

But the point I am making is that none of the stone characteristics are covered in any of the labeling and my concern is that if you down classify, that whole body of science is going to disappear.

MR. ST.PIERRE: We love to control labeling at the FDA. Basically, there is going to be probably a lot of discussion on this because we do have some recommendations for additions and want to elicit some discussion later on to see how we can change the labeling. So, labeling clearly we intend to have as a special control.

So, I think we may address some of those issues and any other -- you know, if we have missed some issues that you would like to see in there then --

DR. YIN: I am pleased you addressed that because this panel is best for those things because all of you are practicing people. So, therefore, practicing physicians that can really help us on that issue.

DR. LEWIN: I am also quite fascinated by your question. Wouldn't that be like encroaching on the final

decision of a clinician, who is deciding what treatment is best for the patient?

DR. BENNETT: Well, I guess it does in a way but I still think that there are lots of devices out there that are able to work on certain conditions and not on others. Let's talk about the biliary lithotripter issue. It is very clear that size has a lot to do with which stones will break up and won't break up. So, in your labeling if you know that 95 percent of oxalate stones or cystine stones don't break up in a lithotripter, don't you think you want to cover that in the labeling?

I mean, that is what labeling is all about.

DR. YIN: It is also the experience of the clinical study and we are supposed to report that in the labeling.

DR. MELMAN: So, it is in the labeling. Okay.

I think we will move ahead to the -- yes? Almost move ahead.

DR. STEINBACH: Sorry. One other point.

There is an adverse events database. Don and you have gone through it. Are there any events? There are probably less than 20 that would not be covered by your special controls.

MS. MARLOW: There are actually a lot of things that aren't in that. In that adverse database, if I am not

mistaken, are also non-lithotripsy-related events. I tried to pick out the ones that were most common, so that I could avoid going off on small tangents in a forum like this.

There is also quite a bit in the published literature. I know for our PMA, we were required to summarize what was known in the published literature. So, the very short answer to your question is there are far many more risks than what I talked about today.

DR. MELMAN: Any other members of the public that would like to make a comment?

[There was no response.]

Okay. I am now going to officially close the open public hearing.

Now, this meeting has been called by the FDA to consider the Agency's proposed reclassification of external shock wave lithotripsies for kidney and ureteral stones. In addition to the scheduled open public hearings, this meeting will periodically be open to public participation, which is a little different than other meetings we have had.

Public observers who would like to question, make comments or recommendations to either the panel or the FDA should step up to the podium to be recognized by the chair. However, I will ask that you hold your questions until the panel completes the classification questionnaire.

Agenda Item: Open Committee Discussion

I am now going to call to order the open committee discussion. The first speaker listed on the agenda is Mr. Donald J. St.Pierre, who is chief of the Urology and Lithotripter Devices Branch.

Mr. St.Pierre.

MR. ST.PIERRE: We are going to try to use technology here. This is the first time we have done this. So, any glitches, we do have overheads.

Good morning. My name is Donald St.Pierre. I am the branch chief of the Urology and Lithotripsy Devices Branch. As is customary, I will give a brief statement regarding our last panel meeting, which was held on April 30, 1998.

The panel made a recommendation of approval with conditions for an original PMA from Medstone International for a biliary indication for their currently approved lithotripter. The Agency is continuing to work on this application.

Please note, however, that the biliary indication is not included in the Agency's proposal, which will be discussed this morning and for which I will now give a brief introduction.

In accordance with Section 513 of the Federal Food, Drug and Cosmetic Act, the Agency on its own initiative, is proposing to reclassify extracorporeal shock

wave lithotripters indicated for the treatment of kidney and ureteral stones.

Since 1984, the Agency has approved 12 PMAs for this device type and indication, most of which have been supplemented with second and third generation models. Lithotripsy has also been reported on extensively in the peer-reviewed literature. Based on the Agency's long history and experience in regulating this device and on the information available in the literature, we believe that special controls can be developed for this device for the indication of kidney and ureteral stones to provide adequate assurance of safety and effectiveness. Therefore, reclassification from Class III to Class II is appropriate to consider at this time.

Today, we are seeking the panel's advice on the classification of this device based on your clinical experiences. This meeting will also be the first of several opportunities for industry and other interested parties to present their views on this topic. I say "first of several" because if after we consider your discussions today, we decide to move forward with a down classification, we will be publishing a proposed rule regarding the down classification, which will be available for public comment.

We will also be issuing a Level 1 guidance document in accordance with good guidance practices, which

we will first publish as a draft for public comment. After we have reviewed the comments and made necessary changes, we expect to publish a final rule and final guidance.

To help with today's discussion, I will outline what we propose as special controls. Essentially, they address four general areas: preclinical performance testing, clinical performance testing, labeling and training.

The proposed preclinical testing special controls include a standard to address mechanical and electrical safety, a standard for guidance on shock wave characterization and localization accuracy and guidance on road testing for mobile and transportable systems.

The clinical special controls include a limited confirmatory study for standard lithotripters, that is, lithotripters that have similar specifications to those that are currently marketed. We still believe that more extensive clinical assessment would be necessary for non-standard lithotripter technology. This more extensive study could be similar to the studies currently conducted for new lithotripters.

Labeling and training requirements would also be important to include as controls for lithotripters. As most of you know, we tend to spend a great deal of time on the labeling of medical devices and due to the complexity of

these devices, we still believe training should be required. Except for some minor labeling changes, these controls simply reiterate what is currently done for lithotripters.

Before you begin your deliberations regarding classification, Dr. Hector Herrera, who is a urologist and medical officer with the branch, will give a presentation of the most common risks associated with extracorporeal shock wave lithotripsy for the treatment of kidney and ureteral stones and outline some of the special controls that we believe will address these risks.

Our guidance to industry, which is being updated and will be discussed in detail in the second part of today's meeting, will provide more specifics on each of the special controls, which I have just outlined.

Now may be a good time to state that this is an unusual type of panel meeting for us and I think it is probably a first for the Agency, where we have actually made the proposal to reclassify and have taken it to the panel for their input.

Typically, industry petitions the Agency for reclassification and we take it to the panel for their recommendations.

Because this is new for us, you shouldn't feel the need to stick to the proposed agenda. I mean, we have arbitrarily broken the meeting up into two sections; one on

reclassification and one to discuss the guidance. If this doesn't work for you and you would like to hear our presentations regarding updating the guidance before you begin filling out the classification questionnaire, then let us know and we can move the talks up.

Also, since we are seeking input from all interested parties, I envision an more interactive type of meeting and I encourage people from the audience to come up to the podium and be recognized by the panel chair if they have something to add to the discussion.

We did send letters out to the lithotripter PMA holders and to the lithotripsy section of NEMA, the National Electrical Manufacturers Association, to make sure that they knew of this meeting. And I have also talked to the health policy people at AUA. So, I am sure there is a great deal of expertise in the audience today.

If we don't hear from you, I hope that you will provide comments in any future guidance or proposed rule. I thank you for your time and look forward to your deliberations. If you have any comments, I would be more than happy to address them now.

DR. DONATUCCI: Don, can I ask just one quick question?

MR. ST.PIERRE: Just one.

DR. DONATUCCI: So, under the clinical specifics,

which you just put up there, you have the option of basically requiring a full scale clinical trial.

MR. ST.PIERRE: Yes, we do.

DR. DONATUCCI: Even though the device is Class II or a non-traditional --

MR. ST.PIERRE: Correct.

And there are some designs we probably haven't even thought about today, you know, that may be available in the future and we want to make sure that we can control for those.

Okay. I will now turn the podium over to Dr. Herrera.

DR. HERRERA: Good morning. I am Hector Herrera, a urologist and medical officer for the Urology and Lithotripsy Devices Branch. I will go over the history and general safety and effectiveness data of the lithotripters. Later in the day, you will hear preclinical and clinical performance tests and specific labelings that we believe need to be discussed.

Extracorporeal shock wave lithotripsy for renal calculus disease was first introduced by Chaussy at Germany in 1980. The high output spark gap electrode power source usually necessitates regional or general anesthesia. The technique gained rapid acceptance and is now the treatment of choice for the greatest majority of renal and ureteral

calculi.

The Cornier-HM3 lithotripter dominated early experience with ESWL, but a number of improvements led to the introduction in 1986 of second generation lithotripters. This generation was characterized particularly by the electromagnetic and piezoelectric technology that enabled treatment to be performed without the need of the patient immersion and for reduced anesthesia requirements.

The technology continued to improve, resulting in third generation lithotripters, characterized by the large aperture of the focusing system, equipped with a combined fluoroscopic and ultrasound localization system and all integrated in a multifunctional table with a more compact presentation; thus, improving the localization system and shock wave energy delivery while at the same time decreasing the treatment time and enabling treatment under minimal anesthesia.

The ability to treat renal calculus disease non-invasively has resulted in a significant reduction of the patient discomfort and has made treatment available to a large number of patients with medical conditions that might preclude surgical intervention.

The overall benefit of these devices is their high efficacy, most frequently combined with a low complication rate. Extracorporeal shock wave lithotripsy successfully

fragments most urinary calculi. Effectiveness as the percentage of patients rendered stone free within three months is typically around 75 percent and can range between 55 and 98 percent. Typical retreatment rates have been reported to range between 1 percent and 25 percent.

Effectiveness can vary based on various stone characteristics. For example, the literature reports a lower effectiveness with cystine, staghorn and stones greater than 2 centimeters in the largest diameter.

Successful treatment outcomes have, however, been attained despite the use of different shock wave generator designs and the wide range of shock wave characteristics. The adverse events associated with ESWL are well known and anticipated. The adverse events that do occur typically resolve on their own with no additional medical treatment.

Now I would like to summarize the most common risks to health associated with ESWL.

Bleeding occurs following most treatments and is secondary to trauma to the renal parenchyma and usually resolves spontaneously in one to two days. Typically, bleeding manifests as either hematuria or hematoma.

Renal hematomas are usually asymptomatic and resolve spontaneously. In less than 1 percent of the cases a clinically significant hematoma occurs and these usually resolve with conservative management. As with bleeding,

patients most likely to develop hematomas are those with coagulation abnormalities, patients taking anticoagulants or aspirin or taking nonsteroidal anti-inflammatory drugs.

This risk can be minimized with labeling; for example, avoiding patients with uncorrected coagulopathy, having a washout period for patients on aspirin or nonsteroidal anti-inflammatory medications; limiting the number of shock waves administered during each session.

Renal injury, with associated nephron loss and/or tubule damage occurs in nearly all lithotripsy treatments and is typically limited to the size of the shock wave focal volume. This can be minimized with labeling; for example, limiting the number of shock waves administered during each session, in the preclinical shock wave characterization testing, which could verify that the shock wave is in the range produced by lithotripters already on the market.

Renal injury often results in scarring of the renal tissue; however, any functional change to the kidney usually resolves completely within 30 days without long term changes in renal function. This can be minimized by labeling; for example, limiting the number and frequency of treatments to the same kidney.

Hypertension is not a frequent risk among generally healthy patients. However, in the elderly and in patients with borderline hypertension may increase the risk

of patient developing chronic hypertension. This can be minimized by adding a caution in the labeling regarding treatment of elderly and borderline hypertense.

Cardiac arrhythmias occurs in approximately 20 percent of patients and is due to vagal and parasympathetic activation and the action of sedo-analgesia. These typically resolve spontaneously upon synchronization, electrocardiogram gating or terminating treatment and can be minimized by labeling; for example, stating that cardiac monitoring required and switching to gating if there are problems. The device should also be designed to limit the firing of shock waves to 120 times per minute.

Urinary obstruction occurs in up to 5 percent of patients and is due to passage of stone fragments. This risk is most likely to occur in patients with large stone burdens and is often easy to treat. Obstruction can be minimized by labeling; for example, contraindicating urinary tract obstruction distal to the treating stone and requiring radiographic follow-up.

Urinary tract infection may be the result of the release of bacteria secondary to fragmentation of infected calculi or due to tissue damage created by the shock wave, bacteria can enter the blood stream, according to the literature infection occurs in less than 4 percent of cases.

Clinical experience has shown that prophylactic

antibiotics reduces the risk of infection. The risks of these infections can be minimized by labeling; for example, clearance of infection should be documented before treatment and through the use of prophylactic antibiotics in high risk patients, those with defective heart valve, cardiac disease, immunosuppression and diabetes mellitus.

There is a potential for injury to adjacent organs during the passing of the shock waves through the patient's body, mainly to the liver, spleen, pancreas, lungs and bowel. Serious injury is rare. According to the literature, careful targeting of shock waves is the best way to prevent damage to air-filled organs.

Pregnancy is a contraindication for lithotripsy. Findings of growth disturbance produced by the shock waves has been identified in pregnant animals.

Due to the observed growth plate disturbances in the epiphyses of developing long bones in rats, even though were they not duplicated in subsequent animal studies, the long term effects of lithotripsy in the pediatric population remains unknown.

Long term effects of extracorporeal shock wave lithotripsy on female fertility remains a concern. There is a potential for injury to the female reproductive organs during treatment of distal ureteral stones because of their proximity to the shock wave. To date, experimental data

reveal no long term severe adverse effects of ESWL to the female reproductive system.

Other minor complications include colic, skin irritation, nausea and fever. These are usually controlled with sedatives/analgesia and are for the most part of short duration.

As has been the case in all lithotripters approved in the past, a training requirement for physicians will continue and should also help to minimize risks to the patient.

To conclude ESWL has a very high effectiveness rate with a good safety profile. If you have any questions, I will be glad to entertain them now.

If not, I will turn the podium back to the panel for your deliberations.

DR. HAWES: Dr. Herrera, I just have one question. Bear with my ignorance in this.

There seems to be a sort of a play off between the power that the generator can produce and the effectiveness of stone fragmentation and the need for algesia. Is there a clear trend in lithotripsy sort of industry -- is there a biphasic trend where we -- it sounds like we had powerful generators at first. They required general anesthesia and I assume more complications.

It sounds like from earlier comments we have gone

through a phase now where there -- with the introduction of the piezoelectric system that we have less power and less analgesia. Is there a trend now in the opposite direction and, I presume, a greater treatment rate and is that trend now changing back into the more analgesia range?

DR. HERRERA: No, I don't think so. The trend is to use the least possible analgesia. In that way they can send the patient home faster.

DR. HAWES: So analgesia, less analgesia is winning out and then people are accepting more retreatment.

DR. HERRERA: Yes.

DR. HAWES: And that probably makes for a greater safety margin --

DR. HERRERA: Because there is more safety with less power. Definitely.

DR. AGODOA: Do we have any data on collateral damage with higher power versus more frequent treatment with lower power machines?

DR. HERRERA: Well, within the years, these have been the data that have been collected and that is why the companies had this idea to bring the power down.

DR. AGODOA: So, with more frequent treatment, the collateral damage -- we have data that show that the collateral damage --

DR. HERRERA: No, the frequent treatment is not

as --

DR. MELMAN: Is not what?

DR. HERRERA: The retreatment only is found in cases that the diagnosis of response with cystine less needs at the first place or have been treated stones with the very large burden. But it is not that is in every single case that you have to retreat a patient.

MS. YOUNG: Please, could you elaborate on the clinical studies with respect to pregnancy?

