be from GE Healthcare.

**GE Healthcare**

**Introduction**

DR. BELL: Good morning, Mr. Chairman, members of the Panel and FDA.

[Slide.]

First of all, thank you for the opportunity to present information on Optison today. We have two presenters. I am just going to introduce them. I am Larry Bell, head of the Regulatory group.

Morten Eriksen is going to present our preclinical information. He got his medical degree and his Ph.D. in physiology from the University of Oslo and is currently a senior scientist with us.

Dr. Feinstein received his medical degree from the University of Minnesota, currently a Professor of Medicine at Rush University Medical Center. He will present the clinical information.

As you have already heard, Dr. Feinstein actually has a long history in ultrasound contrast agents. He was involved in the research and early discovery work of both Albunex, a predecessor of SonoVue--of Optison, sorry, a

misstep--as well as Optison.

By way of disclosure, other than receiving remuneration for his travel expenses, Dr. Feinstein actually has no financial interest in GE and receives no other compensation from GE.

So, with that, I am actually going to turn it over to Dr. Eriksen.

**Overview of Optison CMC and Preclinical Information and Discussion of Animal Models**

DR. ERIKSEN: Mr. Chairman, members of the Committee, ladies and gentlemen, I am Morten Eriksen from GE Healthcare. I am going to guide you through the preclinical information about Optison.

[Slide.]

I will cover the chemistry, manufacturing and control sections, which is quite simple, the preclinical data that we have, and also discuss some animal models, among those will be the pig.

[Slide.]

Optison contains perflutren or octafluoropropane gas in a concentration of 2.8 percent by volume in the final formulation reaction.

Human albumin is used as the shell material around the gas bubbles, and there is also human albumin in a concentration of 1 percent in the vehicle in the fluid between the particles.

Except from the gas, Optison is essentially identical to the previous product Albunex, which contained air instead of perflutren propane.

[Slide.]

The size distribution of Optison can be measured by counter control techniques, and this curve shows the size distribution of Optison particles. We have diameter on the horizontal axis and the relative number of particles on the vertical axis.

We see that the distribution of sizes stretches up to about 10 micrometers. This curve rises is the cumulative distribution of capillary size in the human lungs.

From that curve we can read, for example, that 50 percent of the capillaries are at diameters less than about 6 microns, and the rest of the capillaries are larger than 6 microns.

From these two curves it is possible to calculate the dotted red curve, which is the expected size

distribution of Optison particles after passage through the lung during intravenous injection.

The area between these two curves represents the number of particles that are retained in the lungs during the first pass after injection. However, this number of particles is quite low compared to the total number of capillaries in the lungs and we do not expect this to have any hemodynamic consequences.

[Slide.]

It is also important to look at the size stability of the particles in blood plasma. Because from theory, it is expected that the soft shelled bubble containing a heavy gas, such as perflutren will increase in size when it is dissolved in blood plasma because of inward diffusion of gases normally contained in the blood and the very slow outward diffusion of the perflutren propane gas.

However, when you do the actual measurements of this with Optison in blood plasma, we have these sets of curves that represent size distributions at different time points after mixing perflutren with blood plasma, and we see that there is a monotonistic decline in size of the particles with time and we do not see the expected increase

in size.

The reason for this might be related, for example, to the shell stiffness.

[Slide.]

The preclinical data will be presented now.

[Slide.]

We first have some data about absorption distribution metabolism and excretion of these particles. The particles after injection are cleared from the blood pool in rats during the very first minutes after dosing. The main organ where the albumin is taken up is the liver.

We also see that perflutren gas, which is very inert, is cleared via exhalation and it is eliminated with a half-time of about 40 seconds in dogs. Most of the gas injected is recovered from exhaled air within 15 minutes.

[Slide.]

This table summarizes the general toxicology data that we have in experimental animals for Optison. We have different kinds of studies and we have No Observable Adverse Effect Levels, and the Human Equivalent Doses gained for body surface area, and also the calculated safety factor should be relative to the highest approved human dose.

We see that the safety factors are quite substantial. We do not have calculations of safety factors in human equivalent doses for the teratology data because the repeated dosing and the timing relations makes this quite irrelevant.

[Slide.]

We have not found any toxicity or local irritation after intravascular, perivascular, intramuscular, or topical dermal and ocular administration of Optison.

It is not genotoxic and it is also compatible with human blood in vitro and does not cause hemolysis.

[Slide.]

We have also performed studies that are related to the ultrasound examination procedure in animals. We have checked the compatibility with rabbit blood during ultrasound exposure of the animal, and there we see no hemolysis. And we see a reduction in white blood cell counts which is comparable to what we observed in a latex particle group. So, that is probably a normal physiological reaction to particles.

We have also observed cardiovascular effects in dogs, injecting a quarter of a mL/kg. In dogs grouped in

three groups, one group received only the vehicle or the human serum albumin, one group received Optison, and the third group received Optison and dipyridamole, which is a vasodilator for the heart, and we saw no effects that could be related to Optison at 5-minute interval measurements after the injection.

We also studied endothelial damage in dogs to see if there were any bioeffects caused by the combination of bubbles and ultrasound exposure. We injected and exposed different tissues to high intensity ultrasound at two different mechanical index levels, and there were no findings in this study.

[Slide.]

Optison has also been studied in the microcirculation in different preparations with in vivo microscopy of fluorescent labeled bubbles. Yasu and allies have studied Optison particles and found that they move at the same speed as red blood cells, but that they adhere to inflamed endothelium without causing blockage of the capillary flow.

Dittrich et al. have studied the alterations in arterial pressure, and there were none of those, and

microvascular blood flow was also unaffected. There were no aggregates of bubbles observed either.

The rat spinotrapezius muscle is a quite special preparation where you can inject intra-arterially and get the bubbles through the circulation in the muscle, and this showed occasional blockage of capillaries caused by large bubbles. That is consistent with what we have heard earlier today, that the lungs act as a first pass filter after intravenous injections of these bubbles.

The same retention of large bubbles was also found in the myocardium of dogs after direct intracoronary injections of Optison. But we should remember that this detection of bubbles was with ultrasound imaging, and actually, the efficacy of bubbles for reflecting ultrasound is very size dependent. So very few numbers of large bubbles will give a strong ultrasound echo in the images.

So, to conclude with, Optison does not block systemic capillaries after an intravenous injection.

[Slide.]

I will discuss a few animal models.

[Slide.]

First, starting with the dog model for hemodynamic

studies. That is a typical standard preparation for studying the acute toxicity of drugs, and on anesthetized dogs that is instrumented for simultaneous measurement of several hemodynamic variables, such as pressures in the range of different sites, and we can also measure blood flow in arteries and cardiac output and these can be done with different techniques. Of course, we can also record the ECG.

This preparation can be combined with acute disease models, such as myocardial ischemia, infarction, and reperfusion injury.

However, this model is not very well suited for studying the direct effect of mechanical blockage of capillaries by bubbles. And the reason for this is that if we run intravenous injection of a typical dose in a dog, then, that number of particles that we inject is about 100 million will be with a factor smaller or 1,000 smaller than the number of capillaries that we have in the lung circulation.

So, in theory, if each individual bubble that we injected blocked a single capillary, then, the change in vascular lung resistance will be in the order of 0.1 percent

and that is below detection limits.

[Slide.]

The pig has been discussed earlier today and the pig belongs to an order of animals, together with the goat, sheep and cow, that have intravascular pulmonary macrophages.

These macrophages react to particles in the bloodstream by activation, phagocytosis, and release of thromboxane, which is a pulmonary arterial vasoconstrictor, and this vasoconstriction can be quite severe.

The release of thromboxane and the pulmonary hypertension response can be abolished by indomethacin, which is a blocker of synthesis of thromboxane. But the phagocytosis will still persist so that, even if you treat with indomethacin and prevent this circulation collapse that can be elicited, you will still have a substantial first-pass extraction of particles which will adversely impact our ability to study via distribution, toxicity, and efficacy of the injected substances if they are used as contrast agents.

[Slide.]

This is a recording from a paper published in 1992 showing the effect of Albunex on the lung circulation in

pigs. This graph shows the response after an injection of 0.2 mL of Albunex, and after injection, approximately with a delay of one minute, we see a rise in pulmonary arterial pressure and a drop in systemic arterial pressure, quite similar to what we have seen earlier today.

After treatment with indomethacin, the same pig can be given 3.3 mL of Albunex without any reaction at all in the blood pressures, so this blockade is quite defective and it confirms that these macrophages are responsible for the responses that we see.

[Slide.]

These pulmonary macrophages are present in different species, and this graph here, to the left, shows how intravenously injected particles are distributed to different tissues in different species.

If the particles are distributed to the lungs, it means that the species has a high number of lung intravascular macrophages and, if it is distributed to liver or spleen, it means that it is taken up by the reticular endothelial systems in other places.

We see that the cat, the calf, sheep, goat, and pig have higher numbers for the uptake in the lungs meaning

that they have macrophages while other species have almost no uptake in the lungs after the injection. These species are especially the dog, guinea pig, rat and mouse.

We can also study and look at the hemodynamic responses in different species to injected particles, and this graph, where have been injections of liposomes in different doses with logarithmic scale here, in animals of different species, and here is the resulting response in the pulmonary arterial pressure.

We see that the sheep, goat, and cow all react to these injections, while dogs, cats, and rats do not react at all. We believe that man, humans belongs to this group.

[Slide.]

Thus, the pig is an inappropriate model for screening of ultrasound contrast agents. It has abundant intravascular lung macrophages, not detected in humans to my knowledge, and the acute hemodynamic response to intravenous injected particles is atypical of the human response.

The response might mask other acute effects with relevance for human safety, such as cardiodepressive effects, because that will be overwhelmed by the changes that are caused by the pulmonary hypertension.

Also, the biodistribution of the contrast agents will be predominant to the lungs and the first-pass arterial concentration will be reduced. This will impact the ability to study both the distribution, general toxicity, and efficacy of the substance.

[Slide.]

If we look at Optison and Albunex, they are quite similar with respect to shell material. We have some data from other species than pig and man also. Albunex has been injected in dogs at single doses up to 10 mL without any effects on pulmonary arterial pressure.

If we assume that the gas in Albunex and Optison, even though they are different, they are both inert, then, it is the shell material that potentially could cause any reactions here.