DR. HERRERA: Well, in the animals, they studied animals that were pregnant and they were subjected to the lithotripsy and there was some minor damage. That is why they decided to put the contraindication in the pregnancy.

MS. YOUNG: Are there any human data available?

DR. HERRERA: No. No, because that is one of the contraindications. Absolute contraindications.

DR. BENNETT: It is a contraindication.

MS. YOUNG: Yes. I realize that in the labeling, but, you know, that is an issue that I want to address later on with respect to the labeling.

DR. HAWES: Do you see any need -- is there any separation between the different lithotripters? In your opinion, is there any reason to label a spark gap system more powerful, more collateral damage, more complications differently than either the piezoelectric or the

electromagnetic?

DR. HERRERA: No, I don't think so, no.

DR. HAWES: So,, the safety parameters -- they can be logged together.

DR. MELMAN: I have to say as far as I recall when the piezoelectric first was introduced in Europe, it killed people, you know. It is not that -- there were deaths. So, it is not just necessarily because they are lower power that -- the only thing that is going to happen is that there is a higher retreatment rate. I think it is more complicated than that.

DR. HAWES: That was my question.

DR. MELMAN: I sense the way the machines are bought in the United States depends upon the money that is available in the institutions and the local area and how people want to practice medicine is independent of the machines. The same machines are available to everyone. It depends upon who wants to buy what and how they want to practice medicine.

DR. DONATUCCI: But aren't there -- excuse me. I interrupted.

DR. MELMAN: I think what tends not to be available and maybe should be available is -- because the companies -- I am sure Dornier has data for 14 years that is gathered from all over the world because they have to

produce the data as part of their follow-up study.

Our next thousand number of patients and what happens when you treat such and such a stone, you know, what size in a particular patient and that kind of information would be useful to --

DR. BENNETT: Well, the AUA guidelines -- the AUA went through that and it is all in the guidelines as far as -- you know, that is where the guideline came down to no greater than 2 centimeters should have lithotripsy.

DR. MELMAN: Two meta-analysis.

DR. BENNETT: Yes.

DR. HERRERA: Yes. All the clinical data is in the -- on the labeling.

DR. BENNETT: And they are doing ureter now. They are working on the ureteral stone guidelines. If you read the guidelines for the upper tract stone, all this material is in there.

DR. MELMAN: Okay.

DR. LEWIN: I wanted sort of to help you with understanding that perhaps not the power of the external generator is that important. What is important is the second slide of Dr. Herrera where he showed what is the focal volume of a lithotripter and how much power is actually delivered to the site which is being treated. That is totally independent on a source.

You can have a very high power, which is delivered within a volume of 1 cubic millimeter, with one type of a lithotripter and you can have a less power delivered by a huge volume generator like the electrohydraulic one.

So, it really depends on a stone, I would say, more and the focal volume than what is the external power of the generator.

DR. HAWES: I was thinking mainly in terms of safety.

DR. LEWIN: Yes.

DR. MELMAN: Mr. Brown, you wanted --

Mr. Brown: Thank you. I appreciate that.

I felt compelled to just say a couple of things here regarding lithotripsy and the history of lithotripsy and the various types of lithotripters that are out there. I have been interested in these things pretty much from the very, very beginning in the eighties and especially to Dr. Hawes, your point, on the anesthesia versus the types of device and so on.

I respectfully somewhat disagree with what you are saying, Dr. Herrera, on a couple of issues. I think the issue of the power and the anesthesia -- you were saying that the anesthesia is going down today because the devices are less powerful. I don't think that is the case at all as a general statement. It is the case of the geometry of the

shock wave generator or the reflector.

If I may just in a very crude way -- and I am stepping on Dr. Lewin's area here, but if you imagine the ellipsoid is round and the shock wave is coming off of it, if the shock wave generator has a very low or small diameter, the shock wave comes off in a very acute angle and that acute angle is what really, in essence, causes the pain versus if it came up with a wider ellipsoid and goes in in this direction.

The spark gap generators today -- and, again, I can only talk for my own device, but we are using in many cases zero anesthesia, a little emla(?) cream, and it is a spark gap generator, which is proven to be every bit as powerful as the HM3 in our study.

So, it is not a case of lower power. The lower power is coming, in my honest opinion, because they are cheaper to make and if they are cheaper to make, you are going to have some compromises and this goes back to my comment from earlier, where in all due respect to the FDA -- and I am a big believer in the FDA studies -- we have got a lot of devices out there today that were made cheap, that have gone through the FDA study, but they are showing horrendous retreatment rates because they are much lower power.

I think that is the wrong way personally, but I

just want to say that it is not just a case of the power having a relationship to the anesthesia. It is the geometry of the ellipsoid is the key.

DR. LEWIN: I fully agree. That is true.

DR. SADLER: May I ask the FDA if you have a tabulation of medical device reports having to do with lithotripter experience over all these years? They should have a tabulation of what has been submitted and I wonder if we could hear about that.

MR. ST. PIERRE: Yes. Of course, we have data for every PMA that is approved and that has gone through the process. But I think it is important to note that what we are doing is evaluating safety and effectiveness. We are not saying that this is the best device or that is the one that we are going to approve and the other ones we are not.

So, the companies have to demonstrate safety and effectiveness. So, you know, maybe it is not effective as another device. But, you know, it is just as safe and it has an effectiveness within the range of this other device. And that is okay.

DR. SADLER: There is no question that there is a threshold that they all have exceeded so that most of them work for a majority of patients that they treat, but some are clearly more powerful than others. That is not what I am driving at. What I am driving at is the scope of the

reporting that you have received of problems because we have been through a listing of five or six of the more frequently encountered risks, none of which are of the magnitude that we would have to consider it life-threatening condition or something that would make this really be a dangerous treatment.

I think the refinements in the practice may be as great as the refinements in the machine, that it made it less of a process for patients. Obviously, most people who receive lithotripsy treatment get their stones fragmented if they are properly selected in the first place. Most people who have their stones fragmented have a better clinical course than if they had had to have surgery or some more invasive method to get rid of the stones.

That is why these things have been so successful. But what I want to know is can you tell me some -- give me some tabulation of other risks that we haven't mentioned. We talk about all these things being EKG gated to try to make sure we don't produce arrhythmias.

I have heard nothing since we started considering lithotripters about the induction of arrhythmias. So, it must be a very minor thing. Whenever we have seen something about it, they have said there have been a few PBCs. But I don't know that there haven't been any serious arrhythmias.

MR. ST. PIERRE: I don't think arrhythmias are

minor and they happen fairly frequently. I think it is reported up to like 20 percent or so. So, there is labeling -- I mean, current lithotripters are labeled for that. We have some labeling recommendations that we will be proposing later to address that also.

So, I mean, Dr. Herrera went over it kind of like the general who is associated with it, but I mean there are specific subpopulations that are at an increased risk and we want to control for that also. We think we can control a lot of that with the labeling and the design of the device will be a factor to control that.

So, we do have tabulations. I mean, there are -- the FDA has a number of reporting mechanisms, the MDR reports and the MedWatch system and there those types of reporting systems. We haven't seen anything that, you know, really raises a flag for us that really is a concern, but I mean, clearly, there are issues associated with lithotripsy. I mean, we are not saying that it is absolutely safe and there is no --

DR. SADLER: No, but we have mentioned two things today that in addition to the regulations established by the FDA help to control the practices. There are voluntary standards, such as the AUA sets for its members. There are practice guidelines for almost every significant procedure that is out there. There are reviews and certainly I expect

that if a urologist in a group was having to repeat his lithotripsies twice as frequently as his colleagues, he would be subject to question for that.

DR. MELMAN: Not if he was doing it in a trailer in the back, you know, in South Carolina.

DR. SADLER: If that is outside the scope of what we can do, that is outside the scope of what we can do. We have to understand there are some things you are never going to be able to regulate. And the fact that there is .5 percent of something that you can't regulate doesn't mean that you shouldn't do the best you can with the 99.5.

MR. ST. PIERRE: You are bringing up a good point and maybe what we do -- maybe what it would be nice to do is to change the agenda a little bit and have us go through all the labeling issues that are currently incorporated with lithotripters and what changes we would like to make and maybe we would rather hear that before you go through the classification process.

DR. SADLER: I was going to ask you to give some of the other talks first before we had to make a vote.

DR. BENNETT: Can I -- I don't want to drop this one because this is what you brought was the MDR reporting system and HealthTronics brought up the issue of retreatment rates. I mean, I do a lot of this stuff in my company. So, there is no conflict of interest. We don't have anything to

do with lithotripsy. But I don't think MDR reporting is going to pick up retreatment rates.

MR. ST. PIERRE: No, it is not.

DR. BENNETT: So, here you have probably from the industry's point of view the major factor on what is a good machine. I mean, they are all safe. But what makes machine A better than machine B for society is the retreatment rate.

MR. ST. PIERRE: And I strongly encourage those companies to do controlled trials against other lithotripter companies and see whose machine is better. Then that information becomes available to the medical community. That is not -- I mean, FDA is not not doing that, but I am sure --

DR. BENNETT: But I was addressing John's point about retreatment rates and whether -- his assumption was that the MDR reporting system, I think, would pick that up and it doesn't.

DR. SADLER: My assumption was that that is the sort of thing that might get caught in practice guidelines. I don't expect MDR to do that.

DR. BENNETT: But this is a complication. If you don't blast the stone and you have to put the patient back under treatment, it is a complication of treatment. Theoretically, it should be reported.

DR. SADLER: Well, the health insurance companies

will take note of that because it won't be done for free. That will come back to haunt someone.

DR. MELMAN: We used to have a panel member, who worked for Consumers Reports. What you are asking for is the FDA to be our consumer reporter. I don't think that is their purview. But when the companies send back their data -- this is kind of what I was asking for before -- they send back their five year data, their three year data -- do you publish that anywhere? Could that be available on the Internet so that people who were interested can go and look at it?

MR. ST.PIERRE: The summary on safety and effectiveness on which the PMAs were approved are all publicly available. They are all on the Internet.

DR. MELMAN: The follow-up data, not --

MR. ST.PIERRE: For lithotripsy, there is no follow-up data. I mean, there is essentially a three month study. Well, if you clear, you know, 75 or 95 percent of the stones in three months, you know, what is the follow-up data going to give you? I mean, it may give you -- you may get some additional information on retreatment rates, but --

DR. BENNETT: And MDR reporting is proprietary information. I mean, the company isn't going to disclose unless the FDA tells them they have to disclose it and then you get a warning letter or whatever you get. But a company

is not going to disclose -- even if retreatment rates were MDR reported, that would never become public information, unless it was to the advantage of a particular company.

Mr. Brown: That is why I think that is very important. You have got a very strict point there. It goes back also to a comment you made earlier about traditional lithotripsy. I am really a big proponent of PMA studies because whether we give it 90 day, which Don St. Pierre was talking about or 120 day, whatever the follow-up may be, in essence, we may talk about they are flawed in this direction or that direction, but each lithotripter manufacturer goes through the same hoops to get his product approved.

However, what is not done is that the results of that PMA study are not made open to the public. Now, some of that is proprietary information. I understand that, but that might be a way that might be -- to loosen those ropes, if you will, or those constraints so that the data is known because if company X has very bad results from the FDA study but they still got FDA approval, which is not the FDA's prerogative to cancel that approval, but if they get FDA approval for very bad results, if they have got slick sales guys, they go out and putting out, like I say, cheaper devices with very, very high retreatment rates, which I truly believe is not in the interest of the health business in general in this country.

I think, perhaps, we could think about publishing the FDA results.

DR. AGODOA: What are the medical consequences of retreatment, other than the insurance issues?

Mr. Brown: I think they are known in terms of they might be with hypertension especially, if you are going to blast a kidney with I am going to say 3,000 shocks, then you bring that patient back there 15 days later because they didn't break and give them another 3,000 shocks -- I am not sure there has been a study, but you know the results with hitting kidneys with --

DR. BENNETT: Well, the complication rate is not another lithotripsy. I mean, you may have a failed lithotripsy, extracorporeal lithotripsy, and because of the failure, you have to have either an open procedure or percutaneous procedure. So, it is not just the fact that you need another lithotripsy. You need another treatment, which isn't always a lithotripsy.

So, there is a lot more to it.

DR. MELMAN: Which may have not been necessary had another device been used.

DR. HAWES: Could I ask a question?

For a retreatment, do we have data on -- I mean, there must be tons of factors toward retreatment and surely not the only one is the instrument. Just for my benefit, do

we have a handle on what percentage of retreatments are instrument related as opposed to all the other factors?

Mr. Brown: I don't believe we do. Within the FDA PMA studies that each manufacturer goes through, they are required to treat -- I am going to say a number -- 200 patients, give or take, and they are followed up each for a 90 day period, but once they have done these two or three hundred patients, no matter what the number is, the types of stones that are treated and the size of the stones, it is all recorded within the PMA study. And bottom line, we have at the bottom a retreatment rate.

Now, of course, a number of those stones may be cystine stones, which are more difficult to break, but, by and large, I think we get a very, very clear picture of the efficacy of that device at the end of an FDA study.

DR. HAWES: I mean, the issue at hand here is whether this is part of the labeling, isn't it? Whether retreatment is part of the labeling, isn't that sort of the direction of this discussion is going? Whether or not the FDA as part of this labeling is going to include retreatment.

DR. MELMAN: It could be one of the things we make a suggestion for.

DR. HAWES: Could you do -- let me just -- could you go on and ask the next speaker, Dr. Harris, to make his

presentation?

MR. ST. PIERRE: Well, the next one is me.

DR. HAWES: You are the next one. Okay.

MR. ST. PIERRE: Well, let me just address that one question first.

I mean, I think that -- I hope that that becomes a key part of the discussion as we move -- I mean, identifying what populations are more appropriate for lithotripters or not more appropriate. I mean, as far as retreatment, clearly, there are -- I mean, you are always going to have -- some devices are better than others. I mean, that is a fact of life. So, there is always going to be, you know, this range in retreatment rates.

Well, they are approved and they are on the market. So, they are within an acceptable range for demonstrating safety and effectiveness. You know, are there controls for that? Yes, there are some controls. I mean, there are recommendations and labeling not to treat stones larger than 2 centimeters. So, by treating the smaller stones, hopefully, you will decrease the retreatment rate.

Stone burden, I am sure, will have an impact on retreatment rates. We regulate the specifications for the device. I mean, if it goes Class II, I mean, it would have to be equivalent specifications of something that is already out there.

So, the specifications for the product are going to be, you know, within the range that is already out there. So, there are controls. I mean, nothing that specifically states your retreatment rate can't be higher than such and such. But there are controls for it. And as we see now, there are statements being made that there is a -- some of the machines have a much higher retreatment rate than others.

Well, I am sure that is the case.

DR. SADLER: But you know, Don, every time we have considered a lithotripter, we have been told very specifically you don't compare this PMA to the last PMA. You have to compare it to the general body of medical knowledge about this practice.

So, we have always had reference data that comes from the medical literature and everybody who has brought a product before this panel when I have been present had something that fell into the scope of what was published and in the general range of success. And the variation within those presentations has not been very great. It may well be that much of what comes in those PMAs would be of benefit if it were published and it often is not.

But I think that the performance range, while there is a difference in character, as Dr. Lewin says, the size of the focus and, therefore, the force at that focus

varies from machine to machine. Certainly with the changes over time, we have seen changes in the different kinds of problems that arise.

But as I say, I think some of that is practice, as well as the equipment and we haven't tried to discriminate between them.

DR. YIN: I think Mr. Brown is trying to tell us they are recommending reclassification but the panel needs to be very cognizant of this retreatment rate, if I am hearing you correctly, because they just are saying they recommend that.

They brought up this clinical issue. So, maybe that is what is needed to be discussed by the panel.

MR. BROWN: That is really where I am going with this thing. As a general statement, we can't keep going in the direction we are going. When the first HM3 was approved, it had a retreatment rate of about 8 to 10 percent, give or take a few. We are approving devices now that have a retreatment rate in the 40 percent, 30 percent. That is not the road to improvement. It is the road down hill, in my opinion, as a device manufacturer.

DR. BENNETT: Really, another problem is the guidance. The guidance tells you it is a 90 day follow-up. Well, you are not going to know your retreatment rate until a year. So, that is why the studies that are in the

literature that follow patients longer can tell you what the retreatment rates are; whereas, the PMA is not going to ever be able to do that.

DR. YIN: That is correct. You are right. So, you have to address that issue of how you are address individual classification if you do go for it.

DR. MELMAN: They won't do it unless you ask for it.

DR. BENNETT: It is a 90 day study, Arnold, so you are never going to get -- you will get a 90 day retreatment rate. You won't get really what the retreatment rate for that machine is.

DR. MELMAN: Unless it is asked for.

MS. MARLOW: Actually, after just having gone through the agony -- we only recently completed our study to support our PMA. Ninety day follow-up is required for each patient after treatment. So, as soon as we retreated a patient, the clock starts again and we follow for 90 days. So, we did document the retreatment rate on every single patient because of that.

So, I just wanted to clear that up and I do think that within --

DR. BENNETT: That is assuming that they got retreated within that 90 day period.

MS. MARLOW: Yes, and I think that that is fair

because if you take it beyond 90 days, then you have to do some pretty fancy stratification to determine if the patient has developed a new stone or if it is, in fact, the same one. You know, you do very close measurements for size of the stone that you are trying to target but even only waiting 90 days, sometimes it became difficult to understand what we were retreating. And maybe another stone that was there had migrated and that gets into all kinds of issues.

But I do think that most patients that are still retaining stones and they are symptomatic are going to holler about it within much earlier than 90 days.

Another thing that I wanted to talk about was when I talked to the management of my company about strongly supporting this reclassification petition, the reason I thought it was important to do so was because it is a mechanism to address all these issues, not to ignore them. If this is handled correctly, and I think FDA has done a lot in that direction, we are going to be able to put in recommendations and controls that didn't exist before.

That is why we are all here, you know, very vehemently supporting this because if done the right way it can address a lot of issues that are not being addressed under the PMA regs.

DR. MELMAN: It is curious to me that you are the only company that is speaking out in this public forum.

MS. MARLOW: Me, too.

DR. MELMAN: I don't understand that.

PANELIST: But it isn't our job to create a competitive advantage. They have to create their own competitive advantage.

DR. MELMAN: Dr. Donatucci.

DR. DONATUCCI: I just want to make a statement about retreatment rates and that is, of course, we are talking about a moving target in the sense that the HM3 retreatment rates, when that PMA came to the panel, for basically all comers and they were quite low and I think they have been unequal today.

The clinical practice of stone disease has narrowed the field that the newer machines are -- the varieties of stones that the newer machines are treating. I don't think that a PMA in 1998 is going to take a staghorn calculus and treat it.

So, when we talk about retreatment rates for later generations of machines, comparatively speaking, one has to recognize also that we are actually -- we have already narrowed the indications for who should be treated at all. So, we have to bear in mind that when we go back historically and compare retreatment rates to the HM3, that was basically a treatment for all comers and it still has the lowest retreatment rate.

DR. MELMAN: So, it should have low retreatment. It is not higher retreatment.

DR. DONATUCCI: Well, yes. In other words, if we are accepting gradually progressive retreatment rates are getting broader in a narrower group of patients, that actually represents an even -- it is worse than we are actually presenting.

DR. HAWES: Could we go to -- I stand by my sort of original statement and that is that we are discussing as being very important, a retreatment rate, but it seems to me as an outside person to this, that the machine, the device, may have very little to do with that. So, I don't understand quite where this discussion is going.

On the one part, we are being asked to look very carefully at the retreatment rate in terms of labeling and, yet, nobody has convinced me that the actual machine has such a strong input into the retreatment rate. It could be what stones they do or how much training they have.

DR. DONATUCCI: That is kind of what I was just saying. The evolution of stone treatment has narrowed the parameters at which stones are treated, which size are treated, et cetera. Yet, newer generations are showing higher retreatment rates as we have narrowed the parameters, compared to the original machines, the first machine, the HM3. So, indeed, there is a machine dependent process at

play here.

DR. HAWES: I mean, it is a contributor, but how important is it and, therefore, should it be part of the labeling at all?

MS. MARLOW: Well, Dr. Hawes, this is one of the things I tried to bring out a little bit in my presentation because I do think that there is an aspect of it that is physician dependent but I also think that if any company, any medical device company, is going to put out any product for any indication, they also have a responsibility to make sure that that product is safe and effective for that indication.

There is a lot that we know about lithotripters and there is a lot we know about blast packs and focal zones such that if a manufacturer conforms to certain standards and makes a machine within certain parameters, you should be able or a physician should be able to achieve a certain success rate and a certain retreatment rate.

And some of the things we were talking about -- and, again, I will absolutely embarrass myself if I step on Dr. Lewin's specialty, but there are things we know about shock waves converge and how focal zones are configured that contribute very directly to the retreatment rate. Also, if you have an imaging system that is inadequate and you are just firing shock waves into someone's body, you are not

going to reliably hit the stone every time. That is going to contribute to retreatment rate.

For example, on fixed frequency or non-gated device, sometimes -- and I really should know better to be quiet, but I won't because my engineering knowledge is minimal -- I am a nurse -- but sometimes the generator doesn't recycle itself and the shock waves are not the same configuration from shock to shock. So, it is my strong opinion -- yes, the manufacturers can do a lot to put a very good device into the hands of a physician and minimize the number of times that his judgment and his skill and variations in his technique are going to result in a failed procedure or a high retreatment rate.

DR. HAWES: Well, that is exactly my point. It seems to me that we should -- can regulate things like power at the focal point, aside from the focal point and we ought to make manufacturers come under certain standards and parameters that we set. But we are drifting off into this retreatment rate, which seems to me to have a whole lot of other variables and, therefore, I am not sure -- at least my feeling is that shouldn't be part of what we regulate on these because it is due to a lot of other factors.

DR. DONATUCCI: Isn't retreatment rate another word for saying effectiveness? I mean, that is just another --

DR. SADLER: You are talking about efficacy. Of course, retreatment is a lot more important if you are the patient than it is if you are the operator.

DR. HAWES: You can only standardize the device. I mean, you can't -- unless we put very narrow parameters on what machines are allowed to treat.

DR. MELMAN: Maybe one of the things that would be helpful for physicians who are buying a machine is to know that for any particular type of device for a 2 centimeter stone of such and such a consistency, what percentage of the time that particular machine is going to break up the device. So that there are uniform standards for every machine and then you could say I want this one or I want that one. That is something we can ask the FDA to supply.

So, I want to use that as a segue to move on and I am going to ask Mr. St.Pierre to introduce the next speaker.

Agenda Item: FDA Presentations

MR. ST.PIERRE: I guess it is not afternoon yet. So, good morning, again. I am Don St.Pierre, branch chief for the Urology and Lithotripsy Devices Branch.

As you may know, our latest clinical guidance to industry is dated February 5, 1992 and our latest preclinical guidance is dated January 18, 1991. Needless to say, a lot has happened in this area since the introduction of these guidance documents. Literature on this topic has

grown extensively. Lithotripter technology and the lithotripter industry has matured greatly and FDA has a much greater understanding of this technology.

Keeping all of these changes in mind, we are in the process of updating our guidance to industry. Our updated guidance intends to make full use of international standards and will attempt to shift the focus for "me-too" types of lithotripter technology from the clinical arena to the preclinical arena.

We look forward to your comments and recommendations, as well as input from the audience. I would like to reiterate that this is the beginning of the process to revise the guidance. After we have had an opportunity to consider the panel's recommendations, the guidance will be made publicly available in accordance with good guidance practices.

Over the next half hour, you will hear two presentations. The first will be from Dr. Jerry Harris, an expert engineer within our Office of Science and Technology, who will present specific preclinical performance test information. Dr. Harris will be followed by Mr. John Baxley, an expert scientific reviewer within the branch, who will present the clinical, road testing, labeling and training information.

These presentations will provide a more complete

picture of how we now evaluate the safety and effectiveness of extracorporeal shock wave lithotripters and what changes we believe are appropriate. The key message from Dr. Harris' talk is that what we have been doing has worked well. It is always a relief to be able to say that.

However, it can be improved by taking into consideration international harmonization and the adoption of international standards. The key issue from Mr. Baxley's presentation is the limited confirmatory study for standard lithotripter technology.

This is a significant change from what we currently do and should elicit some discussion. In addition, Mr. Baxley will be identifying some minor labeling changes to how lithotripters are currently labeled.

So, if there are no questions, then we will proceed with Dr. Harris' presentation.

I might add that I didn't know -- I didn't hear Marie Marlow's presentation before today. Had I known that, we may have asked her to help us out with this effort.

DR. HARRIS: Good morning. My name is Jerry Harris and I am with the Center's Office of Science and Technology.

I will be speaking about preclinical testing of lithotripsy devices for shock wave characterization, localization accuracy and system safety. First, I will

summarize the current FDA guidance for shock wave measurements and then I will discuss changes we are considering regarding the use of recently published international standards for lithotripsy equipment.

The current measurement guidance, a copy of which you have in your package, is titled "Draft of Suggested Information for Reporting Extracorporeal Shock Wave Lithotripsy Shock Wave Measurements" and is dated January 18, 1991. This guidance contains a description of recommended devices for measuring underwater pressure pulses, so-called hydrophones.

It asks that these hydrophones be used to measure and report both the temporal and spatial characteristics of the pressure field and the acoustical energy per pulse. Hydrophones having a piezoelectric polymer as the sensitive element are the most widely used devices, but more recently hydrophones based on fiber optic sensors have been shown to provide robust and accurate measurements.

Now, the term "temporal characteristics" refers to how the pressure pulse varies with time. To illustrate, consider the representative pressure pulse depicted here. The instantaneous pressure amplitude, as would be measured by a hydrophone, is given on the vertical axis, versus time on the horizontal axis.

The pressure pulse produced by the three types of

lithotripsy generators shown and discussed earlier by Dr. Herrera do differ somewhat in their temporal shape. For example, the pulse produced by a piezoelectric generator would be expected to be more oscillatory than shown here. However, this so-called typical pulse contains all of the important features found in lithotripsy pressure pulses generated by conventional means; namely, the initial steep rise to the positive pressure peak, the slower decrease to the ambient pressure level and then the relatively longer negative pressure portion of the pulse.

Four quantities are used to describe the pulse, p_c , the peak positive or compressional pressure; p_r , the peak negative or rarefactional pressure; t_r , the rise time, that is, the time it takes the pressure pulse to rise from 10 percent to 90 percent of its peak positive value and t_w , the duration or width of a positive portion of the pulse between the half amplitude points.

These quantities are listed on this next slide. Again, the peak positive or compressional pressure, peak negative or rarefactional pressure and the rise time and pulse width.

Next, the term "spatial characteristics" refers to how the pressure pulses vary in space. To illustrate, consider the idealized focused lithotripsy source shown here. At the top, the focal point of the shock wave source

is shown at the origin of an x-y-z coordinate system and the pressure pulse is shown propagating along the z axis.

To obtain a map of how the peak pressure, either positive or negative, varies with position, the hydrophone can be scanned along one of the three axes, or in a plane defined by any two of these axes. For example, the graph at the bottom of the figure shows theoretical contour plots in the x-z plane.

These plots are constructed by joining the points of equal pressure measured by the hydrophone. And you can see that there are isobar or equal-pressure contours that are below the peak pressure by the various amounts shown. There is 3 dB or 71 percent, minus 6 dB or 50 percent, minus 12 dB or 25 percent and minus 20 dB or 10 percent.

Now, from these plots the following spatial measurement data can be calculated. First, the minus 6 dB beam widths in the lateral, that is, x and y, directions, the minus 6 dB beam width in the axial, that is, z, direction and the minus dB focal volume.

In addition, these data allow the target localization accuracy to be determined; that is, the distance between the point of peak positive pressure and the point where the manufacturer intends the operator to locate the stone. And, furthermore, by combining these spatial measurements with the temporal measurement data, the energy

in a lithotripsy pulse can be computed.

So, to summarize up to this point, these temporal and spatial characteristics of the lithotripsy pressure field, as described in our shock wave measurement guidance, have been used successfully since 1991 in making regulatory decisions regarding preclinical or bench testing data. We plan to continue using this guidance for now, but we do anticipate that our approach will change in the not-too-distant future based on recent developments in the area of international standards.

Specifically, two standards have been published in the past year by the International Electrotechnical Commission that deal with extracorporeal shock wave lithotripsy equipment. One is designated IEC 61846 and is titled, "Ultrasonics -- Pressure Pulse Lithotripters -- Characteristics of Fields." It was developed by IEC Technical Committee 87, named "Ultrasonics," and was published earlier this year.

Like the FDA's shock wave measurement guidance I just discussed, this standard specifies methods for measuring and characterizing the acoustic pressure field generated by lithotripsy equipment. These methods closely follow those in the FDA measurement guidance in part because the FDA guidance was used as a background document by the IEC working group that developed this standard.

Changes in terminology and notation have been made. Terms are more rigorously defined and improvements in measurement technology have been recognized. However, the two documents provide equivalent information. This standard is in the process of being formally adopted by the FDA.

The second IEC standard is IEC 60601-2-36 and is titled, "Medical Electrical Equipment -- Part 2: Particular Requirements for the Safety of Equipment for Extracorporeally Induced Lithotripsy." It was developed by IEC Technical Committee 62, named "Electrical Equipment in Medical Practice" and was published last year. This so-called "Particular" standard supplements the more general IEC 60601-1, titled, "Medical Electrical Equipment -- Part 1: General Requirements for Safety," and dated 1988, with amendments in 1991 and 1995.

As this title suggests, IEC 60601-2-36 specifies requirements for the safety of lithotripsy equipment. Areas covered include electrical and mechanical safety. It should be noted that in the past FDA has dealt with these safety aspects of lithotripsy equipment on a case-by-case basis. That is, there has been no written guidance regarding these safety system matters.

Also included in this standard are labeling guidelines regarding localization accuracy and pressure field characterization. Specifically, Clause 6.8.3 states

that the minimum technical description of the equipment should contain the position and size of the focal volume with respect to the target location, the peak compressional and rarefactional pressures and the energy per pulse. This standard should be formally adopted by the IEC this summer.

So, just in conclusion, I would like to say that it can be said for preclinical testing, established and accepted methods now exist for measuring pressure fields generated by lithotripsy devices. And, in addition, new international standardization will allow greater harmonization and consistency in the regulation of lithotripsy devices with respect to pressure field characterization, localization accuracy and system safety. During your deliberations we would like you to comment on our proposal to use these new standards.