So, a negative finding in the dogs here is also strongly indicating that the same would happen with Optison. The effect of Optison on pulmonary arterial pressure in dogs is none or minimal. That has already been shown. Also, Optison does not affect pulmonary arterial pressure in man measured during coronary arterial bypass graft surgery.

Optison has been injected in about 1 million doses

without any serious events that can be attributed to pulmonary vascular effects.

Thus, the data from pig is not a good predictor of clinical side effects by Optison, and we think that the dog models are better.

Thank you.

I will now pass the word to Steve Feinstein, who will go through the clinical part of our data.

**Optison Clinical Safety Overview and Introduction of Clinical Applications**

DR. FEINSTEIN: Thank you, Morten.

When we started investigating this project, I was Morten's height and with similar--he is 6'8 and a full head of hair. Listen, I am absolutely thrilled to be here, Dr. Rieves, and colleagues.

This is a unique opportunity, having been in the field for 15 years, like Sanjiv Kaul, and I still have more hair than he, although I am on Propecia. Anyway, for 15 years, we have been using contrast ultrasound to save lives in critical care units, and I just want to bring the focus back.

We are asked on a daily basis to go to the CCU/ICU

critical care units and look at the left ventricular function, period. That is all that matters in most of our critical care patients. That is all I have wanted to do when I began this almost 20-some years ago.

I am called to the ICU, the critical care unit, sick patients ventilated. There is one really good technique that gets right to the heart, and that is echo, and we needed contrast to see the LVO.

Secondly, I want to thank Dr. Bell and the GE staff. We have had total and unrestricted access as when we met with the FDA officials in December 11th, they asked us to do that. We have done so.

I would say we have a wonderful team and foremost is Anna Waller, Stephanie Grace, Susan Gillian, Susan White. Hundreds of hours have been put in this project. There isn't a single graph or patient case that is not investigated by us. I am proud to say it was love doing this work.

To the panelists, I do applaud your volunteerism. We have looked at some of these documents. Good luck. Also, your professionalism and your interest in the topic, which is foremost to us, to my colleagues out here, and, of

course, to my wife Linda for hanging in there.

What I would like to do now is present a clinical overview of our work. It will start with the introduction to clinical applications, NDA safety, Optison postmarketing, clinical literature, future uses.

[Slide.]

Let's go back to 2000. This is the statement from the ASE position paper. At present, it is the position of this guideline committee that intravenous contrast agents demonstrate substantial value in the difficult-to-image patient with comorbid conditions limiting an ultrasound evaluation of the heart. Exactly what I was saying in the clinical care units.

For these patients, the use of agents should be encouraged as a means to add increased diagnostic information and to streamline early detection, and in fact, avoid other invasive techniques and save lives.

I want to note Sharon Mulvagh is here today and she was the lead author on this important article.

[Slide.]

What is the heart? Well, this is the apex of the heart seen with ultrasound. This is the lateral wall,

septum. This is the mitral valve and this is the left atrium. Yes, it is upsidedown and turned backwards. That is by convention.

This is the only chamber we really care about of great importance in critically ill patients. What I need to see is the endocardial surface, which is beautifully highlighted here with the use of a half cc of intravenous contrast agent and a standard ultrasound machine.

[Slide.]

When do I use this based on ASE criteria? When I cannot see at least two of six views of the endocardial surface as demonstrated here. I can see at least three here, beautifully outlined, a normal ventricle.

This is all I am asking to do in every critically ill patient to determine left ventricular ejection fraction and volumes. This determines our therapy and patient outcome.

[Slide.]

What does it look like in real-time? Standard left ventricle seen here, mitral valve plain here, the intravenous agent, half cc, was injected I.V., and it is a beautiful representation of the chamber in real-time. What

you also notice is it is not a very good squeezing heart.

This is a bad functioning heart clearly identified by us, a simple bedside exam determined this.

[Slide.]

What is the safety data? Let's go back almost 15 years on this, and I am happy to do so.

[Slide.]

Albunex was one of the earliest products, and Optison. They bridged the use of Optison, used Albunex protocols to become a newer, more efficient product. What is their device? It is basically an albumin shell with a longer acting gas than air. Similar products have been also discussed with fossil lipid shells, differing here, gases similar.

Back in 1994 through '97, roughly 63,000 injections of Albunex were performed safely in patients. What does that consist of? Well, it was basically air plus an albumin monolayer shell, which is used routinely in vaccines as a blood volume replacement today in most surgical units and ICUs. And, for interest, Pulmolite is a regularly administered, up to 700,000 procedures this year of macro-aggregated albumin, allowing the macroparticles to

be up to 150 microns in size. So they purposely trap in the lung with a radionuclide agent so you can identify the evidence of pulmonary embolism in the sickest of all patients.

So, here we have a product made of macro-aggregated albumin, large particles designed to get trapped to determine pulmonary embolism in almost a million patients for probably over 15 years.

What is the difference now between Albunex and Optison? Well, the gas. It is an inert gas perflutren. It is qualified as a device by the FDA and regulated as such, and it is called ISPAN. It is used today in ophthalmologist office for direct intraocular injections for retinal tears.

I was quite surprised by this when I investigated this and I called two ophthalmology offices, and they said, oh, yes, we have a tank of perflutren here and we do inject in the eyeball as an outpatient procedure to seal retinal tears. It is an inert gas. It is incorporated into albumin shell, which is part of the Albunex we now have Optison, 1 million doses 1998 through 2008.

[Slide.]

So, using Albunex as a bridge to the Optison

studies, and mind you this is 13 years ago, these were the six studies designed. FS-1000 was a dose-ranging efficacy, 40 patients, 1 to 10 dose. The first patient got 0.5 and 5, the next 1 and 10, 2 and 20, and 4 in 40.

So, the maximum dose received by patients was 44 mL. Today, the dose is 0.5 per injection, maximum dose 8.7. So, this was 40 patients dose ranging.

Of this group, 5 patients, this is a very important study, immunologic response. They were challenged with intradermal injections and intravenous injections at baseline and a year later.

Importantly, though, 71 patients in three studies were studied for immunologic responses to cytokines and complement, as well as immunoglobulins, and I will describe those briefly.

The mass balance study was 10 patients again receiving large volumes to say where is this perflutren gas, where does it go.

FS-6000 was an interesting safety blind study looking at patients who had cardiac, hepatic, and respiratory dysfunction. They were directly compared to the same equal volume of 1 percent human serum albumin, 50

patients, 25 randomly assigned to either Optison or 1 percent human serum albumin, 20 normals, 10 abnormal hepatic, 10 abnormal cardiac, and 10 abnormal respiratory.

The final two studies are clinical trials Phase III again looking at the doses that we more commonly use today, but this study was a direct comparison to the Albunex product to look at both safety and efficacy.

[Slide.]

In looking over all this data from 13 years ago, I was quite impressed with the design of the studies and how actually intense they were. These are oxygen saturations and I want to focus not on that only, but all these parameters, but particularly oxygen saturation was monitored at minus 2, 2, 4, 6, 8, 10, 20 and 40 minutes, after every single injection of every single study in every single patient.

[Slide.]

The safety data. There were no safety concerns in these clinical trials on physical, neurologic, spirometry and chemistry between Optison, Albunex, or 1 percent human serum albumin, none.

[Slide.]

ECG changes. There were no clinical changes noted between Optison, Optison/Albunex, or 1 percent human serum albumin. I have looked at these three subjects. One subject had a few PACs, one isolated PVC, and one was a baseline artifact. We have looked at every single case reported here. There were no significant changes on any ECG.

[Slide.]

Vital signs. Similarly, no significant changes on any of the trials. This patient, the upper limit considered for respiratory rate was 21. This patient had 22 breaths, it reverted to 21 after.

[Slide.]

Oxygen saturations. I want to focus on that, because that is of concern to the group I believe. These are the studies, the six clinical trials. The one case we identified, who received 40 mL of I.V. Optison, was told to minimize their breathing, so the echo would be good.

She did, she began to cough, and she dropped her sats from 96 to 87 at a 6-minute recovered within 2 minutes to 8 minutes. The criteria for abnormalities was 7.5 percent drop in oxygen saturations on any patient at any

time. She recovered quickly and then was told not to hold her breath after that. There were no changes noted.

I want you to point this one out in FS-6000, which is safety study. A patient was entered into this study with a resting saturation of 76 percent. The patient was allowed to continue on, received 20 mL of Optison at different doses throughout the study. There were no changes in oxygen sat. The patient probably had a paddle pulmonary syndrome which we didn't identify at that time.

Nothing else of significance. I want to point out these are the clinical trials. Notice here one patient declined 8.2 percent after 1 percent human serum albumin at 10 minutes, which was just a human serum albumin.

All right. 3,600 oxygen measurements were measured in these clinical trials, 13 in 5 patients were considered abnormal measurements, 7, which consisted of 4 patients in FS-3500.

[Slide.]

What does this mean? Well, it turned out when we dug into the case reports, and I want to thank Stephanie Grace for this, this was quite painful after 13 years, we had a number of patients here, 3 who decreased their oxygen

saturation transiently, recovered within two minutes, and we had three at least, and four, that increased their oxygen saturation.

So, one could say patients who are composed of these conditions should get Optison to increase their oxygen saturation. Now, probably the interpretation here is it is a bit random, 4 go down while 3, and here is one Albunex patient went down, this one went up, these 3 go up, this one goes down.

None of these changes had any clinical significance or the patient complained. It was simply below 7.5 percent change for a transient period as little as 2 minutes.

Now, one thing we did pick up, though, when we tracked back, a number of these patients were quite heavy. I did part of these studies and I remember the patients were required to lay supine for over 2 hours.

Well, we now know that if you have a large body surface, your chance of having obstructive sleep apnea may be as high as 40 percent, again, didn't recognize that, so I would argue that the increased oxygen saturation following Optison is probably a random variation of body heaviness and

position.

So, no significant changes in any study on any patient due to any oxygen saturation at any time in these studies.

[Slide.]

A very important series clinical immunological responses: None.

Seventy-one patients in 3 studies were compared. They received blood analysis immunoglobulin, cytokines and complement activation. The blood samples were drawn -24, -1h, 2h, and 1, 2, 3 weeks, and then 5 patients at 1 year.

No antibodies to Optison, no increase above normal cytokine or complement activation.

[Slide.]