Thank you for your attention and I will now take any questions.

DR. MELMAN: Dr. Steinbach, do you have a question?

DR. STEINBACH: Yes. Do these propagate at the speed of sound in water or are they some other mechanism?

DR. HARRIS: Yes. They will propagate at the speed of sound in tissue, yes, which is similar to water. And these measurements are made in water, by the way.

DR. MELMAN: These are on stones themselves or on

wave forms that have no relationship to what is happening in the patient in terms of pain or anything else. Right? These are mechanical properties we are talking about.

DR. HARRIS: The acoustical properties, the volume, the pulse characteristics?

DR. MELMAN: Yes.

DR. HARRIS: The focal volume, the pulse characteristics and I mentioned peak positive negative pressures, rise time, pulse duration. They will be different in tissue than they are in water. That is true.

DR. SADLER: Are these ISO standards like most iso standards in terms of requiring what characteristic data must be obtained but giving no scale for what is acceptable?

DR. HARRIS: That is correct. In fact, the first standard I mentioned, the measurement standard, states that -- well, actually let me read it to you. This is from the 61846 standard. After stating what the international standard does specify, that is, measurement parameters and methods of measurement, it states that the parameters defined in this standard do not at the present time allow quantitative statements to be made about effectiveness and possible hazard. In particular, it is not possible to make a statement about the limits for these effects.

So, I think that was the point you were making.

DR. SADLER: Well, I see IEC and ISO standards are

generally broad umbrellas that don't have very many specifics in them, which limits their usefulness to the FDA.

DR. HARRIS: This is very specific in how to make the measurements and how to report the data. In that sense, it is equivalent to what we have been doing since 1991.

DR. SADLER: Right. But we still are not equipped to say it must be within a certain range. That is just what I was driving at, that these standards won't do that either.

DR. HARRIS: Right. They would just help us assure that the device operates as it is labeled.

MR. ST. PIERRE: FDA is still going to be doing that assessment, just as we are doing now. So, the standard that we -- the guidance that we have now is really just the methods. The IEC is just the methods type of deal. All the data, the information that is obtained from doing these tests, we will still look at.

DR. LEWIN: Jerry, I wanted to make sure both IEC standards are consistent. There is no -- any consistency in how they label all those parameters.

DR. HARRIS: That is correct. In fact, the 60601 standard refers to the standard developed by TC87.

DR. LEWIN: And another question which I would have perhaps also to the panel, from the point of view of manufacturers, maybe that it is a very good development here that they would have to follow one standard, which is an

international one and not two different standards, which are generated by IEC and separately by FDA.

DR. HARRIS: Thank you.

If there are no other questions, I would like to introduce the next speaker, John Baxley.

MR. BAXLEY: Thank you. Good morning.

I am John Baxley, a biomedical engineer in the Urology and Lithotripsy Devices Branch. I will be presenting some of the other types of information that FDA believes should be provided in future marketing applications of new extracorporeal shock wave lithotripters, which are in addition to the preclinical testing recommendations just described by Dr. Harris.

I will begin by outlining our proposals for clinical evaluation of new device models, as well as the specific testing that should be conducted on mobile and transportable systems. Following a description of these two test methodologies, I will summarize our labeling and training recommendations for these devices.

The first performance test that I will be describing is a small, confirmatory clinical investigation. We envision that this study would apply to all new lithotripsy systems that utilize existing shock wave generation methods, such as spark gap, piezoelectric and electromagnetic methods, as well as to any system that

undergoes modification to its shock wave output.

Our present clinical study recommendations for premarket approval applications require a manufacturer of a new lithotripter model to conduct a pivotal investigation of 150 patients at three sites, with the objectives of documenting device safety and effectiveness. In light of the growing body of literature regarding these devices, as well as our substantial history reviewing premarket approval applications for lithotripters, we now believe that it would be appropriate to shift the majority of our review of device safety and effectiveness from the clinical evaluation to the review of the preclinical shock wave characterization measurements that Dr. Harris just described.

By this I mean that if a manufacturer demonstrates that their device has substantial equivalent shock wave characteristics to one that is currently on the market, then we have assurance that their device's safety and effectiveness will be bounded within reasonable limits.

However, we still believe in light of this philosophy that some clinical experience with each new device model needs to be reported in a marketing application and, therefore, are recommending that manufacturers conduct a small study. The intent of our abbreviated clinical recommendations is to confirm the functionality of the device and assess the adequacy of the proposed instructions

for use, rather than to de novo establish device safety and effectiveness.

Such a clinical study should evaluate a minimum of patients at two investigational sites, all of who are candidates for shock wave lithotripsy and meet the device's proposed indications and contraindications for use. To satisfy the objectives of this investigation, the following data should be collected both during treatment and, as appropriate, at one week post-lithotripsy: the treatment parameters applied; the types and amount of anesthesia or analgesia used; the radiation exposure delivered; the incidence, cause and resolution of device malfunctions; a summary of any complications; the stone fragmentation results and operator evaluation of system ergonomics.

As I mentioned a few minutes ago, these are the clinical data that we believe would be appropriate for new lithotripters that use a traditional or standard means of shock wave generation and have shock wave characteristics that are comparable to those already on the market. However, I want to emphasize that if a manufacturer proposes to market a lithotripters that uses a novel shock wave generation technology as compared to systems currently marketed in the U.S. or has shock wave characteristics that are outside of the range that are currently available, we believe that a more traditional clinical study will still be

required to thoroughly assess its clinical performance.

The second performance test that I will outline only applies to extracorporeal shock wave lithotripters that are indicated for mobile or transportable use. By the terms "mobile" and "transportable," I am referring to those lithotripters that are labeled for routine transportation between sites.

Mobile devices are permanently housed in a bus, van or trailer, which can be driven from site to site and function as a mobile lithotripsy suite. Transportable devices are also intended to be driven from site to site, but are temporarily unloaded at each site for treatment within the health care facility rather than within the transportation vehicle itself.

In order to verify that mobile and transportable systems can withstand the stresses and vibrations experienced during transportation, set-up and stowing without significant degradation in performance specifications, we recommend that the function of the device be evaluated before and after being transported on a challenging worst case road course.

During the test drive, the device should be loaded and stowed in accordance with the proposed directions. Before and after the drive, the lithotripter should be set up according to the manufacturer's directions and evaluated

for proper shock wave intensity, stone targeting accuracy and overall system functionality. To successfully pass this test, the post-drive results should be unchanged from those obtained prior to transportation.

This test does not represent a new premarket requirement to industry. The requirements of this performance test are identical to what FDA has obtained for all previous mobile and transportable lithotripters.

Next, I will go over the labeling information that we believe is necessary for the safe and effective use of urological extracorporeal shock wave lithotripsy, which primarily consist of the sections listed on the screen. We are proposing that the contraindications, warnings, precautions, subpopulations at potential risk and adverse events sections be standardized in the labeling of future lithotripters and serve as special controls.

Many of the labeling items proposed in these sections already appear in the operator's manuals of approved lithotripters. So, I will only briefly describe these items during my presentation rather than state them in their entirety.

However, your panel package contains representative labeling of currently marketed lithotripters so that you can refer to the specific language if desired. On the other hand, some of the labeling items that we

believe now should be used as special controls are either new or revised. And I will present those items in detail. During your deliberations and discussions of the panel charges and the device classification, we would appreciate any comments that you have on our proposed labeling special controls and guidance.

The list of patient characteristics that we believe should be contraindicated is similar to what we have identified in the past. In particular, we believe lithotripsy should be contraindicated in the following patients due to an unreasonable risk of injury or death: confirmed or suspected pregnancy; presence of coagulation abnormality, including those currently on anti-coagulant therapy; presence of an arterial calcification or vascular aneurysm in the lithotripter's shock wave path; history of chronic or acute cholecystitis, cholangitis or pancreatitis; urinary tract obstruction distal to the stone; and anatomy, which precludes focusing the device at the target stone, such as severe obesity or excessive spinal curvature.

Similar to the recommended contraindications, most of the warning statements that we believe should be included in the labeling of future lithotripters are unchanged from what is included in current labeling. Specifically, warnings regarding the following topics are expected to be included to alert the user of either certain safety measures

that must be followed or specific subpopulations that are at increased risk of serious injury: the importance of cardiac monitoring for all patients for early detection of arrhythmias; the use of prophylactic antibiotics when treating infected stones to decrease the incidence of infectious complications; the importance of using separate treatment sessions for bilateral stones to reduce the risks of serious renal injury and total urinary obstruction and the necessity of avoiding the delivery of shock waves to air-filled organs, which could result in serious bleeding.

However, several new warnings that we are proposing are based on recent literature and were not typically included in previous labeling. Since the literature indicates that many subjects on long-term anti-coagulant therapy can safely undergo lithotripsy provided this therapy can be temporarily stopped, we are proposing the addition of the following warning:

Patients receiving anti-coagulants, including aspirin, should only receive extracorporeal shock wave lithotripsy after such medication has been temporarily discontinued to prevent severe hemorrhage.

Regarding the treatment of patients with pacemakers and implantable defibrillators, we previously recommended that manufacturers state that the safety and effectiveness of lithotripters was unknown. However, based

upon current clinical knowledge, we now believe that the following language is appropriate:

To reduce the incidence of malfunction to a pacemaker or implantable defibrillator, the pulse generator should be programmed prior to lithotripsy to a single chamber, non-rate responsive mode for pacemakers or an inactive mode for implantable defibrillators and evaluated for proper function post-treatment. Do not focus the lithotripter's shock wave through or near the pulse generator.

Next, since many lithotripters are now labeled for shock wave delivery without ECG gating, we believe that the following warning should be provided, consistent with the literature if such a claim is made:

If a patient experiences cardiac arrhythmia during treatment at a fixed shock wave repetition rate, shock wave delivery should either be terminated or switched to an ECG-gated mode. As a general practice, patients with a history of cardiac arrhythmia should be treated in the ECG-gated mode.

The last warning that we are proposing concerns patients with cardiac disease, immunosuppression and diabetes mellitus, as has been reported in the literature:

Prophylactic antibiotics should be administered prior to lithotripsy treatment to patients with cardiac

disease, including valvular disease, immunosuppression and diabetes mellitus, to prevent bacterial and/or subacute endocarditis.

Next, cautionary statements regarding the following issues are similar to those in current user's manuals and will continue to be recommended in guidance: treatment practices to reduce the degree of renal injury, such as use of the minimum number of shock waves necessary to achieve sufficient fragmentation and limiting the number and frequency of treatments to the same kidney; the need for radiographic follow-up to minimize the risk of silent obstruction; the importance of minimizing the total fluoroscopic exposure during treatment; the decreased effectiveness of treatment of impacted and embedded stones, as well as staghorn and large stones; the risks regarding electrical shock hazard; and the potential for electromagnetic interference between the lithotripter and surrounding equipment.

For those devices that are indicated for the fragmentation of mid and lower ureteral stones, we believe that the following additional precaution should be included, regarding the benefits of conservative treatment in some cases:

Small middle and lower ureteral stones, 4 to 6 millimeter in largest dimension are likely to pass

spontaneously. Therefore, the risks and benefits of extracorporeal shock wave lithotripsy should be carefully assessed in this patient population.

The next aspect of the labeling that I will present is a section that highlights the unknown safety of lithotripsy in certain subpopulations. The purpose of this section is to include information regarding the unknown effects of shock wave lithotripsy in children, as well as in women of childbearing potential with lower ureteral calculi, identical to what is included in the labeling of current lithotripters.

Next, the labeling of each device should include a standardized adverse events section, which includes the following list of complications of lithotripters along with their approximate incidence:

Gross hematuria, pain and renal colic and skin redness occur in greater than 20 percent of patients.

Cardiac arrhythmia, urinary obstruction and steinstrasse, hypertension, urinary tract infection, skin bruising, fever and nausea and/or vomiting are reported in 1 to 20 percent of cases.

Clinically significant renal hematoma and renal injury are reported in less than 1 percent of patients.

For the risk of hypertension, we believe that the following additional information should be stated:

Although an increase in blood pressure may result after lithotripsy for the treatment of kidney stones, the literature suggests that the level of increase is not clinically significant.

Likewise, regarding the risk of renal injury, the following statement should be provided:

Extracorporeal shock wave lithotripsy procedures have been known to cause damage to the treated kidney. The potential for injury, its long term significance and its duration are unknown. However, lithotripsy is believed to be less damaging than the persistence of the disease or alternative methods of treatment.

The last labeling recommendation to lithotripter manufacturers is to include a section on safe radiation practices.

This section should present an overview of the practices governing the safe use of ionizing radiation, such as stressing the importance of using the minimum technique factors and exposure durations necessary for adequate stone imaging and localization; listing the maximum technique factors that should be used, as well as providing an indication of the maximum radiation dosage that would be expected to be delivered to a patient during a single treatment; and providing guidelines on how to minimize radiation exposure to the device operator and other health

care staff. This section is especially important for lithotripsy systems that use fluoroscopic imaging with high energy capabilities, which can easily harm patients if liberally used.

The final recommendation that I will present is for manufacturers to develop a training program for each lithotripter model. The training program should provide potential users with detailed instructions regarding how to operate the proposed system, along with the general practices for the safe and effective use of extracorporeal shock wave lithotripters.

Due to the complexity of extracorporeal shock wave systems, in addition to the vast amount of information that has been collected over the years regarding ways to minimize risks and maximize effectiveness, training programs represent extremely valuable tools for increasing the safety of this procedure. FDA has always required that each lithotripter manufacturer offer training programs to new users of their device.

This concludes my presentation. But before I turn the podium over, I would like to encourage the panel to provide us with any comments or feedback regarding our recommendations for future lithotripsy marketing applications, particularly in the areas of our clinical testing and labeling recommendations. At this time, I would

like to invite any questions that you may have regarding my presentation.

DR. LEWIN: I only have one here. You had a sentence, "Do not focus the lithotripter's shock wave through or near the pulse generator." Which pulse generator did you have in mind?

MR. BAXLEY: Either a pacemaker or implantable defibrillator.

DR. AGODOA: We have had about 15 years of use of these devices. And what kind of renal functional follow-up done in these patients is there, especially in regard to your recommendation about adverse events, renal injuries, that there hasn't been any significant injury to the kidney? Do we have any renal functional studies, such as proteinuria, GFRs in these patients?

MR. BAXLEY: All of the PMAs that we have reviewed in the past that had the 150 patient study had a subgroup of 30 patients or so that had renal function assessed by nuclear scans pre and post-treatment that showed resolution of any renal --

DR. AGODOA: Within 90 days or 120 days.

MR. BAXLEY: Within the 90 day period.

DR. AGODOA: I am talking about long term, like proteinuria in these patients.

PANELIST: I would have to say that I have never

seen a lithotripsy PMA that had adequate follow-up because the patients who get relief of their stones don't bother to follow-up and they haven't been pursued satisfactorily. For follow-up, we don't have the data, but the data that is there doesn't indicate that there is a significant population, but the data is somewhat fragmentary.

DR. BENNETT: There are several papers in the literature with long term follow-up of lithotripsy patients as far as hypertension is concerned. I don't know about GFR or proteinuria. But if you go look in the literature -- and I am sorry I don't have any sources for you, but over the years I have seen a number of papers that have dealt with the hypertension issue. They may have also dealt with the proteinuria issue.

DR. AGODOA: Well, I have not seen one, but I don't follow this literature that closely, but so to make that recommendation about adverse events concerning renal injury, I think we should be a little bit more cautious if we don't have the data not to make that kind of statement.

MR. BAXLEY: Okay. And that is some of the recommendations that we would like to hear later on that we are inviting.

MS. YOUNG: Yes. With respect to the labeling in two areas, one is pregnancy and the other one concerns children who are mentioned as a subpopulation at potential

risk. In the example that you sent to us on the current lithotripsy labeling, in reading on the contraindications, warnings or precautions, there is a statement about -- there is a warning about pregnant women and it reads that patients in whom pregnancy is suspected and I would certainly to recommend that that labeling be strengthened. It is too vague and it certainly should be suspected and confirmed or and/or -- no, it should be and confirmed. So, that is one area.

As far as children are concerned, I think that the labeling should be specific in terms of age parameters, if possible, because by the time that you are -- you know, when is a child not a child? And are adolescents considered children? In other words, what are the upper limits of the age as far as children are concerned and what are the lower limits?

I just wonder if the labeling is putting children at potential risk and I wonder whether we should consider that the labeling recommendation lists children under "Contraindications," rather than just a subpopulation at potential risk? Seeing no information or I gather there are no data about what the effectiveness in children and the risk as far as children are concerned.

MR. BAXLEY: Well, there is no data that we have or there is no experience we have with PMAs with pediatric

lithotripsy. The literature is quite extensive.

DR. BENNETT: Unfortunately, we don't have a pediatric urologist on the panel, but there is an extensive literature.

MR. BAXLEY: But I would like you to also save that comment for your deliberations or recommendations to us after I am done.

DR. AGODOA: I have one more question. You cut on the number for the clinical trials from 150 to 20. What is the basis for that sample size of 20?

MR. BAXLEY: The basis is it is a size that we feel would give us enough device uses that we could find out from the operator if a device is easy to use, if the instructions are easy to follow, is the device user friendly and are there any major problems in the clinical arena with device malfunction. And we recognize it is not enough to assess clinical outcomes.

DR. HAWES: I would like to bring the important discipline of gastroenterology into this conversation.

Would regard to your contraindication and perhaps some clarification on pancreatitis being a contraindication, did you imply acute pancreatitis, chronic pancreatitis or was it non-specific pancreatitis. And I raise this issue because in Europe it is now standard of care. In the United States I am not aware of how many, but I know that there are

a reasonable number of IRBs that are looking at extracorporeal shock wave lithotripsy in the treatment of patients with calcific chronic pancreatitis.

So, I think that we ought to eliminate at least chronic pancreatitis from the contraindications for lithotripsy, would be my opinion.

Dr. Melman is looking at me sort of like -- it is coming to New York maybe in the next decade or so.

DR. MELMAN: No, but you know, at the AUA that we just finished, there were two studies from Europe that talked about using lithotripsy for Parone's(?) disease. That doesn't mean we should -- if someone is doing it somewhere else, does that mean we should eliminate it as a contraindication here?

DR. HAWES: I don't think chronic pancreatitis should be a contraindication to renal stone lithotripsy. Perhaps acute pancreatitis.

MR. BAXLEY: Okay. I can provide a little background to what previous lithotripters have and then maybe I will turn it back over to Mary Jo Cornelius since it sounds like you are beginning your thought process about, you know, what should be in the labeling.

In currently approved lithotripters it is non-specific pancreatitis. I think some manufacturers took the conservative road and kept it that way. But now is when we

are rethinking it. So, we would look forward to any recommendations you have or guidance.

DR. MELMAN: Any other questions?

DR. STEINBACH: Is this contraindication your way of saying that if you are going to treat pancreatitis with this device that you need a separate PMA? Or is this an attempt to address this issue or not?

MR. BAXLEY: No. It is just an attempt to find out those patients with neurolithiasis(?) that are not at unreasonable risk of serious injury.

DR. BENNETT: The whole European treatment of pancreatitis, which includes stents, as well as lithotripsy now, came way after this pancreatitis contraindication was written for the current lithotripters.

DR. MELMAN: So, maybe it is not a contraindication.

DR. HAWES: Exactly. At least not chronic pancreatitis.

DR. MELMAN: Okay. Let me just poll the panel. Do you want to stop for lunch or do you want to work through lunch? Is there anyone who wants to work through lunch?

DR. LEWIN: I think it would be useful to the recommendations in labeling, which the FDA proposes and that may be giving us something to think about during the lunch.

DR. MELMAN: That is a different question. What I

am really asking is do you want to take a break and then come back or do you want to have lunch here and we will keep working? So, who would like to take a break? So, we are just going to have lunch here and we are going to keep going. And the people in the audience can do what they want? Mr. St.Pierre is going to raise objection to that.

MR. ST.PIERRE: Not an objection, but since you guys have your lunches available for you out in the hall there and can eat, we may want to also give the audience an opportunity to get something to eat also.

DR. MELMAN: Okay. Do you have any other presentations that --

MR. ST.PIERRE: We are done.

DR. MELMAN: That is it. So, why don't we come back here promptly at 1 o'clock. Okay. We will come back at 1:00.

[Whereupon, at 12:25 p.m., the meeting was recessed, to reconvene at 1:00 p.m., the same afternoon, Thursday, July 30, 1998.]

A F T E R N O O N S E S S I O N [1:00 p.m.]

DR. MELMAN: Okay. We are going to restart the panel now. In this afternoon session, Dr. Craig Donatucci is going to serve as the moderator. He is going to lead the panel discussion on the proposed reclassification. I would like to remind the panel that we are here to classify this device only. Other types of devices, drugs or other indications are not part of this discussion.

Dr. Donatucci.

**Agenda Item: Discussion on Proposed
Reclassification**

DR. DONATUCCI: Thank you.

If the panel will get out their work sheets from the folder, we will go through the questions one at a time. Please mark and sign the classification questionnaire. They will be collected after we make a recommendation. We are going to start with page 1, Form OMB 0910-0138, General Device Classification Questionnaire.

DR. SADLER: Only for voting members?

MS. CORNELIUS: You can fill it out. That is fine.

DR. DONATUCCI: Does everybody have it?

Okay. Question No. 1 -- we are talking, of course, about ESW machines -- is the device life-sustaining or life-supporting?

Why don't we start on that side of the table and give me your opinion to that question.

MS. YOUNG: Yes.

Well, I would say life-supporting.

DR. DONATUCCI: Well, I think in this context they are really talking about life supports, such as ventilators or --

MS. YOUNG: Okay. No.

DR. VERTUNO: Concur.

DR. DONATUCCI: Do we have any disagreement in that regard?

Okay. So, our answer to Question No. 1, is the device life-sustaining or life-supporting is "no."

Therefore, we go to item 2. Is the device for a use, which is of substantial importance in preventing impairment of human health? Again, I will allow you to -- if you wish to begin, to begin giving us the answer to that.

MS. YOUNG: Yes.

DR. DONATUCCI: Is there consensus then? Anyone on this side of the table who would say "no"?

DR. STEINBACH: I would say "no" because it doesn't -- I mean, the health is already impaired before they use the device.

DR. HAWES: I would agree. I thought that "no."

DR. DONATUCCI: It is impaired but it will -- the

health can be impaired further if it is not treated -- if the stone is not treated certainly.

John.

DR. MULCAHY: I think a worry here is "substantial importance." I think it is a very important device for the treatment of kidney stones to prevent the use of invasive things like lithotomies, open lithotomies. So, I would say -- I would vote "yes."

DR. MELMAN: The natural history of the large stones that have struck the kidneys is it leads to trauma.

DR. SADLER: If you consider yourself a potential stone --

DR. STEINBACH: I agree the condition it treats is serious but it is the -- the condition is not caused by the device. The condition occurs naturally.

DR. DONATUCCI: You were taking issue with the word "prevent." The device doesn't prevent the formation of stones. It treats a stone that is already present.

DR. SADLER: It prevents further impairment from the stone.

DR. DONATUCCI: It does prevent further impairment from the stone. So, in that case, I think the answer is "yes."

Question No. 3, does the device present a potential unreasonable risk of illness or injury?

MS. YOUNG: No.

DR. DONATUCCI: I would agree. Anyone take issue with that, that the answer to this question would be "no"?

Okay. The panel is in agreement that the answer to the Question No. 3 is "no."

We will go to item 4. Do we answer "yes" to any of the three questions and the answer again here is "yes." That is self-evident.

We will now go to Question 7. Is there sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness? The first part of that, of course, is the "yes" or "no" answer. And I would start this by saying I believe the answer to that is "yes." Disagreement?

DR. MELMAN: Well, I don't know -- what is the postmarket surveillance?

DR. DONATUCCI: Well, we haven't gotten there yet. I mean, the first question is --

DR. MELMAN: Well, you will notice that if we answered "yes," it automatically goes to Class II.

DR. DONATUCCI: This is in part, I think, a little bit of a problem with the questionnaire itself. We ran into this the last time we classified a device in that if we answer the question "yes," before we go on to the -- we automatically classify the device as Class II.

So, let's spend a little more time. Let's restate that question.

Is there sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness. Now, I would still say "yes" and I would argue that we have ten years of experience with at least ten different devices that have gone through the PMA approval process. We have ten years of clinical experience in the urologic literature. We have guidelines for treating stone disease that certainly would establish certain classes of patients both who do well with the machines and those who should not get stone treatment with ESW.

So, I think that the patients who should be treated with the device have been well-described. I think the literature holds good data, both in terms of effectiveness among different patient populations, also in terms of its adverse effect profile. So, I still would suggest that the answer to that question is "yes."

Certainly, at this point anybody who wishes to make a comment or who disagrees, it is open for discussion.

DR. VERTUNO: I would agree.

DR. FOOTE: I would agree also. In fact, this is part of what we were discussing earlier today. If we felt that there had been enough that had been done both in the clinical literature, as well as what was available to the

FDA, to demonstrate that certain controls placed upon the device as a level II device would be adequate. I would agree that I believe that there enough -- we could talk specifically about what type of controls are necessary.

DR. MULCAHY: If special controls are definitely needed, is there anything else that needs to be needed?

DR. DONATUCCI: That is the question. Do you have an answer to it?

DR. STEINBACH: It is a question of what are the special controls needed.

DR. DONATUCCI: Okay. But are we in agreement then that the answer is "yes"? Because as soon as we say "yes" as a panel, we are recommending Class II. Okay.

Now, let's go through the following -- the second part of the question is -- we have to go through each of the following: postmarket surveillance.

DR. SADLER: Could we start by saying that clearly the earlier discussions say we need performance standards and we need test guidelines and then do we need any of the other?

DR. DONATUCCI: So, rather than take them in the order that they are on this form, let's start with performance standards. Why don't we start with performance standards.

Now, this got to the discussion about retreatment

rates and myself, I am a little bit confused and, again, will turn to the FDA in the sense that as we -- in the past, as you have gone through this process and each application has come before you. You have made determinations about safety and effectiveness and, obviously, these devices were not all the same in terms of their effectiveness; yet, each did reach the threshold that you felt was approvable.

So, I think the question really is -- I don't think there is any question in anyone's mind that a lithotripter, and ESW is effective. The question is: Is there a threshold that needs to be described in order to -- as a special control.

I am not sure and from an FDA point of view that you actually want to establish a threshold because it may not be appropriate in all circumstances. I would like to hear what your feelings are about that.

DR. YIN: You have to have all the specifications for some of the devices that would help us. So, we need those specifications. Would we all agree to that?

DR. DONATUCCI: So, this is what in a sense we were talking about later on in the guidance dialogue, preclinical and clinical.

DR. YIN: Yes.

DR. DONATUCCI: Okay. I think what John was saying is that it was his feeling that with the experience

that you have now, FDA would suggest that if a unit, even a new unit, uses a same -- either EHL or electromechanical or piezoelectric and that you can describe the weight characteristics as similar to what is in use now, that is a standard that should, therefore, be sufficient, as long as you have a limited clinical trial to prove that you actually do that.

Am I correct at how I interpreted --

MR. BAXLEY: Right. Correct. We feel comfortable proposing that if we know the shock wave output and if a manufacturer can show that that output, as described by Dr. Harris, those measurement parameters, is the same as another device they point to, and there are 12 or so to choose from on the market, that they would not need the full-blown clinical trials to show safety and effectiveness are bounded within some comfortable limits.

DR. LEWIN: And I would agree, I think, that the technique of measurements of those lithotripters is very well established and I think from Dr. Harris' presentation the two new standards coming up, which are not only in agreement with FDA guidelines, but they also are consistent mutually between themselves. So, that is a good indication.

DR. SADLER: But those are process standards rather than performance standards. They tell you how to test it, but they don't tell you what the range of

acceptable values is.

DR. LEWIN: That is fully correct, John. But I think that in all fairness one of the comparisons of those lithotripters has to be based on something which we can measure and we know what we do. And the characteristics of the shock waves can be well-defined for each of those. What you and some other panel members are referring to is for me a little bit more difficult to assess because just purely through the biological variability between each human being, you can have one person going through the treatment and being very happy and not showing up for the follow-up and another one, which would have a recurrence of a stone within those 90 days or 120 days.

DR. SADLER: I am not worried about recurring treatment. I am confident that the health insurance companies will point that to the right attention and that that will cease to be an issue. If a machine is associated with recurring treatments, pretty soon nobody will pay for the use of it.

DR. STEINBACH: I think the answer to your question, what are the performance standards, and the answer is the existing machines, those are the standard.

DR. SADLER: That is what I would think. That is the scale.

DR. STEINBACH: That is the standard and the IEC,

whatever, is the way of measuring.

DR. DONATUCCI: The second part of Mr. Baxley's proposal, I think, was that a non-traditional method of creating the wave does need to go through the traditional pathway, full-blown protocol. So, the performance standards that we would be recommending here is just that, for a new device that uses the same -- one of the three methods that we talked about already, proving that the shock wave characteristics are adequate would be -- and then a small clinical trial would be adequate. The non-traditional method of generating the wave would go through full clinical trial.

DR. LEWIN: Let me just ask John to clarify that. If you have a new method, let's assume that there is a company bringing up a lithotripter, which would generate shock waves based on the laser-induced breakdown. Would that go through the full-blown PMA?

And let me just follow-up it up. The shock wave characteristics would be, let's say, within the parameters of what already is on the market.

MR. BAXLEY: No. We would still require a clinical trial in that case.

DR. STEINBACH: The full-blown?

MR. BAXLEY: Yes, full-blown, yes.

DR. DONATUCCI: I thought about that when you were

presenting it and what I was thinking was this: Do we know -- if you are using a non-traditional, meaning the first three methods, do we know that while the wave characteristics are the same when they get to the focal point, is the transmission through the body the same? I mean, is there some interaction that could occur that we don't know about? Or can you infer from the fact that this machine creates the same wave, that the wave transmission through human tissue will be the same?

DR. LEWIN: The generation of a wave happens outside the tissue. I only referred to the shock wave generator itself.

DR. DONATUCCI: That is why I am saying that I agree with you. That is true. If we are only discussing the generation of the wave, that that wave then has to be transmitted through the body. And can we infer necessarily that that is going to happen in the same way that the other three methods occur?