Definitions. When we define adverse events--and I wanted a specific definition because going through the report, it is very confusing--this means any event, any event that happened during the study period, whether temporally related or causally related, doesn't matter. It's an adverse event. That is the definition we will use.

[Slide.]

Over all the clinical trials from 1995-96, these

are all adverse events, and they were all considered mild to moderate, no severe. These are Phase III trials. These are all trials combined. Please note that the incidence of adverse events is considerably lower in the Phase III trials than it appeared in any of the combined trials.

[Slide.]

All right. Let's look at impaired patients, and the impaired patients is defined by their medical history, and in this case, an ejection fraction below 40 percent, do the impaired cardiovascular patients have higher adverse events than the non-impaired in the Phase III clinical trials. No. In fact, they have less considerably, and certainly less than all the trials combined. So, it is not specific to impaired cardiovascular patients by definition.

[Slide.]

Similarly, pulmonary impaired patients, by definition, emphysema, pulmonary hypertension, bronchiectasis, do the Phase III patients who have impaired lung function react or have more adverse events than not impaired?

Again, the opposite, just like cardiovascular, they have, in fact, less, and much less than the total

population.

[Slide.]

End of clinical trial, move to postmarketing surveillance.

[Slide.]

We are talking about a million patient doses over a 10-year period, and we have 12 reports of serious adverse reports. Chest pain 1 hour post; I want to look at this one. ER visit for chest pain and ventricular tachycardia. The patient was shocked, had a convulsion and recovered. I did read the report. The clinician didn't feel that the convulsion was related to the Optison, perhaps the cardioversion from V-tach, but it is reported.

I want to come back to this one reported alleged case of a death from Optison and I will get back to that in just a second.

[Slide.]

These are the first 6 cases. These are the other 6 cases of the total 12 in 10 years of a million injections. This, I think we can look at, hypoxia, anaphylactic-like reaction, is that know to albumin? It is known to albumin as a vaccine, as a blood volume replacement, and a pulmonary

injection for Pulmolite. This is a reaction. The antidote is well known, antihistamines, fluids, and/or steroids, they recover uneventfully.

These are the body of the 12 adverse reactions that we could find.

[Slide.]

Now, I want to focus publicly for the first time to adjudicate this openly. The one alleged reported death related to Optison.

This patient was from the UK. Admitted July 18th. After one week of angina, found to have an acute inferior myocardial infarction. Three days later the patient was stable, was enrolled in a low-dose dobutamine stress echo on a research protocol which received Optison.

One hour later, the patient was found in EMD, electromechanical dissociation, consistent with pericardial rupture and tamponade.

It turned out during CPR, which was unsuccessful, an urgent 2-D was performed at the bedside. There was, in fact, a new effusion. I will point out that during the low dose dobutamine when contrast was used, there was no evidence of a pericardial effusion or rupture at that time,

an hour before.

The diagnosis post MI myocardial rupture.

[Slide.]

Now, we are fortunate to have with us, and you have met Dr. Roxy Senior, was a consultant investigated in this case. He sent me the documents. These are the first time I think they have been presented publicly. This alleged case needs to be identified fully.

"In the conclusion, it appears from the report of Dr. Hillis that it is highly likely that the death of this unfortunate patient occurred as a result of spontaneous cardiac rupture and is not likely to be related to the procedures that were carried out prior to the incident."

[Slide.]

Optison Literature.

[Slide.]

A quick review headed up again by Anna Waller, 56 cases, 9,200 cases, I want to focus. There are 2,100 cases of ICU cases. There were no concerns expressed in any paper on adverse events or safety parameters.

This is data loaned to us by Kevin Wei, a colleague of Sanjiv Kaul, of the paper he cited. It is a

subgroup of patients in the ICU with chest pain and non-diagnostic ECGs, but worried about unstable cardiac conditions, 975 patients, no ST-elevation, 3 mL Optison were used. No adverse event, no cardiopulmonary death. 105 patients were continuously monitored - ECG, oxygen sats and hemodynamics.

No changes. 975 patients, unstable with cardiac pain in the unit.

[Slide.]

This is a most remarkable paper again identified by us thanks to our colleagues at the FDA. How it escaped the rest of us, I have no clue, when Optison was in the title, Intraoperative Contrast Echocardiography with IV Optison Does Not Cause Hemodynamic Changes During Cardiac Surgery.

Most remarkable. Subgroup of patients, 35 ASA Class IV patients undergoing open heart surgery received bolus injections of Optison at 0.3 mL through the central venous line directly into the lungs.

There were no changes in ST, heart rate, arterial and central venous pressure, $O_2$ sats, index, LV, regional wall motion 5 and 10 minutes.

These patients are on continuous ventilation with PEEP. I talked to the senior author, Jack Schoeneweis, who is now at Columbia and asked him is this, in fact, what he found, and he said yes.

I asked him if there was anything interesting in the study, and he said no. He is an anesthesiologist. I want to point this out. There were absolutely no changes, 97 injections, 35 patients. That means repeat injections, ASA Class 4, people sick, and ASA means disease limits activity and is a constant threat to life. Please look at their PA pressures. Absolutely no change. A very important study and again we didn't identify it, it was the folks at the FDA.

[Slide.]

This one we did. This was Herzog recent editorial in JAMA. 112,000 patients studied, 16,000 received contrast. All patients were routinely monitored for 30 minutes. Patient groups were similar. Null, zero adverse events after Optison, none.

[Slide.]

Future Uses.

Now, if I can just take a break here and collect

my thoughts. Can I just have the house lights down just a bit.

This is a very important topic as we have already heard. I don't want to leave the topic of LVO, though, without stressing that over and over again. We must go to the intensive care units on a regular basis and identify LV function with contrast. That is our main life blood.

[Slide.]

What I show you now is the future, what I am saying when I go back to practice tomorrow, we will back in the SICU/CCU and I can do in a few minutes what nobody else can do and tell you what the filling volumes of that patient are and wall motion.

We have a big problem in this country and the world. We still die of heart disease, lots of strokes, lots of TIAs, but the problem is it is going to get worse. A third of us are either with diabetes or at risk, and this is a huge incidence of cardiovascular disease.

[Slide.]

Why do I present this? We need better, quicker techniques to get at the population before they get sick. Our focus in the last eight years has been enhancing the

carotid artery for three reasons.

One, when we use ultrasound contrast, we can identify the lumen morphology better. We can identify the carotid intima medial thickness, which is a marker and a surrogate marker of atherosclerosis and we can look at something absolutely remarkable, which is the vasa vasorum, the new blood vessels of plaques which Judah Folkman described in 1971. But nobody has ever seen in real-time. We will start.

[Slide.]

This is a carotid artery exam. This is the standard artery. Here is the carotid now receiving a half cc of contrast agent I.V., and what you see is that the lumen ulcer plaque. This is the next case, a half cc I.V. This is the intima medial thickness. We can measure this and determine the patient's cardiovascular risk as a surrogate marker.

[Slide.]

What next? Well, let's look at this one. This is a patient we studied in 2003, and it was the first time. I read this about 7 o'clock at night, and I thought it was an error. This is the carotid artery of a human, this is the

common carotid, the internal carotid, the brain is here, the shoulder is here, the skin line is here.

What you will see is the outside layer of the artery white, which is filled with a contrast agent, which are the vasa vasorum, which we all have, but we have many more when we have a big tumor like atherosclerosis sitting in the middle of the internal carotid in an asymptomatic patient.

[Slide.]

Let me show you what it looks like in real-time. These are the vasa vasorum on the outside of the wall of the arteries which exist on everybody, just the magnitude varies. This is abnormal. This is a plaque or a tumor filled with microvessels, and Folkman was bang on.

These tumors called atherosclerosis are quite alive and well, they are perfused beautifully, and we can detect this at the bedside within 15 minutes with a portable unit and a half cc of a contrast agent.

[Slide.]

Is it reproducible? Yes, courtesy of Hans-Peter Weskott in Hannover, Germany. Here is the carotid artery with accumulate mode software. I want you to notice. Here

is the plaque, right? No. Here is the plaque.

This is negative remodeling, this is positive remodeling. This plaque is filled with antiogenic vessels which are markers of an unstable vulnerable plaque. So, is this perhaps the best way in the future we will begin to look at an unstable plaque by the degree of vascularity.

[Slide.]

All right. If we proceed, and that is why I am presenting here what will be our dose. The dose will be the same, the MI will be less than we currently use, so the MRI is the peak negative pressure divided by the square root of the ultrasound transducer. It is a relative marker of energy. We are going to be considerably less, it's in log terms. What safety parameters? Much as we described.

Who will we be doing in Phase II? People with unsuspected disease like I showed you.

Phase III? More serious patients I believe.

[Slide.]

In conclusion, based on the preclinical, clinical, and postmarketing experience, number one, I would like to say that preclinical studies indicate that Optison is safe. The pig is probably an inappropriate model due to what

Morten said it may mask other events, and it has, an abundance of intravascular macrophages in the lungs, which is not common in other species that we would use including the dog.

Clinical NDA. Now, this is probably more important at least as our clinical perspective. What have we learned from the NDA? There were no safety concerns whatsoever in the studies that we have investigated, but importantly, now, the proof of the pudding is in the tasting of it. Over a million patients.

This is an excellent safety profile. There were 45 non-serious reports, 12 serious adverse events, which I have gone through with you, and the one reported death, alleged death, does not appear to have anything to do with Optison. In fact, it was a cardiac rupture after low-dose dobutamine in a patient three days prior who had suffered a myocardial infarct.

The literature supports the safe use in intensive care patients particularly in critically ill patients who have a pulmonary artery catheter in them during surgery, under ventilation PEEP, and there was absolutely no change in the ventilatory efforts.

Thank you very much.

Dr. Bell.

**Concluding Remarks**

DR. BELL: Thank you, Steve.

On behalf of GE, I just want to thank the Chairman and the panel and members of the FDA for their time and attention.

As you begin your discussions and deliberations of the questions that the FDA have asked you to consider, I hope the information that has been provided to you both in the background packages and at your hearing today is useful in gaining a better appreciation and understanding for not only the current benefit of ultrasound with contrast agents, but also the potential future benefit of contrast agents.

I also hope the information is useful in gaining a better oversight and understanding of the safety profile of the use of these agents. Specifically, for Optison, we hope the information has been useful to gain an overall appreciation of the safety profile.