DR. STEINBACH: Well, if it is a speed of sound pressure wave, then it has -- as Dr. Lewin is suggesting, it doesn't matter how it was originally produced because it is basically linear propagation and summation and --

DR. LEWIN: I am sorry to say it is unfortunately non-linear but that is an interesting question. The generation takes place outside the body. Once you have got

the shock wave, maybe the efficiency will be different, but that is to be assessed.

But let's assume that the company is coming -- the shock wave generator, the way of generation of the shock wave is different. We do not use electrohydraulic, electrodynamic or piezoelectric way of generating shock wave. We will use laser and a target, which would produce plasma and then when the plasma expands, we will have a shock wave.

MR. BAXLEY: I still think we would look for more clinical assurance of the clinical outcome and that the detail and expanse of that study might be dependent on how similar the shock wave characteristics are.

DR. SADLER: Then it might matter what it generates other than a shock wave if it is a different method.

MR. BAXLEY: Right. But I am assuming it would have some differences in shock wave characteristics that could be specific to that method and, therefore, we would need something to show equivalence besides the shock wave data, which will be the full clinical study.

But if the shock wave characteristics were very similar, then that might be a reason to do a large study but not the full-blown.

DR. YIN: I want just to add a note on what John

just said. If the technology is so different, okay, we may determine that this advice is not substantially equivalent to all the others, ten or whatever, on the market. Then we would have this go through the PMA again. We are allowed to do that and we do have a 510(k) chart to tell us two things. One is new intended use. We discussed that. It is automatically not substantial. It probably will require a PMA.

And the other one is new technology and then we would determine that do we have performance data that we can judge that it could still be substantially a problem, but if we cannot do that, then we will call this not substantially a problem and this one goes through a PMA again.

DR. DONATUCCI: Lillian, let me just ask you about that. So what that means is you already have in place a mechanism to handle this question. Do you definitely need then the larger trial?

DR. YIN: That is correct.

DR. DONATUCCI: It would seem to me from what you just said that this -- there would be no need then for the traditional trial because you will make the determination, whether it is substantially equivalent or not. If the answer is "no," it goes to PMA anyway.

DR. YIN: But remember now it is when it is obviously not substantially equivalent or sometimes it is

like quasi, what Dr. Lewin said, it is really not -- the technology is really not that different but not really give you that warm feeling. Then you want to do the traditional because you hate to throw it into the PMA arena.

I don't know why not, but however the company is very, very leery about that. So, at that point we don't have to, but in some the technology is so different even though everything looks good, you have data to support it, but we have put it in the PMA because we don't really know. Okay?

MR. ST. PIERRE: I just want to expand a little bit on what Dr. Yin is saying. Basically, there is a process already set up for Class II products where if the technology is different, it could -- if it raises new types of questions that the standard technology doesn't, then that pushes this up to a Class III product again.

If it doesn't raise new types of questions but we still have questions as to is as effective or is it as safe as the other technologies, then the process says you can get performance data to show that it is substantially equivalent. Now, that performance data can be best testing. That can be a clinical trial.

So, I mean, it encompasses the whole gamut. This process for Class II products is very well-established and has been used for many years. So, there is a mechanism for

pushing it back up to Class III. If it is substantially different, that raises new questions in our mind and there is a process to say, yes, that is outside of specifications.

However, it is not so far outside that it raises new types of questions for us and then we can get data and have it go through a Class II.

DR. DONATUCCI: Okay. You had a comment?

MS. YOUNG: Yes. I would like to go back to the retreatment issue because from the patient's perspective, I really think that there are some very serious implications here and I disagree with my respected panel member on my left, who says it should be left to the insurance industry. You know, they will jump on it and they will take care of it. You know, I don't want to leave it to the insurance industry to do that.

I think that the FDA should -- if they don't have set up some way of monitoring retreatment, I think that they should consider setting up some sort of monitoring of retreatment. I mean, if we have gone from a 10 percent retreatment rate to now 30, 40 percent rate, I mean, that is a big difference and something is going on here that I think we need or the FDA needs to get a handle on and needs to get information from manufacturers about what is happening.

MS. MARLOW: If HealthTronics could once again comment, Marie Marlow.

As Dr. Yin suggested on the debate about lunch, maybe there is a compromise here. Perhaps it is not well-known that currently manufacturers are not required to disclose their retreatment rates in their labeling. That might be a first step, without trying to make things more complicated or ask for additional testing. In that way, as Dr. Sadler suggested, the marketplace could take care of it more easily and it also might address this situation without putting very onerous requirements on both FDA and industry.

DR. SADLER: What I was saying was not -- I wouldn't want to attribute any beneficial characteristics to the health insurance industry. So, don't get me wrong. What I am really saying is I don't think it is realistic to believe that FDA can get the data and can act on it.

Now, there are two controls. One, the health insurance industry does have to pay for it and they pay very much attention to what they pay for. And, secondly, the manufacturer's sales force knows more about the competition of the current machines than they do about their own.

So, I am sure that the information about retreatment rates is available to anybody who is buying a machine.

DR. DONATUCCI: I think that is a -- I want to interrupt this just for a moment because I think we have kind of worked our way back to postmarket surveillance. We

are going to return there, but let's finish up, please, with performance standards first. I think the discussion that we were having was basically Mr. Baxley presented the idea that we would -- for a traditional generator, we would accept preclinical standards and a small 20 patient clinical trial as the performance standard. And for a non-traditional mechanism, you do want, from what I understand, the ability to go back and ask for a larger trial, short of the PMA.

So, that is really what we are going to ask right now. "Yes" and "no" on that question, are these the standards that we want to adopt.

Yes?

DR. HAWES: Well, just again a clarification and maybe John can address this, but on the issue of performance standards, it sounds like -- I think we all agree that we can measure it and the question now is -- and it was proposed that performance standards are now going to be categorized by existing lithotripters that have been accepted. So, that means, John, that if I have a lithotripter that has a slightly bigger focal point than the biggest one on the market now and slightly less power than the least powerful one on the market now, that I would not fall under being essentially equivalent to those in the market.

MR. BAXLEY: No. You could be considered

equivalent, but you would have to provide more evidence to us than the 20 patient study and a shock wave testing to show you are equivalent.

DR. MELMAN: I would like to recommend that on Question 8, which is what we are talking about --

DR. DONATUCCI: No. Actually we are still on 7.

DR. MELMAN: I thought you made a suggestion of going to 8, talking about priorities.

DR. DONATUCCI: Question 7 was two parts. The first part was -- we answered "yes," and then the second part of the question if "yes," check the special controls needed to provide such reasonable assurance. We were working through those.

DR. MELMAN: Okay. I thought you switched then -- you did switch down to 8 at one point, I thought.

DR. DONATUCCI: I am sorry if I gave you that -- we are going to return here to 7 for just a moment.

DR. MELMAN: But under "Performance Standards," which is Question 8 -- Part B is "Performance Standards," and then Question 8 asks whether we think it is important. I would like to suggest that they have a high priority. But there are two performance standards. You are talking about two different things. One is what are the physical characteristics of the wave and the other is what does it do to specific stones in the patient.

I would like to recommend that clinicians, that we have equivalence of what it does to a specific stone in patients and that that be the performance standard that we could use to say how good the machine is and that that be included --

DR. DONATUCCI: But you don't have that now. You are not suggesting that all the companies that have products on the market, 10 to 12 of them go back and --

DR. MELMAN: No, but they have the data.

DR. DONATUCCI: No, they don't have in vitro studies on --

DR. MELMAN: No, not in -- in vivo studies. They are going to do 20 patients. They know whether it goes through a 1 centimeter stone, what the success rate is.

DR. SADLER: There is enough complications between the generation of the shock wave and the final clinical outcome that I think they can obfuscate that. They can't obfuscate the generation of the shock wave and some general data to indicate that a stone is fragmented in a human being.

DR. MELMAN: I know, but, say you are going to buy a lithotripter, Dr. Sadler, and you read that it gives out minus 10 decibels in the z axis. How are you going to make your decision whether or not to buy the lithotripter based on that?

DR. SADLER: I am going to have go read about the other --

DR. MELMAN: I mean, it doesn't help you.

DR. HAWES: I would agree with Arnold. I mean, I think that it sounds like everybody is concerned about retreatment, but as you indicated I think you just can't throw that out there as a single figure. I think you are going to have to -- if we are going to insist on tracking this, on surveillance and you are going to look at retreatment, it seems to me that you have got to stratify those patients. But you can't just say, well, this lithotripter has a global retreatment rate of 10 percent. This one has a global retreatment rate of 40 percent and then say that, you know, that is either acceptable or not acceptable.

I think we are going to have to -- if we are going to have retreatment as an important part of labeling, then it is going to have to be stratified by stone size, et cetera.

DR. MELMAN: It is not so much retreatment as efficacy of breaking up a stone.

DR. LEWIN: May I comment? I think you are fully correct in saying that there are two types of characteristics, which we are talking about. Now, the physical characteristics of a device are sort of an

objective measure. You can measure it. You can quantify this. But once you have got the human factor involved or the patient, then, at least in my opinion, it is very difficult to say, well, this lithotripter is significantly better than the other since it may well be that all of the sudden there are a series of other parameters, which you have to take into account.

That may be the basin. That may be the way the lithotripter is being operated. Is it operator dependent or is it operator independent? If you set the lithotripter for a treatment of a given stone, which the company recommended to you, is it valid for every patient? I do not know how it is possible without a study to extract data like that.

DR. BENNETT: In the HealthTronics PMA, do you list your retreatment rates?

MS. MARLOW: Yes.

DR. BENNETT: So, it is in your labeling.

MS. MARLOW: We list our retreatment rates and we also -- we followed the FDA guidance document for a clinical study, I hope, exactly, which requires that we report on stone sizes, stone location, failure rates, which are distinguished from retreatment rates. And a failure is a failure to break up a stone that results in another procedure.

Retreatment is a failure to break up a stone that

results in another lithotripsy procedure.

DR. BENNETT: So, I would assume that all the PMAs have in their labeling what their study was. So, the retreatment rates, Arnold, are -- if we took out all 12 PMAs, I think you could find out what the retreatment rates are.

MS. MARLOW: Excuse me. That is a fine point that Mr. Brown tried to raise before and that I tried to bring up with this labeling issue. Only some of the data -- the full clinical report in our PMA is very thick and the summary of safety and effectiveness is some 10 or 12 pages. That is a good system because what you are going to release publicly comes out of the usable data. So, you try to melt down everything into something that is usable if you are going to pass out a document to physicians.

Nobody is going to read a, you know, 500 page clinical report. But the problem is maybe we need to take a look at what information does get disclosed in the labeling because things that are in the summary of safety and effectiveness, which is publicly available but not easily accessible, is not always the same information that gets into the labeling.

Maybe we need to look at what data points from the study actually get into the labeling.

DR. DONATUCCI: I just reread this question and I

think, in essence, what the question actually asks is only whether we need it, "yes" or "no," as opposed to what it should be. So, we might discuss that later under guidance -- continue this discussion under guidance, but for the purposes of the questionnaire, I think it is clear that the answer to the question for performance standards is "yes." There will need to be one.

The next question would be would the devices need to have a postmarket surveillance. In a sense I think, if I understand the panel, and correct me if I have the wrong understanding, that because of this question of effectiveness and retreatment, that postmarket surveillance would --

DR. BENNETT: That implies something totally different. Postmarket surveillance implies that you are going to require a study by the company following approval, which is a whole different thing.

DR. DONATUCCI: Is that, indeed, what this means?

DR. YIN: There is two types. One, you can require each company to do their own or another type is that FDA can design a study and then each company could contribute to that big study.

DR. DONATUCCI: But there is -- what this does, if we answer "yes," this does mean that there is -- we think there needs to be a study.

Now, I would now, with that understanding, say the answer to that question is "no," because, again, there are ten years of accumulated clinical experience.

DR. BENNETT: I would agree.

DR. DONATUCCI: So, we leave that blank. Do we need a patient registry? Again, I don't think so. Anyone else?

[There was no response.]

Device tracking.

DR. BENNETT: Well, the interesting thing about device tracking is that this is where the MDR reporting system would come into effect. If you indicated to the lithotripsy companies that we want you to report your retreatment rates -- I mean, if a patient exploded, if you take the worst example, under lithotripsy, that would be reported under the MDR system.

The question is if you are really interested in retreatment rates from the point of view of getting that information, if you indicated that that is part of the MDR reporting system for lithotripters, then you would really get the true data. That is what device tracking would do for that because all you are getting -- and by looking at retreatment rates on the PMA study or the 20 patient study if it happens to be equivalent, all you are getting is a very small snapshot of what the product is.

When you go out on the market, then you are getting thousands and thousands and thousands of uses and sometimes you are surprised at the difference in complications or MDRs, whatever you want to call them, once, you know, 10,000 people get treated rather than 200.

DR. DONATUCCI: But Alan, I guess, when I think of MDR and device tracking, I think, for example, take the penile prosthetic device assay as an example. I mean, that is tracking a specific device for a mechanical failure and we are required, I think, under the regulations to -- the physician is required to notify.

Is the MDR the appropriate mechanism to track retreatment rates? I don't know first off whether there is regulatory authority to do so.

DR. BENNETT: I guess it is a definition of what failure of treatment is. I mean, I am not proposing -- I am saying this would be a mechanism other than postmarket surveillance. This could be a mechanism that you could get some information on retreatment rates.

DR. YIN: You have to consider that there is always going to be failure. Not retreatment is because of the problem with the device. It could be a problem with the patient or even with the physician. So, therefore, it is not that straightforward an equation. So, you really have to consider that.

Then we don't have at this moment enough MDR experts telling us that whatever that is important so far, nothing in there would trigger us to do the tracking.

DR. DONATUCCI: All right. I mean, I think the medical literature is probably the appropriate forum for this. So, I think the answer is we won't check that box either.

Testing guidelines. I think we all know the answer to that one is "yes." Anybody wish to disagree? Okay.

For the panel, any other suggestions in terms of standards for safety and effectiveness?

DR. STEINBACH: Isn't this where labeling comes in?

DR. YIN: Yes, labeling. Perfect.

DR. DONATUCCI: So, labeling.

MS. YOUNG: Training?

DR. DONATUCCI: Those are already in existence, obviously.

DR. STEINBACH: They have been suggested.

DR. DONATUCCI: Well, I mean, they are in existence for the existing devices. So, we are going to adopt them here.

Okay. And I think we already have the -- anything else for Question 7, any other comments?

[There was no response.]

So, the consensus of the panel is that the answer to Question 7 is "yes." There is sufficient information to establish special controls to provide reasonable assurance of safety and effectiveness and that the special controls needed to provide such assurance include performance standards, testing guidelines, labeling and training.

Move to Question 8 now. If a regulatory performance standard is needed to provide reasonable assurance of the safety and effectiveness of a Class II or III device, identify the priority for establishing such a standard.

Dr. Melman earlier suggested high priority. I think it was seconded by the panel. Any disagreement with that?

DR. STEINBACH: Could this have already been established in the literature?

DR. SADLER: Or the adoption of it in the development --

DR. YIN: I would like to interrupt a little bit. See, when you talk about regulatory performance standards, in fact, right now we only have one. I think what Dr. Melman is suggesting may be a voluntary standard that we propose to adopt. Is that correct? Dr. Harris proposing two voluntary standards. Does that make sense? Not

regulatory. Okay? Just voluntary.