We accept and acknowledge that there are inherent limitations in any database. That is almost always a true statement, if not always a true statement. However, GE

Healthcare still believes that in total, that there is an excellent risk-benefit profile for Optison and specifically, looking at all of the currently available information that there is no signal detection for Optison.

Thank you and we will be available for questions at the appropriate time.

DR. HIATT: Let me bring the lights up. Thank you for that.

The last series of presentations will be by Lantheus Medical Imaging. Dr. Hibberd is going to introduce the speakers.

**Lantheus Medical Imaging, Inc.**

**Introduction**

DR. HIBBERD: Good morning. Thank you, Mr. Chairman, members of the Advisory Committee, and Dr. Rieves, members of the FDA, and also members of the public, ladies and gentlemen. My name is Mark Hibberd. I am Senior Medical Director at the new Lantheus Medical Imaging Company. It is truly a pleasure to be here to introduce the Lantheus presentations today.

It is always tough to go after so many extremely energetic and high-quality presentations that have covered

all of these wonderful potential indications and indications, and also safety.

What we are going to do is take a complementary and slightly different tack and focus on our very large clinical trials, safety experience, and also some large clinical outcomes, safety analyses that we have done very recently and which are in the briefing document that you have, and hopefully, try and answer as many of the questions that the FDA is looking for answers for and perhaps pose one or two new ones in relation to microbubble contrast agents.

[Slide.]

We are going to do this with two speakers. First of all, in a moment, I am going to introduce Dr. Michael Main, Medical Director of the Echocardiography Laboratory at Saint Luke's Mid-America Heart Institute in Kansas City.

I should say that Dr. Main is here entirely at his own expense and has not received any consultation fees for any of the work associated with this presentation.

I will also introduce Dr. Simon Robinson, who is Senior Director of Preclinical Discovery at Lantheus Medical Imaging, and he will be talking about some of our animal laboratory research.

[Slide.]

So, the framework and overview of what we are going to do today is as follows. First of all, Dr. Main is going to focus on the clinical trial experience that we have in nearly 4,000 patients with particular attention to special populations that may be at risk for events and placebo-controlled studies that provide value and understanding the safety of Definity.

Then, Dr. Robinson will go over the nonclinical safety studies, show how the animal models can be useful at different stages of development for showing the safety profile of Definity, and how they integrate with the clinical trial results.

Finally, we will close with the postmarketing safety surveillance experience that we have had in over 2 million patients or so, and go beyond the spontaneous reporting of these events and report initial results from a large retrospective database mining experience, which I hope you will find most interesting and stimulating.

Overall, then, the data that we are going to be showing today we think show that Definity enhanced echocardiography provides a diagnostic test with a very

positive benefit-risk profile.

With that, let me introduce Dr. Main.

**Definity Clinical and Postmarketing Summary**

DR. MAIN: Thanks very much, Mark. It's a pleasure to be here today. My colleague, Steve Feinstein, made reference to his advancing hair line, the fact that Sanjiv Kaul has the same problem.

As most of you can probably appreciate, I am in the same boat. As far as I know, there has been no safety concerns raised with respect to alopecia and people who work with contrast agents perhaps will need to look to look at that in the future.

[Slide.]

As Mark just explained, we are going to start basically with the clinical trial program and some background on that to start with.

First of all, Definity was approved in 2001 in the United States following extensive nonclinical and clinical programs, and to quote from the product insert, Definity is indicated for use in patients with suboptimal echocardiograms to opacify the LV chamber and to improve the delineation of the left ventricular endocardial border.

You have heard a lot about future indications and efficacy, we will be focusing entirely on the improved indication and safety considerations today. Each vial contains PFP and a blend of three endogenous lipids. This is activated by rapid agitation.

Each dose can be given either by bolus injection or infusion, 1.3 mL maximum over 30 to 60 seconds generally, and according to Arlington Medical Resources data, approximately 2 million patients have received Definity since prior to approval, so somewhat more doses than you heard earlier today.

[Slide.]

Let's turn to clinical safety in the clinical trial program.

[Slide.]

There have been many studies in the clinical trial program, 48 pre- and post-approval clinical trials. The majority of these have been in echocardiography as you can see, 26.

Twelve abdominal ultrasound studies evaluating liver and kidney, many of these patients with cancer, 8 special safety assessments including pharmacokinetics, and 2

retrospective safety evaluations.

Twenty-seven of these studies were included in the U.S. NDA, 40 in the European Union Marketing Authorization Application.

To subdivide that a little bit, 5 pivotal studies have been performed in the echocardiography realm with approximately 360 Definity treated patients, 3 pivotal studies in the ultrasound area with over 300 Definity treated patients, overall, nearly 4,000 patients involved in the clinical trial program, over 3,600 with at least 1 dose of Definity.

[Slide.]

This is just an overview of the current and previous clinical trial program studies, a total of 51 studies now including 3 which are currently enrolling patients.

[Slide.]

Let's look at adverse events in clinical trials since that is the subject of this panel today. First of all, let's look at serious adverse events.

There were a total of 34 serious adverse events in the clinical trial program all reported as "unrelated" to

Definity, and there have been 8 fatal outcomes in the clinical trial program.

All of these importantly occurred at least 35 hours after Definity dosing, and we have outlined exactly when those deaths occurred, one at 35 hours, one at 4 days, two at 5 days, one at 7 days, two at 12 days, and one at 15 days. So, knowing what we know about this drug's pharmacokinetics, it is obviously unreasonable to assume that these deaths were related to Definity.

All of these patients were at least 58 years old with significant underlying medical conditions or complications from surgical procedures with the exception of one man, 33 years old. But he was not healthy. He was status post heart transplantation. As I said, most of these patients had serious cardiac illnesses and/or cancer.

Reference was earlier made that the experience in the clinical trial program may not very well reflect current use in the clinical arena. I think that this data does speak against that statement.

Overall, the frequency of serious adverse events in the clinical trial program was about 1 percent.

[Slide.]

Let's look at all adverse events. These were fully evaluated in over 2,900 subjects in 40 studies. Twenty-six percent of subjects had at least one adverse event. But only 7.6 percent of these were reported as drug related.

When we look at the most common drug related adverse events occurring with a frequency greater than 1 percent, these included things such as fatigue, headache, dyspnea, back pain, nausea, flushing, and dizziness. Very importantly, however, there was no dose-response relationship found with either bolus or infusion of the agent with respect to any of these adverse events.

[Slide.]

Well, it's important to have a placebo-controlled group to determine whether an adverse event is attributable to the active agent or not, and we do have some information from placebo-controlled studies within the clinical trial program.

Overall, in placebo-controlled studies, adverse events occurred at a frequency of 56 percent, in Definity treated subjects 48 percent, in other words, no increase in adverse events with respect to Definity over placebo.

When we look at rest-stress, echocardiography placebo-controlled studies, we found the same thing; adverse events in placebo subjects occurred at a frequency of 63 percent, those in Definity somewhat less, 56 percent.

Now, the overall AE frequency was increased in both groups, and that is attributable to the stress procedure itself, not to the active drug.

[Slide.]

Well, what about safety in the pivotal echocardiography and radiology studies? AE rates in Definity-treated subjects in all of the pivotal studies, in echocardiography and radiology, occurred at a frequency of 24 and 25 percent.

When we look at the placebo-controlled pivotal echo studies, a 26 percent incidence in placebo-treated patients, 29 percent in Definity, no significant difference between those groups.

Overall, we can say no difference in AE rates between Definity and placebo.

[Slide.]

Let's turn to some specific safety parameters. As most of the panelists are probably aware, and as appears in

the product insert, 221 subjects who were studied prior to the U.S. NDA, 29 percent of those patients did manifest greater than 30 millisecond prolongation in corrected QT interval. It is important to know that there was no placebo group at this time.

A very more recent analysis, which does not appear in the U.S. product insert, was performed for the EMEA approval. We have aggregate data in 672 patients, and it indicates that there is actually no change from baseline between placebo and Definity groups with respect to QT interval.

[Slide.]

This is that data in somewhat more detail. Shown here are the percentages of patients in placebo and Definity dosed patients who manifest an increase of greater than or equal to 30 milliseconds in QT interval. You can see this occurred at 18.6 percent in the placebo, but 16.9 percent in the Definity group, actually less.

What about a decrease in QT interval? There is some interest in this as well. Again, this occurred with a frequency of 26 percent in the placebo and 20 percent in the Definity. So, I think we can now say that there is no

change in QT interval with respect to Definity dosing.

[Slide.]

What about premature ventricular beats? There has been some interest in this, as well. Retrospective evaluation of 75 subjects exposed to a variety of ultrasound protocols indicated no increase in premature ventricular beats.

Importantly, the product insert recommends mechanical index of less than 0.8, which will certainly limit any tendency towards this effect although none has been discovered in patients who have been studied so far in the clinical trial program.

With respect to hemodynamics, in the clinical trial program, frequency of transient hypertension or hypotension less than 1 percent. Overall, no evidence of systemic or hemodynamic compromise.

[Slide.]

Well, you have heard a lot today about potential immune responses. This has been studied in Definity. In a high dose safety study at 50 mcl/kg involving 12 healthy subjects and 12 COPD subjects, now let me put that in perspective. That is, 2.5 times the upper dose recommended

on the product insert for use in patients.

Well, in these patients, no meaningful change in IgA, IgE, IgG, or IgM in serum, no meaningful change in total complement, tryptase or histamine. There was a transient increase in activated C3 at this very high dose of Definity. No anaphylactoid responses were observed, and an independent immunologist concluded the complement activation, which was occurring, was not leading to any mast or basal cell activation.

[Slide.]

Well, special patient populations have received a lot of attention recently in patients dosed with ultrasound contrast agents, and, in fact, special patient populations were the subject of the contraindications last fall.

Definity has been studied in these patient populations including COPD patients. The prospective study, which I earlier referenced, with respect to immune response, other parameters were also measured including lung clearance of the agent, of the fluoropropane gas, half-life 1 to 2 minutes, similar in both groups, in other words, no persistence in patients with severe lung disease.

No SAEs reported in this study, and, in fact,

Definity-related adverse events were actually less in COPD patients as compared to the healthy group of patients receiving Definity.

In a separate integrated summary of safety analysis, 46 patients were identified among 765 patients dosed in 12 echo studies who had COPD.

AEs were reported in 29 percent of the COPD population, but nearly 33 percent of the non-COPD, and when we look at the Definity-related adverse events, again, they are actually lower in the COPD patients.

So, adverse event frequency is not increased in COPD patients that have been studied, and there have been no new adverse event types observed.

[Slide.]

Well, there are several other special patient populations who have also been studied, those undergoing mechanical ventilation, patients obviously with respiratory failure, patients with heart failure, and patients with acute myocardial infarction. All of these groups were also subject to the contraindications issued in the fall of 2007.

In the mechanical ventilation study, 38 patients were studied. No clinically significant abnormalities

reported including parameters such as arterial $0_2$ sats, temperature, $ETCO_2$, blood pressure, heart rate of central venous or pulmonary capillary wedge pressure.

In a heart failure study, 211 patients in this study. No serious adverse events observed, and the overall incidence of new adverse events was not different between Definity and placebo-treated patients.

Finally, in an acute myocardial infarction study, 100 patients, there was one serious adverse event reported. This was mild chest pain occurred two days after dosing, obviously, not drug related, and the new-onset adverse event rate observed in subjects with acute MI was very low, only 5 percent attributed to the agent.

So, again, AE rate not increased in all of these special patient population and no new types of adverse events observed.

[Slide.]

Well, let's turn to the peer-reviewed literature. There have been 52 publications which have described Definity use in a lot of patients, almost 24,000 patients, the vast majority of these in the echocardiography subset.

Four publications and 1 case report provide some

safety data in over 1,800 patients. In all of these, Definity was well tolerated and the adverse event rates, which were reported, were similar to those experienced in the clinical trials.

In your briefing package from the Agency, there is a case report, and this is a little detail on that. The serious adverse event in the peer-reviewed literature, let's put this in context. It was an 83-year-old woman hospitalized with sepsis.

She had atrial fibrillation, hypovolemia, she had also had a pacemaker placed in the past. She had coronary disease, diabetes, a GI bleed, and meningitis. She developed hemodynamic instability about 3 minutes after she was dosed with Definity during an echocardiogram.

She developed hemodynamic instability after going into atrial fibrillation with rapid ventricular response, and as is often done in cases where we are not sure exactly why a patient is hypotensive, she was treated for a variety of things, including potentially anaphylaxis, sepsis, and hypovolemia, and she ultimately recovered.

[Slide.]

So, to put the clinical trial in perspective, the

clinical trial program in perspective, the overall findings show a low serious adverse event rate of 1 percent despite a patient population that had multiple comorbidities including severe cardiac disease and cancer in a number of patients in the radiology studies.

No dose-response relationship was noted for adverse events, importantly.

In placebo-controlled studies, the majority of adverse events were not Definity related. The overall AE rate is higher in these rest and stress studies, but it is similar between placebo and Definity groups, and the overall higher rate is attributable to the fact that these patients are undergoing stress studies.

In the special populations, special patient populations, including patients with COPD, ventilated patients, acute myocardial infarction and heart failure patients, adverse events are not increased, and there is no increase in cardiovascular effects.

As you have heard previously from Drs. Kaul and Feinstein, and Senior, the efficacy of these agents has been demonstrated quite well, and we will not talk on that anymore at this point.

Overall, Definity has a very positive benefit-risk profile in a variety of clinical settings and patient populations.

[Slide.]

I am now going to turn this over to Dr. Simon Robinson, who will review some of the nonclinical safety data.

**Definity Nonclinical Summary**

DR. ROBINSON: Thanks. We have intentionally put the nonclinical safety section after the clinical, so I can compare the findings from the animal studies with those from the clinical studies.

[Slide.]

Starting with the pharmacology and toxicology areas, we performed some cardiovascular safety studies in dogs, and we saw no cardiopulmonary effects at up to 25 times the clinical dose.

When we went to extreme doses, up to 50 times the clinical dose, we did see some respiratory rate increases, pulmonary arterial pressure increases, and decreases in arterial pressure and cardiac contractility.

In toxicology studies in the rat and the primate,

we did see some clinical signs at high multiples in the clinical dose which were consistent with the cardiopulmonary effects we saw in the cardiovascular safety studies.

We did, however, note that there was an effect of the rate of dose administration, so if we dosed very rapidly, we precipitated more clinical signs than if we dosed at a time or clinical relevant dose level.

We were careful in our toxicology studies to try and be representative and conservative in how we did this.

Overall, the safety margin that we see is consistent with the safe clinical use at recommended dose levels that you just heard from Dr. Main.

[Slide.]

We did some mechanism-based studies to try and better understand the cardiopulmonary effects that were seen at the very high dose levels.

In the primate, we dosed at a monumental level of 150 times the clinical dose. This dose level we did precipitate collapse and clear respiratory signs, so we really pushed this very hard to get effects.

There were no meaningful changes in hematological parameters or in plasma levels of histamine, tryptase or

complement. We did, however, see some abnormal electrocardiographic changes including ST-T segment depression followed by cardiac arrhythmias within 1 minute.

The lack of the histamine and tryptase we took as indicative that we weren't getting any mast cells or basophil cell degranulation occurring, and overall, this was suggestive of transient myocardial ischemia, and not an anaphylactoid type response.

As we heard previously from our colleagues at the GE and Bracco, the pig has been talked about and discussed extensively. There is a large literature on the pig. There have been two reports with Definity in the pig model.

At clinical dose levels of Definity in the literature reports, there are mild and transient pulmonary arterial pressure changes. However, in the literature, there are no changes in heart rate, systemic pressure, partial pressure of oxygen, or left ventricular systolic function.

You heard previously, and I also echo, the pulmonary intravascular macrophage in the pig is a clear difference from the human. I see that, potentially, it's a good model for initial screening to look for agents and

identify possible risk. However, I see it is much less valuable when you get into the mechanism part to try to understand how one would ameliorate because of the physiological differences.

So, the nonclinical testing suggests frequent anaphylactoid mediated events at clinically relevant dose levels are unlikely, and you will hear from our postmarket this is consistent with clinical experience that yes, there have been some. They were at a very low frequency and the pig model to identify how something could occur with 1 in 10,000 and 1 in 100,000 is unreasonable.

[Slide.]

Moving into some other model testing, we used a variety of models to look at potential theoretical risks, and one of the obvious concerns is the potential for occlusion microcirculation.

Similar to the data that was presented earlier, we used a rat spinotrapezius muscle preparation that allowed fluorescent labeled Definity to be examined in the microcirculation as it traversed through the microcapillary bed, and being examined with intravital microscopy.

Here, we could actually follow the microbubbles as

they went through this microcirculation. The vast majority of those microbubbles traversed right through the microcirculation, and were not impeded. A low proportion were transiently retained, and of those that were transiently retained, the vast majority changed shape and dissipated and moved through within 10 minutes.

There was no detrimental effect to the regional microcirculation that we could see even at 40 times the clinical dose, suggestive that the microcirculation could compensate for any small degree of occlusion that was occurring.

That is in the normal muscle. Now, we were concerned that potentially if one went to a situation where you occluded some of the vessels ahead of time, one might precipitate more of an effect, so we moved to a pulmonary hypertension model.

In this, we used the dog and administered sephadex microspheres. These microspheres were in the 100 to 600 micron range, and I just want to emphasize much, much larger than the size of the microspheres in Definity.

These were intentionally put in there to occlude some of the capillary bed and resulted in increase in the

pulmonary arterial pressure either to a moderate or severe degree.

Definity was administered at a variety of dose levels up to 10 times the clinical dose, and even at that, we did not see any change in a variety of cardiac or pulmonary functions that we measured, suggestive that we weren't causing any meaningful additional occlusion.

So, consistent with the clinical testing in COPD subjects, we didn't see any effects in the hypertension. I do recognize that microspheres in the dog model versus COPD, there are clearly differences.

[Slide.]

We looked in the mechanical ventilation system, so again we chose the dog. Dogs were anesthetized and mechanically ventilated, and again we go increasing dose levels of Definity, and we dosed up to 25 times the clinical dose.

At this dose, we again didn't influence any cardiopulmonary parameters as we measured. We also looked at the persistence of Definity in the arterial circulation to try and identify whether the mechanical ventilation was altering the viability of the microspheres, the Definity

microspheres that pass through the lungs, and examining on the circulation, we saw no change in the ultrasound attenuation levels versus time in that circulation, suggesting that we weren't altering the profile of Definity.

There have been several reports in the literature about potential bioeffects. These literature reports have included both Definity and other ultrasound contrast agents. These literature reports indicate that one can see cellular and tissue effects if one combines high dose levels of contrast agent and/or high mechanical index and/or high extended ultrasound exposure.

I believe that the summation of the literature data is indicative at the low dose of Definity in combination with low mechanical index and a short duration of scan in any particular plane will mitigate the potential to produce microscale bioeffects.

The clinical findings have suggested no bioeffect issues in any of the parameters that we have examined. This includes what was presented on the PBCs, and we believe our approach, our ALARA approach, as low as reasonably attainable, is the right mindset to go into these studies.

In the PI, we are recommending less than 0.8

mechanical index and less than 10 microliters on any single bolus administration.

[Slide.]

So, to try and put some perspective into our learnings from the animal studies, I see that in the nonclinical and early clinical phases of development of agents, the use of disease models to assess theoretical risks, so that when one does go into larger numbers of subjects, are clearly of great potential value, I see the pulmonary hypertension, mechanical ventilation, and potentially the use of the pig for initial screening purposes.

As one gets into the late clinical phase, I see the use of in vitro and in vivo models in support of the clinical observations from the trials to help identify specific issues identified with the individual agents.

When one gets to the postmarketing phase, I then move a bit away from the try and identify or predict human risk, and it is more into understanding how to ameliorate issues that are being seen, so there I see the use of in vivo/in vitro systems to examine the mechanism and pathways involved in safety concerns that I identify from the

clinical use.

As Dr. Hamlin was indicating, mechanism is key and you need to understand the species you are in. We need to understand the mechanism from the clinic and make sure any animal testing is in an appropriate mechanism to look for how one ameliorates or identifies the subpopulations.

[Slide.]

On that note, I am going to pass it back over to Dr. Michael Main.

**Postmarketing Experience**

DR. MAIN: Thank you very much.

[Slide.]

We will close with postmarketing safety evaluation, which I do think you will find quite compelling.