DR. SADLER: It becomes regulatory once you adopt it.

DR. YIN: Yes. That is correct.

DR. STEINBACH: For example, of those 20 patients, how many failures would we accept, we the public, through the FDA?

DR. DONATUCCI: Well, the 20 patients, as I understood it, were just to make sure the machine is functioning.

DR. YIN: We just got a reprieve. You could skip Questions 8 and 9, if we want to. Do we want to?

DR. SADLER: No. Eight is a very important question.

DR. YIN: Oh, okay. So, I would suggest that that should be what Dr. Harris suggested as a voluntary standard that we adopt. So that would save -- you know, that everyone will measure the same way instead of you do it this way, I will do it that way and then FDA would have a lot of --

DR. DONATUCCI: And the priority would still be high priority.

DR. YIN: Okay.

DR. DONATUCCI: High priority with the voluntary standard.

DR. LEWIN: I have just one comment directly. I am a little bit confused here. The guidelines of the measurements, they are already in place. Everybody is required to measuring the same way.

DR. YIN: That is correct. However, right now they think that why don't we use that standard instead of FDA because that is already published. Right, Jerry? So, that is already published. So, therefore, it is a moot issue, whether high, low or whatever because we are using it already.

MR. ST.PIERRE: If I could add something, a performance standard for FDA has a particular meaning. It is not an IEC standard or something. It is something that we have actually identified as a performance standard. If we adopted the IEC, let's say, I mean, that is a standard that we are using but it is not, quote, unquote, like a performance standard. So, we could still use it. It is considered a voluntary standard, which we require for determining safety and effectiveness.

So, I think it is a semantic issue. I think we are all on the same page.

DR. YIN: But one thing, though, if it is a voluntary standard, what advantage, if I am company A, I decided I don't want to use that method. I use my own and justify. I am willing to do that. FDA would have to accept

that. Now, if I take the regulatory standard, everybody must follow that one period. I cannot be, you know, the interface. But if we adopt a voluntary standard, it would be easier for all the companies, domestic companies and the foreign countries.

DR. LEWIN: Would that make life easier for FDA?

DR. YIN: Oh, definitely. Right, Jerry?

DR. LEWIN: As a voluntary standard, not the regulatory?

DR. YIN: But let me share with you Question 7. If we change that to performance characteristics, I think it would be easier for all of us to adjust to it. Right? Rather than calling it a standard because we could have other characteristics that may not be in the standards but we can also require it.

DR. DONATUCCI: I have no objection to that. That is just the way the questionnaire is written.

DR. YIN: I apologize. You know, that is why I am saying -- maybe someday --

DR. SADLER: No matter how voluntary the standard is, once you all adopt it, it becomes a regulation.

MS. SHULMAN: Performance standards go through rulemaking and all. So, you are talking more of guidance also.

DR. SADLER: Some of our other voluntary standards

have been adopted by your sister organization at HCFA. They are regulations now.

DR. YIN: Oh, we are different here.

MS. SHULMAN: Dr. Yin is correct. We will go with performance characteristics and skip Questions 8 and 9 because Question 8 is meaning what is the priority for writing the standards.

DR. DONATUCCI: Are there any comments?

DR. LEWIN: The comment is that the standard de facto is already in place. So, you don't have to spend time reinventing the wheel.

MS. SHULMAN: Right. And go through rulemaking and all.

DR. YIN: If you look at the words "performance characteristics," that would make sense.

DR. DONATUCCI: We could add that under "Other."

DR. YIN: Oh, that is a good idea.

DR. DONATUCCI: Arnold, you had a comment earlier about that. Do you still --

DR. MELMAN: Well, what about the issue of standardizing the effectiveness on specific stones?

DR. YIN: Isn't that labeling?

DR. DONATUCCI: Do we need to address that here at this point --

DR. MELMAN: It could be in the labeling.

DR. DONATUCCI: Okay. So, we are going to skip -- did you say 9 and 10 we skip?

DR. MELMAN: No, 8 and 9.

MS. SHULMAN: 8 and 9.

DR. MELMAN: Ten we skip because it is --

DR. DONATUCCI: So, we are now at Question 11a. Can there otherwise be reasonable assurance of its safety and effectiveness without restrictions on its sale, distribution or use because of any potentiality for harmful effect or the collateral measures necessary for the device's use?

MS. SHULMAN: That is referring to prescription labeling.

DR. DONATUCCI: Please speak up if you wish to volunteer.

DR. SADLER: The answer is "no" because it has to be prescribed and even got the option of, again, verifying that we think people ought to be trained.

DR. MELMAN: Well, if it has to be prescribed, isn't the answer "yes," or am I reading something wrong?

DR. SADLER: The question is written upside down. The answer is "no."

MS. SHULMAN: You are correct.

DR. YIN: Maybe you need to say "yes" because I don't think --

DR. SADLER: If the answer is "yes," you skip 11b.

MS. SHULMAN: Right. It is "no" and you go to 11b.

DR. SADLER: So, you have to say "no" so you get to go to 11b.

MS. SHULMAN: Correct.

DR. YIN: You are right. You have to say "no" in order to go --

DR. DONATUCCI: Let's all agree that we need to go to 11b and that automatically makes the answer "no" or "yes," whichever is appropriate.

11a, the answer that we agree is "no" because we have to get to 11b. Okay.

11b is identify the needed restrictions. First choice, only upon the written or oral authorization of a practitioner licensed by law to administer or use this device. I think the answer to that would be "yes." Okay.

Second, use only by persons with specific training or experience in its use. And we have earlier said training was necessary. So, again, that would be necessary.

Use only in certain facilities.

DR. STEINBACH: That is contradictory for a transportable device, isn't it?

DR. DONATUCCI: Unless you define the facility as a transportable device. That seems to be -- this is a

semantic issue.

DR. LEWIN: But certain facilities are covering mobile devices.

DR. DONATUCCI: So, you would suggest that the answer -- we need to indicate that that is a restriction.

DR. LEWIN: I don't think that I would like to be treated in a back alley, but --

DR. STEINBACH: I assume the facilities you need would be like a Code Blue Team handy essentially, not do need but might need.

DR. DONATUCCI: Right. Would we then not in this -- we are not going to interpret this then meaning that the facility be specifically designed to have -- to accommodate lithotripsy alone, but that facilities have -- be a medical facility for basically having good -- all the principles of delivering a procedure, including resuscitation.

DR. LEWIN: I think that if we go with the example of childbirth, you wouldn't mind to deliver the baby in the maternity home instead of a hospital, providing that you know if there is any complication there is qualified personnel, which can be there within five minutes.

DR. DONATUCCI: That is one way to interpret it. I think the other --

DR. MELMAN: If you are in a birthing facility bleeding to death and you don't have an operating room

nearby, it doesn't matter if there is a qualified person there. You are still going to bleed to death. So, really for the lithotripsy shouldn't it be within a hospital or adjacent to a hospital if you have an arrest -- I am not sure why it is so vague. Why not within the hospital or adjacent to a hospital.

DR. DONATUCCI: I think what Dr. Steinbach was saying, you have to have full resuscitation. It is a medical -- an appropriate medical facility as opposed to a -- so, the answer, I believe, if I am getting -- if no one objects is that we should say that this should be restricted to use only in certain facilities.

PANELIST: Medical facilities.

DR. DONATUCCI: Okay. Any other restrictions that I would wish to introduce at this point?

DR. LEWIN: Would that preclude use in the mobile --

DR. DONATUCCI: No. That is an appropriate medical facility.

DR. STEINBACH: A small hospital would not buy a lithotripter but could handle a cardiac arrest, most small hospitals.

DR. MELMAN: But people could take mobile lithotripsy --

[Multiple discussions.]

-- rural Massachusetts in the woods.

DR. FOOTE: I think that is an interesting question. I mean, why can't I have a mobile lithotripter in the parking lot outside my office? Maybe it wouldn't be such a good idea -- maybe if I had an ambulatory surgical center, it would be a good idea to resuscitate people that would be appropriate that outside of a facility that did not have those abilities. I think that is a good question to ask.

DR. DONATUCCI: Yes. Again, clinical experience today, I believe, with these mobile units, fully equipped are driven up to the back of the office and patients are treated. So, I mean, it is occurring as we speak with, I don't believe, any adverse effects. But the issue, of course, is that that is an appropriately configured transportable unit with resuscitation equipment and appropriate medical care. I think that is the restriction that we are making, only not trying to just say, well, you can't put it into a tent. Having operated in a tent, it can be done. But it just has to be an appropriate medical facility.

Any other restrictions?

[There was no response.]

So, we have identified the needed restrictions as being all three.

DR. LEWIN: I am sorry to be -- to ask you to come back to it. What about a kidney stone treatment center, which is in the middle of nowhere and not that close to, let's say, five miles from the hospital. Would that be okay? Ten miles from the hospital?

It is basically Jenelle's issue of coming with a mobile lithotripter close to the office and treating the patient.

DR. DONATUCCI: I think this gets back to a question that we discussed -- actually, you brought it up, Bob, earlier -- who can do the treatment and where can they do it. We are getting into the question of appropriate medical practice and I don't know that -- then FDA needs to do that.

DR. YIN: Good. You take care of it.

DR. DONATUCCI: Okay.

So, any other final comments on the part of the panel concerning the questionnaire?

Okay. Thank you very much.

DR. MELMAN: Did you want to say something?

MS. SHULMAN: [Comment off microphone.]

DR. YIN: You will love it. Summarize the whole thing for us.

DR. LEWIN: You mean, you are leaving all the jobs to us?

DR. SADLER: [Comment off microphone.]

DR. DONATUCCI: Okay. Well, let's go through this one then. I think we will start with Question 3. Is the device an implant? I think we can agree that the answer is "no."

Question 4, indications for use prescribed, recommended or suggested in device's labeling that were considered by the advisory panel. I believe the indications were the treatment of renal and ureteral calculi.

Do we agree that those are the indications?

MS. YOUNG: Yes.

DR. DONATUCCI: Okay. Question No. 5, identification of any risk to health presented by the device.

DR. STEINBACH: Well, hematuria.

DR. FOOTE: Why can't we just look at the list --

DR. SADLER: Can we refer to that?

DR. YIN: That is in the overhead. So, you can reference that.

DR. DONATUCCI: Let's get it out and write them down.

MS. SHULMAN: Just reference Dr. Herrera's presentation. It is all in the slides.

DR. LEWIN: Also, in Dr. Baxley's presentation.

DR. YIN: What page?

MS. SHULMAN: It is page 2 of this handout are the slides and he has the common risks/controls.

DR. DONATUCCI: Is it sufficient to say that?

MS. SHULMAN: Yes, that is fine.

DR. DONATUCCI: And they were both general and specific categories mentioned there.

Question No. 6, recommended device reclassification priority. I believe we have decided to recommend classification Class II.

MS. SHULMAN: Class II and this is where the priority comes in on how fast would you like us to get the reclassification through and published. And it is usually high, medium or low.

DR. STEINBACH: Medium.

DR. DONATUCCI: I would tend to say as soon as possible, but you need --

MS. SHULMAN: That is high.

DR. DONATUCCI: In a sense, to answer this question, I would suggest that it -- I don't know what else you have on your plate, frankly. It doesn't seem to be that burning an issue for me to say that you have to move this forward at a high priority.

DR. YIN: Mr. John Baxley is very efficient.

DR. DONATUCCI: High. We will put high.

No. 7, if the device is an implant -- it is not --

or is it life-sustaining or life-threatening. I think we have determined already that they are not. So, we can skip Question 7, it looks like.

Question 8, summary of information, including clinical experience or judgment upon which classification recommendation is based. Well, I believe that is -- 15 years of clinical experience and the literature.

MS. SHULMAN: That is fine.

DR. DONATUCCI: Okay. We will move to Question 9 now.

MS. SHULMAN: And that can be answered just by referring to Question 11a on the first questionnaire you answered -- filled out.

DR. DONATUCCI: Okay. Refer to Question 11a, original handout.

MS. SHULMAN: Question 10 only refers to Class I devices.

DR. DONATUCCI: We have no question 10.

MS. SHULMAN: Oh, I am sorry. Turn it over.

[Multiple discussions.]

DR. STEINBACH: We can write on blank paper.

MS. YOUNG: Can you read it, please? I can't read it from here.

MS. SHULMAN: [Comment off microphone.]

DR. STEINBACH: That would include the x-ray,

right?

DR. YIN: We do have x-rays, a mandatory standard already.

DR. MELMAN: Do you want us to list those?

DR. YIN: You say what we discuss earlier. That is fine. Then we fill in the blanks. Is that okay with all of you? We don't want to do your work, if you would like to do it.

DR. MELMAN: Any other discussion on this?

MS. SHULMAN: I know I don't have anymore forms.

DR. MELMAN: Dr. Donatucci,, could you -- would you like to make a motion recommending a classification?

DR. DONATUCCI: So moved.

DR. MELMAN: No, make a motion.

DR. DONATUCCI: I recommend that we classify the devices Class II.

DR. STEINBACH: Second.

DR. MELMAN: It has been moved and seconded that the reclassification as discussed be recommended to the FDA as a Class II device. Those in favor signify by raising your hand.

Anyone opposed to this?

[There was no response.]

We have one other vote.

DR. YIN: If we have a quorum, Mary, we don't need

that.

DR. MELMAN: No. Okay.

So, this portion of this open -- we really combined things here. We will consider issues related to the update of the draft guidance with respect to preclinical and clinical performance requirements and labeling of the ESWL for kidney and ureteral stones.

If there is anyone wishing to address the panel or the FDA, please step up to the podium and be recognized. Is there anyone else in the audience from any of the other companies that have anything to say that they would like to add?

[There was no response.]

Okay. Mr. St.Pierre, would you like to say something at this point?

MR. ST.PIERRE: I have no questions.

DR. MELMAN: Okay.

Agenda Item: Updating of the Draft Document for Labeling

All right. So, there are certain issues that we have to address, which are really for updating of the draft document for labeling. It is preclinical issues. In addition to what was presented earlier, there are other preclinical performance tests, which could be used to characterize the performance of the ESW lithotripters.

Is there anything else anyone else would like to see?

[There was no response.]

Okay. So, I guess what you outlined and the recommendation that we made we continue to accept.

From the clinical perspective, considering the extent of preclinical performance testing. The first question is a small limited clinical study as presented earlier and was recommended with 20 patients, which demonstrates that the device functions as is intended, sufficient to provide a reasonable assurance of safety and effectiveness for the traditional types of lithotripters that we have discussed.

Does anyone have any objection to the use of 20 patients? No? We all think 20 patients is sufficient? Okay.

MS. YOUNG: Can I just comment? It seems like an awfully small number to me, but perhaps when one considers the experience, the length of experience with a particular device, 20 patients is okay. But normally, you know, a research study with 20 patients, well, you know, you would look at that and say heavens above, you know, that is --

DR. MELMAN: Yes, but this is not a -- this is really just showing --

MS. YOUNG: I realize that, yes. Okay. I am not

objecting.

DR. MELMAN: Your non-objection is noted.

DR. LEWIN: Is this like statistically significant?

DR. MELMAN: It just shows that it works.

Part (b) is a large pivotal study as outlined in the 1992 Draft Guidance for Information on Clinical Safety and Effectiveness Data for ESWL of Upper Urinary Tract appropriate for each new lithotripter, which uses non-traditional technology; that is, technology not used in lithotripters currently marketed in the United States?

I think what you are asking is should you require a PMA for those devices. And I think --

DR. YIN: Or more extensive 510(k).

DR. MELMAN: Is there anyone who objects to that? No? Okay.

The third question is: Hypertension associated with ESWL was a major clinical concern when the first lithotripter was approved in 1984. Is this a major clinical issue today? Should this be addressed as a precaution in the labeling, a statement in the clinical summary of the labeling or left out of the labeling?

So, Dr. Vertuno, who is a nephrologist, what would your comments be?

DR. VERTUNO: I don't think it is a major clinical

issue today.

DR. SADLER: Just in the clinical summary. You know, they did a study, which is not public, but which I reviewed, and I am content to say that we should mention it in the clinical summary of the labeling.

DR. YIN: I think we have to be careful because that particular study was considered proprietary.

DR. SADLER: Yes, that is right.

DR. YIN: So, unless we can identify what is in the literature --

DR. SADLER: The literature also.

DR. YIN: Also say that.

DR. SADLER: [Comment off microphone.]

DR. YIN: If we reference a list --

DR. SADLER: [Comment off microphone.]

DR. STEINBACH: Perhaps under "Labeling" on page 2, "Common Risks," hypertension is essentially -- if someone already has hypertension, they should not undergo this procedure.

DR. SADLER: No, that is not so.

DR. VERTUNO: Any renal -- hypertension is so common, the cause and effect is almost impossible --

DR. SADLER: If you had a large population of people with kidney stones and didn't find at least 15 percent of them had hypertension, it is not representative

of the American population.

DR. MELMAN: I guess my question is why put in something that you are saying really doesn't happen.

So, how many people on the panel are in favor of eliminating that phrase anywhere? 5.

How many want to continue the -- to be in the summary? 2.

So, we would recommend as a panel that just that phrase that talks about hypertension be eliminated.

Does the labeling information, which was presented earlier contain the appropriate indications, contraindications, warnings, precautions and other clinical information for ESWL?

Well, I would like to recommend that the information that I asked for earlier, which is -- be included, and that is let the efficacy of a -- that device is on a very specific stone and that that be a standard that people could use in deciding whether to --

DR. DONATUCCI: The specifics being both size and composition?

DR. MELMAN: Yes.

DR. SADLER: [Comment off microphone.]

DR. MELMAN: I don't know -- 150 pounds is a long time ago.

DR. SADLER: But you can bet that if you don't

specify, that the manufacturers know what your best interest are. All of this is why I think it is difficult to set a standard onto it.

DR. MELMAN: Well, you could put less than some -- you know, a standard person, 1.72 meters and, you know, 200 pounds, 180 pounds. It gives you something; whereas, you have nothing to look at.

Does anyone object to that?

DR. FOOTE: No.

DR. MELMAN: Dr. Young.

MS. YOUNG: The issues I raised earlier as far as children are concerned, now, I am not specifically -- I just think that there should be some sort of precautionary information. I don't know where you want to put it in the labeling, but I think that the issue of pregnancy, not just being suspected but being confirmed, that issue. I think something in there about children. And I don't know whether you want to put in age limits or not, but, you know, the fact that we haven't got a pediatric urologist here to speak to that particular issue and I am not familiar with the literature on it. But I just feel that because there are some questions there, that there should be some precautionary thing.

And cardiac abnormalities was another area and I am not quite sure if that is already written into the

labels, labeling or not, but as a precaution or a warning or something or other.

DR. FOOTE: Is it possible to defer the decision about pediatrics to get the opinion of some pediatric urologists because we are all aware of reports in the literature and no pediatric urologists who are using ESWL safely on children but I don't think that -- it doesn't seem that anyone here has the data and the expertise at this point to make a determination of that.

So, I think there should be something about kids in there, if anything, to say that it is safe for kids up to a certain age because we have that data now, but I don't think we can make that determination now.

DR. YIN: If either one of you want to search it out, you can direct FDA to do that. It is up to you. Which way?

DR. DONATUCCI: I am just going to read you a paragraph from Topics in Clinical Urology: New Developments in the Management of Urolithiasis. "Pediatric patients may also be at increased risk of renal damage. Small kidneys suffer a greater degree of injury than do adult kidneys in comparable doses of shock waves. Potential for progression and permanent damage in the long term is of greatest concern in the pediatric population."

So, it is an issue.

DR. MELMAN: Could I recommend that the FDA consult a lithotripter, who specializes in children and ask them to make -- because we really don't know.

DR. YIN: Okay. Consider that done.

MS. MARLOW: With your permission, if I could go back to the issue about stone composition. The current FDA guidance document for clinical studies didn't require us to analyze stone composition. We didn't do it in our study. I am not sure any of the other companies did.

Certainly, on anything that we can measure non-invasively and easily, I am all for disclosing that and including those requirements in the labeling. I am not sure I know how we can easily analyze stone composition and --

DR. MELMAN: I don't think you could -- if what you are afraid of is that you are going to be asked to go back and do other studies, I don't think --

MS. MARLOW: No, not so much -- I suppose you could require all of us to do that.

DR. MELMAN: I don't think that is the --

MS. MARLOW: But that probably wasn't your intent.

DR. MELMAN: No.

MS. MARLOW: So, if you want information on how each lithotripter behaves in the presence of different types of stones. I am not sure that that is available from the manufacturers right now.

DR. MELMAN: I can't believe that people who do lithotripsy don't know what stones -- when the fragments come out, they are not fragmented into powder, that people pass fragments and that someone must measure what the stones are when they come out.

MS. MARLOW: I am sure someone does. We didn't. And I am not sure that the manufacturers reliably did. So, that information may be with physicians rather than with manufacturers.

DR. DONATUCCI: Some of that information is in the literature.

DR. STEINBACH: How much can you tell from an x-ray?

DR. MELMAN: You can tell a lot.

DR. BENNETT: The other thing -- for a 20 patient market test or whatever you want to call this study, you are not going to get the kind of information in numbers that are going to make any sense.

DR. MELMAN: Maybe 20 is not the right number.

DR. BENNETT: But, again, this is a predicate device. You have already qualified the fact that this device is similar -- has performance characteristics of 10 to 12 devices on the market.

DR. MELMAN: See, I am surprised. You have spoken for an hour here today and Mr. Brown is the president of the

company and has made a big point of saying his product is better than everyone else's and following that, a lot better, and, yet, you didn't do the information that I would expect you would have. It is a bit of a surprise to me. Why not?

MS. MARLOW: We did not.

DR. MELMAN: I know you weren't required, but --

DR. BENNETT: Nobody has done that.

MS. MARLOW: I think another thing is I am trying to think of how many patients we had specimens on that we could have sent for analysis. Sometimes it is true that all they are passing is very fine sand. Very honestly, the cost of that is a lot.

When you have a good success rate and a good retreatment rate, the motivation to look further, especially when there is a big financial impact, probably isn't very good.

DR. BENNETT: Well, the only reason for doing a stone analysis is if you have the current stones and you are following -- you know, you are doing a medical management of the patient. That is, you know, up to the referring physician and whether it is an issue. So, I mean, it is not -- it is only done for specific medical reasons.

DR. MELMAN: I understand that, but I am looking at the point of a person who wants to go out and get a

lithotripsy now and you have 12 companies who tell you theirs is the device to use. It would seem that some method you have of comparison would be to say this is what you should expect and yours is really going to give you an 85 -- I mean, it would be in the interest of the company to want to do that.

MR. BROWN: Dr. Melman, you know, there are two things. I wasn't trying to make a sales pitch for you, but the fact of the matter is that when we do these FDA studies, whether that be my company or anybody other company, they do them according to FDA guidelines. And within the framework of the FDA guidelines, as they are written today, there is no requirement to break down those stones.

Secondly, somewhere along the line, we have to, I guess, look at these differences in these stones, the composition of these stones. There are a few stones that you can easily recognize, where you have the radiography, exactly what type of stone they are, how dense they are, composition and shape.

But by and large there will be -- I won't say how much, but a certain amount of laboratory work necessary to analyze those stones. Make no mistake about it, these FDA studies are not cheap in the first place and we are just going to make the thing even more expensive that way. But be that as it may, the point being that these are not

requirements for us and that is why we don't do it.

DR. MELMAN: I understand that. But we are here, we are spending our day and we are asked to give our opinion about how to make things better. I think that is one of the ways that we can make things better.

DR. DONATUCCI: I am just kind of sitting here thinking about this, but -- I would say the difference of stones, of course, occur with different frequencies in the population. However, I am not sure that -- and I am not aware and maybe this does occur that there is a geographic variability in the incidence of a particular type of stone. So, basically all of the studies then -- assuming that that doesn't occur, all of the studies were done on patients -- the composition of stones should be somewhat proportional between all the studies.

Therefore, the efficacy rate if you use retreatment as your end point should be a reflection, unless there is a bias, that one study had more proportion of a particular type of stone, they should be comparable, except for size.

MR. BROWN: Within the frame of a study, the sizes of the stones are broken down and that is why it is a multi-site study. This is not just a one site study in one particular area. I think, by and large, Don, there mostly were three four site studies for the most part. And the

stone sizes are categorized within the framework of the study. But, again, the stone composition is not.

MR. ST. PIERRE: I see the point that you are trying to get at, Dr. Melman, and there are a couple of points that I would like to make. We could go to the literature and get like a general summary of lithotripsy in the treatment of certain types of stones and certain stone characteristics. I don't think that is going to give you what you want because you want it broken down for this lithotripter or that one. I don't know that anybody can actually do that at this point.

But be assured that if a company wants to come in and say, you know, we have got -- we are the best for treating cystine stones or, you know, we have got -- our effectiveness for treating cystine stones is 80 percent and that is better than any other company, I mean, we would ask for the data. I mean, if they want to make specific claims regarding certain types of stones or certain stone characteristics, we will get the data because we will need that and they will need it to support their claim.

We still probably wouldn't let them say that they had better than any other company unless they studied every other company in addition to theirs. But if they want to put an effectiveness rate for a certain type of stone, we can get that data.

DR. STEINBACH: Wouldn't they tend to do it in
a --

MR. ST.PIERRE: If they do a study, they get the
data, you can be sure assured that it will be in the
labeling and they will promote it. So, you will get it.

DR. STEINBACH: Wouldn't this show up in the
literature? If somebody wants to, you know, get a paper, so
he might use something like this.

DR. DONATUCCI: Maybe yes, maybe no. If it is
done within the confines of a study, not all protocols wind
up in the literature.

DR. YIN: Before you get the competition, is there
any diagnostic method when you are going to put it
underneath that? How are you going to know what stone
composition is? Are there ways of determining first before
you zap it on me and come out and then you can tell what it
is?

DR. MELMAN: Usually from the x-ray you can tell.

DR. YIN: You can tell what kind of composition?
Maybe they should describe that. How many types of
compositions there would be. Do we know in the literature?

DR. BENNETT: There are probably five different
categories.

DR. YIN: Then do we have some general idea of
which 3 or which --

DR. BENNETT: Well, 80 percent are calcium oxalate. Some people think they can differentiate a monohydrate and dihydrate. The next most common category is uric acid, about 10 percent and then 5 to 8 percent are stuvite stones.

DR. FOOTE: I think we are getting bogged down in this question. I think to answer Dr. Melman's concern to have one standard, if you say a 1 centimeter radio opaque stone, we know that 80 plus percent of those are going to be calcium oxalate and that probably the geographic distribution is going to be the same.

So, if you say a 1 centimeter radio opaque stone, then that is -- you know, the number of patients that have cystine stones in that group is going to be pretty unusual. And I think that that should be adequate.

DR. MELMAN: You have that.

MS. MARLOW: We have.

DR. HAWES: Moving from composition, I would like to entertain the issue of pancreatitis again. I didn't hear anybody mention pancreatitis as a risk for -- at least as a high risk for lithotripsy. That is number one.

Number two, I assume that this label was probably carried over from the original labeling when, obviously, pancreatitis potentially was a concern. But what I think we have learned now is that may not be and I would suggest

-- and with the addition that we are actually targeting the pancreas in some cases, I would suggest that that pancreatitis be eliminated from the list of contraindications for shock wave lithotripsy.

DR. MELMAN: Dr. Agodoa, who had to leave, asked me to make two points. One is that -- which speaks to that issue is that people with acute pancreatitis really are at risk, that it should not be done. Would you agree with that? If someone has acute pancreatitis, you don't want to give them --

DR. HAWES: I don't think anybody wants to try to do lithotripsy for kidney stones in somebody with acute pancreatitis.

DR. MELMAN: Well, I am stating what he suggested. Maybe someone out in North Carolina might want to --

DR. HAWES: I think the problem I have with acute pancreatitis, even leaving it as acute pancreatitis is a semantics problem that we have and that is that if you look histologically at people with pancreatic stones, there is some degree of inflammation. So, I would prefer just to leave pancreatitis off completely.

DR. SADLER: As I recall, the reason that got in there was because when early lithotripsy was done, they were screening for a little bit of everything and they saw the amylase go up in a few patients and so they decided they

ought to protect the pancreas. I don't think we ever had any real evidence beyond that.

DR. MELMAN: Well, in that vein, if someone has cholecystitis and you are doing a left sided stone, should it be a contraindication for left sided stones?

DR. HAWES: I was wondering about that as well. Again, we are targeting the gall bladder, as we learned at our last meeting, and the cholangitis issue as well -- I don't know so much about the blast path or whatever in right sided kidneys, but I am not quite sure why cholecystitis and cholangitis are in there either.

DR. MELMAN: So, you are making a recommendation that we eliminate that. Is everyone in favor of that?

So, the panel would like to eliminate those, cholecystitis, cholangitis and pancreatitis from the labeling. Any other labeling issues?

PANELIST: I have not seen since 1984 any reports on ESWL on retreatments. They just don't come in to our database and if the panel would just touch on that one more time, I would appreciate it.

DR. BENNETT: I think we did. I thought we had covered it. It would be scientifically nice information for everybody, especially for the new purchasers of lithotripsy, but it sets up -- and I think Lillian had indicated it would be very difficult because it is not in the modus of anyone

that does MDR reporting at this point in time. And we are talking about -- I mean, we are talking about a new machine here. We are not talking about the 10 or 12 that are out there. I think it would be very hard to do. I think you just have to use the literature and the companies know how to go out and get the information if they have a product that is better than someone else's product.

DR. DONATUCCI: I agree. When we had this discussion a little while ago, we decided, I think, the literature was the more appropriate venue for that.

DR. MELMAN: Does the labeling information presented earlier lack any pertinent information that would be useful to the user?

DR. STEINBACH: I think you made the point.

DR. MELMAN: Dr. Agodoa also asked me to -- talking about adverse effects that this comment about "However, lithotripsy is believed to be less damaging than the persistence of the disease or alternative methods of treatment," just be stricken from the label also. That was kind of redundant.

I would agree with that. I would like to recommend that.

Any other comments from the public, from the panel, from the FDA?

[There was no response.]

I would like to thank everyone on behalf of the panel for their participation.

[Whereupon, at 2:26 p.m., the meeting was concluded.]