We will divide this into three separate parts. First, the postmarketing spontaneous reporting from the medical community, secondly, two, single-center safety outcomes studies which were just very recently published, and finally, a very large multi-center safety outcomes database, which is currently under expedited review at the Journal of the American College of Cardiology.

[Slide.]

Again, as I mentioned earlier, there have been about 2 millions doses of Definity based on data from Arlington Medical Resources database.

What is this use like in clinical practice? About 60 percent of doses are used during resting echocardiography, about 40 percent during stress. Of patients who received Definity, around two-thirds are hospitalized inpatients and 33 percent are outpatients.

Most of this use is in the United States, but other countries and regions under which Definity has been approved include Canada, the European Union, Australia, and Latin America.

[Slide.]

Let's first look at spontaneous serious adverse event reports from the medical community in the period December 2000 through December 2007.

Overall, 277 patients with reported serious adverse events, a frequency of about 1 in 10,000, very similar to what you have heard today with respect to other agents. Fourteen fatalities have been reported. Seven of these have occurred within about 30 minutes of dosing. Importantly, these patients who died were critically ill and

unstable clinically.

What are the types of serious adverse events? Ninety-one serious cardiopulmonary events have been reported and 106 events which have been characterized as hypersensitivity type reactions.

Overall, as I stated, the frequency of these serious adverse events is low, about 1 in 10,000, and it occurs often in very medically complex patients.

Now, these spontaneous reports do provide a profile, but what they do not do is assess the potential impact of pseudocomplications.

[Slide.]

What do we mean by pseudocomplications? Well, as all the clinicians here know, adverse events that occur after any medical procedure could be due to one of two things. The procedure itself or the underlying disease state, and this term "pseudocomplication" describing events which occurred due to the underlying disease state was initially coined by Hildner and colleagues.

They performed a study in patients undergoing coronary angiography and looked at event rates in the period prior to the study and in the 72 hours after.

What they found were that the event rates were similar in patients scheduled for coronary angiography in the 24 hours prior to the study and in the 72 hours following the procedure. This is important if we are to know what the true event rate is with any medical procedure or drug.

My colleagues, Paul Grayburn, Jonathan Goldman, and I explored this pseudocomplication effect with respect to ultrasound contrast agents in a viewpoint article which we published in the Journal of the American College of Cardiology last fall. It was titled "Thinking Outside the Box: the Ultrasound Contrast Controversy."

Now, Definity, as we know, is often used in patients with serious underlying heart disease and other comorbidities. It is critical we distinguish pseudocomplication from Definity-related effects to understand true adverse event rates, and we will present some data to that effect shortly.

[Slide.]

Dr. Senior, in his presentation earlier today, did spend a little time looking at risks of alternative diagnostic modalities. Some of this I think bears

repeating.

What is the rate of mortality with coronary angiography? I am talking about the diagnostic tests alone, not intervention. It is 1 in 1,000. Exercise testing is associated with a 1 in 2,500 risk of myocardial infarction or death, and the lifetime rate of fatal malignancy in patients who undergo arrest, stress, SPECT examination or radionuclide ventriculography ranges from around 1 in 1,000 to 1 in 10,000 after a single examination. Obviously, this risk is much greater in young people and also in women.

TEE is very interesting, but causal mortality rate with transesophageal echocardiography is 1 in 10,000, and that data is from a large Mayo Clinic series and a large European study.

Why would a patient die during a TEE? Well, it's an invasive test as was pointed out earlier. There is a risk of esophageal perforation, methemoglobinemia, laryngospasm, hypotension, respiratory failure, all of these things. That being said, we perform TEE quite frequently and, in fact, it is the test we go to most commonly when unenhanced echocardiography is nondiagnostic.

Now does these compare, these other tests compare

with Definity contrast echocardiography? Well, the associated rate of serious adverse event, and I say associated because we don't know if there is any causal relationship for most of these events, is 1 in 10,000, and the mortality rate associated with ultrasound contrast agents is probably in the range of 1 in 100,000 based on the 2 million doses and the reported events from the medical community.

That being said, contrast echocardiography risk appears lower than commonly utilized alternatives. Even with these risks that we see with these other tests, they are performed without much trepidation and there is a good reason for that.

All of these tests allow us to diagnose cardiovascular disease and treat it early, and as you know, cardiovascular disease is the number one killer of people in this country.

[Slide.]

Now, let's turn to two single institution safety assessments authored by Herzog in the Journal of the American Medical Association earlier this year, describing his experience at Hennepin County Medical Center in

Minneapolis. Steve referred to this study with respect to the Optison-dosed patients in his presentation for GE.

This was a retrospective study and 12,975 of these patients actually received Definity, a much greater number of patients actually received Definity in this laboratory.

In this lab, all adverse events are documented prospectively by the nursing staff. These were reviewed. Electronic medical record data was abstracted and the relationship of these adverse events to Definity was adjudicated. Non-fatal complications, which were attributable to stress testing were excluded. So, what does the adverse event rate look like in clinical practice?

Adverse event rate with Definity was 0.12 percent. The serious adverse event rate was 0.03 percent, no fatalities.

Interestingly, the serious adverse event rate of 3 in 10,000 compares quite favorably with the spontaneously reported serious adverse event rate of about 1 in 10,000 from the medical community.

There is always concern that spontaneous reporting may underestimate the true serious adverse event rate. Given the data we present here, that does not appear to be

the case for ultrasound contrast agents.

[Slide.]

A second study, Kusnetsky et al., I was the senior author on this paper. This describes our experience at St. Luke's Health System in Kansas City. This was a retrospective study design, 18,671 consecutive echocardiographic studies in hospitalized patients, in sick patients, between January 2005 and October 2007.

Now, about two-thirds of these studies were non-contrast, and about one-third, over 6,000 patients received Definity. We use contrast very frequently like the other speakers today in our laboratory.

We use this to help us determine left ventricular systolic function, as Dr. Feinstein indicated, so critical in the management of our patients, and also to enhance endocardial border delineation, the approved indication, when that is not readily discernible based on a non-contrast study.

Now, in this study, vital status within 24 hours of the echo is available for all of our patients using our electronic medical record. What do the results look like? The endpoint was mortality at 24 hours.

The non-contrast group experienced a mortality rate of 0.37 percent, Definity enhanced group 0.42 percent, no statistically significant difference.

Now, I should mention that these groups, the non-contrast and the Definity enhanced groups were not well matched, that is for sure. The Definity group was much sicker. They had significantly more LV dysfunction, more coronary disease, more COPD, more days in the ICU.

So, based on that, we concluded that it is a very conservative estimate of contrast ultrasound safety. I do not have adjusted odds ratios for mortality for you. We are working on that data now and we will be happy to forward that data to any interested parties in the very near future.

Importantly, what are our conclusions? No increased risk of fatality associated with Definity in this study, and a new finding that had not been appreciated, and that is, the ambient short term or 24-hour mortality in hospitalized patients undergoing echocardiography is about 0.4 percent, almost 1 out of 200 patients die within one day of echocardiography in the hospital. These are sick patients.

[Slide.]

Well, I think this is the most compelling data that you will see today. This is a large multi-center safety outcomes database study, which we recently completed. As I mentioned, it's under expedited review at the Journal of the American College of Cardiology.

The date here was derived from the Premier Perspective database. The Agency is well familiar with this database. This included patients undergoing in-patient echocardiography between January 1, 2002, and October 31st, 2007.

It was a retrospective study design very similar to our single center experience at St. Luke's Hospital. I think by anyone's standards, this is a lot of patients - 4,300,966 consecutive resting transthoracic echocardiography studies.

Almost 60,000 of these were performed with Definity, and our analysis included several things.

One, a severity of illness and baseline risk of mortality in all of these patients using a proprietary algorithm developed by the 3M Corporation; all cause 1-day mortality was available for all these patients, and we went a step further in this study in comparison to our single

center data.

We performed multivariate logistic regression analysis comparing 24-hour mortality for the non-contrast versus the Definity group, controlling for the case mix and clinical covariates.

[Slide.]

This is what we found. What were the mortality rates at one day? Mortality rates for non-contrast echos, 1.08 percent.

What about the Definity enhanced echos? 1.06 percent, no significant difference between these groups.

Now, the most important data. When we subjected this to multivariate logistic regression analysis, Definity enhanced echocardiography was associated with a 24 percent statistically significant reduction in mortality.

Now, why would that be? Well, that was beyond the scope of this study. We are certainly looking into that both in our single center data and this multi-center data.

The most likely explanation is the clinicians here will recognize if we do not make an accurate diagnosis, we cannot administer proper therapy, and certainly as we know, contrast echocardiography allows us to make an accurate

diagnosis.

Top-line conclusions. There was a decreased risk-adjusted mortality in patients receiving Definity in comparison to patient undergoing unenhanced echocardiography.

Additionally, in this study, the background 1-day mortality rate was 1 percent among an inpatient population, somewhat higher than in our single center data. Two potential reasons for this.

One, death, short-term mortality was defined as death on the day of the echocardiogram or the day following instead of a strict 24-hour stipulation.

Secondly, we were not able to exclude patients who underwent echocardiography following cardiac arrest or in whom brain death had already occurred, which we were able to do in our single center data.

[Slide.]

So, to sum up our postmarketing safety summary, spontaneous reporting has demonstrated a very low SAE reporting frequency of about 1 in 10,000, similar to what you have heard today for other agents. Even this low rate, though, has to be confounded by pseudocomplications.

There is no doubt that pseudocomplications are playing a role in even this very low event rate.

The Herzog report from Hennepin County corroborates this finding, a serious adverse event rate of about 3 in 10,000, similar to the spontaneously reported frequencies.

The report author, the first author by Kusnetsky from our institution and the Premier Perspective database study, which we have submitted for publication, indicate Definity is used in a patient population with a very high ambient mortality rate. Again, these are very sick patients, and this ambient mortality rate over the short term ranges from somewhere around 0.4 to 1 percent.

Importantly, both of these studies demonstrate I think quite conclusively that there is no increased risk of fatality associated with the use of Definity.

[Slide.]

Well, let's put this all in perspective. What is this low event frequency for serious adverse event imply in terms of studying this in the future?

We are going to need extremely large subject populations to quantify this in prospective studies. It is

also critical, as we have done in our last two studies, to include a control or background population to identify whether these events are attributable to the agent or not.

What about going forward in terms of safety surveillance approaches?

We think that further database mining to identify safety in specific subpopulations will be valuable. We need to continue to evaluate this periodically to look for significant trends and incorporate these findings into guidelines and, of course, into product labeling as well.

[Slide.]

Well, to sum up our presentation today, the clinical trial population, which we described including the special patient populations and placebo-controlled studies have provided a lot of value in understanding safety, as shown in these Definity trials.

The nonclinical safety studies have been useful. They are certainly useful at different stages of development to demonstrate safety, and as hypothesis-generating studies.

Postmarketing safety surveillance obviously is quite important. We need to go beyond spontaneous reporting as we have done, and perform large retrospective database

studies to determine the true frequency of these events and the true safety of Definity.

As I mentioned just few minutes ago, there is now evidence that risk-adjusted mortality in patients receiving Definity is actually lower. Overall, these data show that Definity enhanced echocardiography provides a diagnostic test with a very positive benefit-risk profile.

Thanks very much for your attention.

DR. HIATT: Thank you all very much. I think that concludes the sponsor presentations. We now have a few minutes for questions from the Committee, and since we are going to be discussing these issues this afternoon, I would assume that we will be wanting to ask the sponsors a variety of questions, as well.

Let me open this up to the Committee now for any questions you might have.

**Questions to the Presenters**

DR. RAMSEY: Ruth Ramsey. I am a neuroradiologist. I am intrigued by the particulate injection even intracarotid and repeated statements that this is particulate injection and yet looking at hundreds of thousands of patients who have received this without adverse

brain effects, I am surprised, I guess, but obviously, they don't seen to have any.

I am just wondering how both the rats, if you will, as well as the humans were evaluated for the presence or absence of changes in the brain, say, CT scans or MRI, or how were they evaluated. I am addressing this to any of the speakers. I know Dr. Williams discussed it a bit, Dr. Feinstein, and our last two speakers.

DR. HIATT: I suppose the format for responses would be to have the sponsors just elect to send someone up to the podium to address these questions, because they will be targeted broadly enough for a particular agent.

So, I might just ask any of the sponsors if you want to address that particular question, please come forward.

DR. WILLIAMS: I just would comment on the rat study that was conducted by Bracco. My understanding is that that was done histopathologically, so there weren't any scans in that particular study. But there was detailed histopathology.

DR. HIATT: [Inaudible.]

DR. WEISS: Excuse me. Can you repeat for the

transcriptionist what the comment was and your response, and for the rest of the audience, as well.

DR. WILLIAMS: The endpoints in the intracarotid study were histopathology of the brain and neurospecific amylase in the brain.

DR. FEINSTEIN: Thank you, Dr. Ramsey. Steve Feinstein also from Chicago.

What is unique about those studies, those are all intravenous studies. None of our clinical studies ever do intracarotid injections. They circulate from the vein, through the lungs, to the left ventricle, out the carotid.

You will first see the carotid artery highlighted, never the vein. These are not intra-arterial injections, any of them. So, the entire cardiovascular system is identified from an intravenous injection.

In the clinical trials with Optison, those Phase I studies were done with neurologic exams for all intravenous injections. We don't use intra-arterial for any of our patients.

DR. HIATT: I think as we go forward with this, there will be questions about the preclinical data and the clinical data. I don't know if we want to just try to have

random comments, organize ourselves.

Ultimately, our charge is to understand these concerning safety signals in the postmarketing environment particularly around these temporally associated deaths with these agents. I guess I would like to ask Dr. Main a few questions.

That is the most recent presentation, but I think it does address more directly some of our concerns. The first set of questions has to do with your published report from your single center.

You noted 72 deaths I believe in total, and you did comment that the population receiving contrast was sicker than the population not, that you didn't adjust for those differences at baseline.

Had you done that, I suppose the net rates might have been adjusted a little lower on contrast, but I wanted to comment in particular and get your reaction to the number of events.

I do agree with the way you have put the issue before us, is that with very low frequency events, that are not seen during randomized trials, there is generally a concern about how to interpret those events and was that the

background disease, was the patient going to die that day anyway, in fact, at the moment, you might have given the contrast, or was it causally related to the contrast.

Understanding that question is best done under randomized controlled trial environments, but if the event rates are low, it is hard to gather enough data.

What I want you to comment on specifically, is that with 72 events, what would be the confidence interval around those event differences between contrast and uncontrasted. Take that first, and then let's try to use that in context of the data that's in submission.

DR. MAIN: Well, I agree with what you said, and first of all, one of the main concerns has been this, what has been called a striking temporal relationship.

When we look at 0.4 to 1 percent of patients dying within 24 hours of echocardiography, those are normally distributed, of course, a significant number are going to occur within a fairly short time of the echocardiographic study.

It is important to recognize also that echo is often the last test, and the only test that can be performed on critically ill patients, when patients decompensate or

become sicker, that is the test we call for as you know.

I cannot tell you what the confidence intervals are around that. As I indicated, we are currently working on calculating an adjusted odds ratio for mortality in the Definity arm of our single-center data, and I will be happy to forward that data to you as soon as it's available.

As you will note, the paper itself is in your briefing packet. There is a demographic table in there describing the clinical differences between those groups, and I think they are quite striking, p-values less than 0.001 for basically all major comorbidities, much higher in the Definity arm.

That is about as much as I can tell you about that. As I earlier stated, I think that this does represent a very, very conservative estimate of contrast echo safety based on those issues.

DR. HIATT: Let me use the question to illustrate a point, which is not just related to this particular topic today, but to drug safety in general.

That is, with low frequency events, 72 events particularly, the confidence intervals around that point estimate, if, in fact, there is neutrality between contrast

and non-contrast, they are still going to be quite broad.

My guess is they are going to be maybe a confidence interval that might have an upper boundary of maybe twofold. So, if the relative risk is 1.0, and you have 72 events, by definition, if we just run the statistics, the upper end of the confidence interval is still going to be quite high.

What that means is that you are trying to describe a safety event. You are not hypothesis testing. Therefore, the more events you have, the tighter the confidence intervals. The upper boundary defines a boundary of safety with which you can exclude a certain amount of safety risk.

My question to you again is, how much risk could you exclude in your single-center study. You don't know.

DR. MAIN: Well, I recognize the limitations of that study. We certainly did and that's basically what led us to explore this in a much, much larger group of patients, no doubt about it. We only had 6,000 patients with Definity in our group, and a fairly low event rate as you indicated.

The confidence intervals in our multi-center study, as I think you saw, 0.7 to 0.82.

DR. HIATT: That is correct. So, as a segue, then, to that study, which has a lot more events--

DR. MAIN: A lot more patients and events, correct.

DR. HIATT: Exactly, but it is not--it's patients are important, that's exposure, but event rate and the number of events you have is really what matters.

DR. MAIN: Correct.

DR. HIATT: So, now you have upper end of the confidence interval of 0.82 which is below 1, as your conclusion was maybe there is something different, I can't conclude that except that it does exclude a safety concern I suppose based on that particular observational study.

DR. MAIN: Well, we think so. We think it's a long ways from a potential safety signal to a potential benefit in terms of mortality, absolutely.

DR. HIATT: Right. So, I guess that is just to try to illustrate the point, the number of events is critical to understand the boundaries, the margins around a particular safety concern.

DR. MAIN: We certainly realize that, and we realize that our single-center study was limited at the

time. It was the largest safety study that had been performed in this population, but I certainly concur with everything you have said.

DR. HIATT: Let me just close with one final comment. This is a retrospective but adjusted approach to this question. Any thoughts about prospective observational databases that might include adjustments, such as propensity scoring to understand this a bit further?

DR. MAIN: Well, I think important to perform, the reason that we thought it was very important to perform the retrospective study, at the time it was performed, sick patients were excluded from receiving contrast agents, and we really didn't think it would be possible to ever do that again. It was, as you know, only recently that the product labeling was adjusted and that those contraindications were revised to warnings.

Even so, the medical community is not using contrast agents in sick patients. It has had a chilling effect on the use of contrast agents clinically, o I think a prospective study in sick patients, especially a large-scale contrast safety study, is going to be difficult without some more direction basically from this panel and the Agency.

DR. HIATT: Except to comment that it sounds like from these presentations, off-label use is going to be more and more common, extended use across a variety of populations where we really don't understand the safety would be a challenge here.

DR. MAIN: I guess I would tend to disagree with that especially with respect to our study and the Premier Perspective database. This describes on-label use. This was not stress echocardiography, not perfusion, not carotid scanning, this was for the approved indication.

Now we certainly say well, Definity has not been studied in patients on the ventilator with Staph aureus sepsis. That is true, but usually, product indications do not go into so much detail. This is all on-label use for the approved indication.

DR. HIATT: I appreciate that. I am just thinking about things going forward.

DR. MAIN: I understand. Thank you.

DR. TEERLINK: Actually, Dr. Main, if you could come on back right here. I think you are to be congratulated on some very nice work. It is going to be hopefully forthcoming in JAMA and we will be able to see the

whole study shortly.

Actually, Bill asked the first part of my question, which was the confidence intervals on these issues, and got to some very important points. I think one of the other important points, you brought up some of the risks of the other competing agents, and when we look at the studies that are being presented, we have 30-minute data and 24-hour data.

So, what is the 24-hour incidence of causing a malignancy with SPECT and RBG?

DR. MAIN: Dr. Teerlink, I think you know the answer to that.

DR. TEERLINK: A rhetorical question. So, as we look forward to having these agents being used more frequently at higher doses and things like that, how do we get at the issue of long-term safety?

You know, we are assuming perflutren is inert and there is a lot of data to support that. If you actually look at the package inserts for the actual material forms from it, it does have high tissue, it is labeled as a high tissue affinity agent.

It is used as an agent to etch electronic circuit

boards. It has this potential risk to it, and in addition, all these other agents that we are giving, we don't know. I am looking more forward, beyond these agents.

How do we and how would you suggest we look at long-term, you know, is 180 day mortality endpoint important for future approvals of these agents? Do we need to look at adverse events beyond this time period?

DR. MAIN: In my opinion, no, and to my knowledge, the only safety considerations that have been raised with respect to these agents are the short-term risks.

When we look at the pharmacokinetics of the agents, and how they are eliminated from the body, the perflutren gas through the lungs in a matter of minutes, the shell through the RES system in the liver, also very short term, I have seen no data to suggest that there is any long-term safety signal in these agents, absolutely none.

How would we study that? I am not an epidemiologist, I don't know to be quite honest with you and as you see, even the short-term mortality in patients whom we study, as you know, the echo lab, is quite high. These are sick patients.

So, if there is a tiny safety signal there, it

would be very, very difficult. Getting back to your remarks regarding the hazards of ionizing radiation, that is under appreciated obviously by the medical community in this country, very much more appreciated in Europe.

For instance, we do not keep any information in this country on doses administered to patients. The young and women receive repetitive examinations, CTAs of the chest, stress SPECT examinations, and so forth. So, I think that risk has been underestimated and the risk of contrast ultrasound greatly overestimated.

DR. HIATT: There are a couple of questions over here and I just think there are going to be so many questions that we really should continue this after lunch.

DR. NEATON: Let me just throw out a question now or a point that I think we should come back to after lunch, and it deals with risk-benefit, because I wasn't clear about the benefit that I saw in all the presentations. And so, even to a statistician, it is really clear on these beautiful slides the better imaging, but the one study that was cited by Jeetley is perhaps one we could come back to.

There, there was long-term follow-up that could address the consequences of using a contrast media versus

not, and I didn't really understand the life table that was presented because I think what should have been done was present the groups, both randomized groups, instead of the subsets that were at low risk. And there was a study cited in the Definity package about the greater use of diagnostic procedures that were associated with a higher risk.

So, I accept that some of the procedures that have been mentioned by all the groups are associated with higher risk, but I saw little data in the background packages or in the presentations about benefit.

When I think of benefit, I don't think of just seeing a prettier picture, I want to see benefit that this can actually lead to better treatment that has better long-term outcomes for the patients.

So, if we could see more data on that after lunch, it would be helpful.

DR. WARNER STEVENSON: I would just like to expand on what Dr. Neaton said. I think clearly, this is pointed out to us, the difficulty of translating our usual concept of risk-benefit when we are talking about a diagnostic technique.

I think very elegant demonstrations this morning

suggested that the risk is quite small of this, and benefits when we just talk about diagnostic accuracy is not the same as a therapeutic benefit, and certainly from a clinician's standpoint, there are different groups of patients.

There are some in whom a large quantitative error would be quite acceptable in a screening. On the other hand, if you actually miss a diagnosis totally, that has an ill effect or, as has been suggested, if you have to go on to a diagnostic technique with higher risk, that is also important. But I really don't think that we can conclude that everyone who goes to an echo has the same risk of these errors, if you will.

So, I think we have to think about efficacy in different groups and thus the risk-benefit ratio is going to be different for different diagnoses.

DR. FLACK: Has there been any thought about looking long term, which actually you could do with linking these to some death indices? You have these large databases, you have people who have gotten both multiple modalities of cardiac imaging, and it probably wouldn't be that hard to do.

I agree based on what you have shown, you wouldn't

think there would be any long-term risk. On the other hand, you don't know until you look. And, in fact, you may actually, with either adjustment and/or propensity score, type analyses, be able to show something in the opposite direction, which I think some of the data that you presented did show were maybe lesser risk. Is there any thought about doing that?

DR. FEINSTEIN: I know we are going to follow up right after lunch. We didn't address efficacy, we didn't address utility of what we are doing. We addressed only safety, which we felt was the first step.

I believe this afternoon we have a whole series of presentations which we presented to the FDA on December 11th on efficacy, why we used contrast. It isn't just pretty pictures. They do translate to saving lives.

So, I will say that as we adjourn for lunch, we will address this through a whole series of open mikes on this topic.

DR. FLACK: Could you just maybe answer the question directly? Are you planning on doing that or not?

DR. FEINSTEIN: The efficacy and the life-saving utility of contrast echo?

DR. FLACK: Linking the data you already have to longer term mortality at various time intervals down the road, which you could easily do. I don't know, maybe you haven't thought about it, but if you haven't, it's probably okay to say so and maybe chew it over.

DR. FEINSTEIN: Chew it over lunch.

DR. FLACK: I would chew it over longer than that.

DR. HIATT: Perhaps we should conclude the morning session. We will adjourn until 1 o'clock when we will have the open public hearing and continue the discussions. Thank you, the sponsors, presenters, and the Committee.

[Luncheon recess taken from 12:01 to 1:05 p.m.]

AFTERNOON PROCEEDINGS

1:05 p.m.

**Open Public Hearing**

DR. HIATT: Open public hearing presentations, evidently there are three. There is some necessary paperwork we have to read before they begin their presentations. So, as people are wandering in, maybe we can go ahead and do that.

MS. FERGUSON: Both the Food and Drug Administration and the public believe in a transparent process for information gathering and decisionmaking. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement to advise the committee of any financial relationship that you may have with the sponsor, its product, or, if known, its direct competitors.

For example, this financial information may include the sponsor's payment of your travel, lodging, or

other expenses in connection with your attendance at this meeting.

Likewise, FDA encourages you at the beginning of your statement, to advise the committee if you do not have any financial relationships.

If you choose not to address this issue of financial relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance on the open public hearing process. The insights and comments provided can help the Agency and this committee in their considerations of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for this open public hearing to be conducted in a fair and open way where every participant is listened to carefully and treated with dignity, courtesy, and respect.

Therefore, please speak only when recognized by the Chair. Thank you for your cooperation.

DR. HIATT: Thank you very much.

I know we have several speakers, whoever would like to come forward first.

As we pull up your slides, if you could introduce yourself.

DR. GOLDBERG: Barry Goldberg, Director of Ultrasound at Thomas Jefferson University in Philadelphia. They have been doing ultrasound since 1964, before some of you may have been born.

While they are still putting up the slides, I remember doing my first ultrasound contrast a few years after Ray Gramiak did it in 1968, so in 1969--that is how I started my interest.

Time is short, so if we could dim the lights a little bit, and I have printed materials that are at your desk. I am here representing, as you can see here, the ACR, the AIUM, and the SRU.

This is something of my background, which you will get a chance to look at.

I have no financial interests with any manufacturers. The organizations that are going to pay my transportation and food are the ACR, the AIUM, and the SRU, no drug companies.

I have done a lot of research over the years and have participated in animal and clinical trials as you can

see.

All imaging modalities we know have value. They have advantages and disadvantages, but we, representing radiology, ultrasound, we want to have a full gamut of imaging options available to them so that they can exercise medical judgment.

We have heard about ultrasound, I am sure all of you know about ultrasound, it's real-time, non-ionizing, portable, relatively low cost.

There is a key element in the evolution of medical imaging technology has been the advancement from plain imaging to contrast, and we see that in CT and MR, nuclear, and so on, and since 1990s, the introduction of ultrasound with contrast has added a great deal.

We have heard a lot about the risks associated, so I am not spending any time on this slide. You have heard probably more than you want to hear, all good, but what I wanted to do--and I have to make sure I point it there--as you recognize, there is overutilization, as has come out in the press and in literature, increased ionizing radiation, the use of CT and MR can be problematic as we heard, some recent things with renal insufficiency and the nephrogenic

effects. So, no agent is free of some maybe toxicity.

So, ultrasound contrast agents, as pointed out before, remain in the vascular system, not excreted into the renal collecting system. They are not known to be nephrotoxic.

In the United States, the detection of a liver mass with conventional ultrasound--and by the way, we use it all the time, the cases that are sent to us--if we are not sure we see something, we have to send it to CT with contrast.

There are increased delays, increased patient anxiety, increased costs.

So, in the absence of any specific evidence of risk and with demonstrated patient benefit, the prudent use of contrast should be appropriate, and we believe it provides clinically significant information. Not performing such a procedure, we believe, may increase medical risk to patients as alluded to.

Here are some examples. Here is a liver, and if you look over there, I think you can all see, and you don't have to be a radiologist to make a diagnosis. This liver looked normal. But, as we injected the contrast

intravenously I think that, as you watch the real-time on this side, you will be able to see dark areas. These dark areas are metastases, would be seen on CT and MR with contrast.

Ultrasound is currently being utilized--outside the country. You have heard of all the countries around the world, and these are listings, and some of these were mentioned, and I will try to show you some examples of this.

There are numerous investigations showing that ultrasound with contrast is comparable to CT and MR for both detection and characterization, and is no longer considered sufficient to perform only non-CEUS in many countries around the world. And we heard that from the earlier speakers.

This is an example of characterization of detection. This is a liver. If you look carefully, it is hard to see any masses. We gave contrast and I think again you don't have to be a physician even to look at this liver. The white is normal. The dark are multiple metastases, again with the simple use of contrast and that is why we saw earlier statistics showing that, in fact, with the use of contrast, significantly better, almost double the capabilities that ultrasound would have with contrast.

There, you can see the metastases quite easily now, not seen without contrast.

This now is an example of characterization. This is a case in which we can just about make out a mass in that liver over here without contrast. We give contrast. This is a very vascular tumor, and this was hepatocellular carcinoma.

And those who know about characterization, it is the same as you would see with CT or MR with contrast. But here we are not sure we see something. We do the injection. It can be done at the bedside, it can be done in the emergency room, it can be done in the operating room, and can be done without having to reschedule a patient for a separate study. So, detection and characterization.

Here is a case of an indeterminate mass seen on CT. We can see that mass. This is the kidney. There is contrast. Here it is with ultrasound. There are a few little reflections within it.

Here now, this area, for a characterization, we can see it right here. This area here has vessels within it, so in terms of telling what it is, it is a cystic renal cell tumor which couldn't be characterized in CT.

So there are examples in which ultrasound gives more information--so, we talk about using CT and MRI as the gold standard, that is not going to be maybe as easy, because, in fact, there are cases where ultrasound sees things that CT may not, and, of course, there are other cases that may be in the other direction. You can see that vascularity quite easily.

Now, here, we use this and we have had a number of grants from the National Cancer Institute. This is one where we are looking at flow, this mass here, looked like a cyst or at least suspicious, perhaps there was some echos, measuring only about a centimeter.

Let's go back one. Let's see if that works now. If we watch this now, watch the center of this dark area. Cysts, of course, should have no flow in it, but notice it becomes white. Those are all little tumor beds, so this is a very vascular breast tumor, easily diagnosed by ultrasound, not diagnosed so easily with standard ultrasound or even mammography.

Here are cases, and some of these were provided by my friends around the world. Again, they are doing them routinely, but not here, of course. Two different patients