UNITED STATES OF AMERICA

DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY DEVICES PANEL

MEETING

THURSDAY,
OCTOBER 28, 1999

The Committee met in Room 020B, 9200 Corporate Boulevard, Rockville, Maryland, at 9:12 a.m., Henry C. Nipper, Ph.D., Panel Chair, presiding.

PRESENT:

HENRY C. NIPPER, Ph.D., Chairman
BEVERLY HARRINGTON FALLS, M.D., Member
SHERWOOD C. LEWIS, Ph.D., Member
BARBARA R. MANNO, Ph.D., Member
NADER RIFAI, Ph.D., Member
ARLAN L. ROSENBLOOM, M.D., Member
DAVIDA F. KRUGER, M.S.N., Consumer Representative
ALTON D. FLOYD, Ph.D., Industry Representative

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PRESENT (cont'd):

STEPHEN CLEMENT, M.D., Consultant
BASIL T. DOUMAS, Ph.D., Consultant
JAMES EVERETT, M.D., Ph.D., Consultant
JANINE E. JANOSKY, Ph.D., Consultant
ROBERT REJ, Ph.D., Consultant
MARY M. KIMBERLY, Ph.D., Consultant
VERONICA J. CALVIN, M.A., Executive Secretary
STEVEN I. GUTMAN, M.D., M.B.A., Division Director

ALSO PRESENT:

ARLEEN PINKOS
ANN HAWTHORNE
DAVID G. BROWN, Ph.D.
JIM CONNOLLY
SUNIL ANAOKAR, Ph.D.
MARK DEEG, M.D.
JOHN PASQUA, M.D.
MARGO ENRIGHT
TELBA IRONY, Ph.D.
HENRY GINSBERG, M.D.
CAROL BENSON
NEAL R. GROSS

XIV. Adjourn

XIII. Closing Remarks

XII. Final Recommendations

XII. Open Committee Discussion

X. Open Public Hearing

IX. Question and Answer Period

VIII. Guest Speaker

VII. Presentation

VI. Question and Answer Period

V. Presentation - Polymer: Technology Systems, Inc.

IV. Open Public Hearing

III. XK

II. Call to Order

I. Closed Committee Discussion
CHAIRMAN NIPPER: The panel and the audience should come to order.

At the beginning of the panel meeting, I must respectfully ask that the table right behind the projector be cleared until we're ready to have you occupy that area. Are you able to do that with minimum disruption to what's going on there? Okay. Thank you.

I'd like to call on Veronica Calvin, the Executive Secretary of the Clinical Chemistry and Toxicology -- Clinical Toxicology Devices Panel -- for opening remarks, introductions, and a conflict of interest statement.

MS. CALVIN: Good morning and welcome to the meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel. Today the committee will discuss and make recommendations on a pre-market notification for an over-the-counter device that measures triglycerides from whole blood finger sticks.

Before we move into today's agenda, I will provide...
brief summary minutes of the last panel meeting.

The Clinical Chemistry and Clinical Toxicology Devices Panel last met on February 26, 1999, to discuss a pre-market approval application for the continuous glucose monitoring system presented by Minimed, Incorporated. The panel unanimously recommended approval of the PMA subject to the following conditions: submission of additional data regarding interference, validation of the calibration algorithm, and use in some patient groups not previously selected for the study, and labeling changes. On June 15, 1999, the device was granted full approval to the market.

At this time, I would like to acknowledge special guests who will be participating in the meeting today. Dr. Henry Ginsberg, our guest speaker, is the Director of the Irving Center for Clinical Research at the College of Physicians and Surgeons of Columbia University. He is also head of the Division of Preventive Medicine and Nutrition in the Department of Medicine at Columbia, and an expert for the National Cholesterol Education Program, to name a few.
of his highlights.

Dr. Mary Kimberly, from our sister agency, the Centers for Disease Control and Prevention, she coordinates the Cholesterol Reference Method Laboratory Network, which you will hear more about later.

Lastly, Dr. Alton Floyd, industry rep for the Hematology and Pathology Devices Panel, is substituting for Dr. Robert Habig, who could not be here today.

Also, I bring you regrets from Dr. Martin Crowell, who could not be here. He called late yesterday to inform me that a matter arose at his hospital requiring his immediate attention and presence today.

Now I would like for the panel members to introduce themselves, beginning with Dr. Robert Rej.

DR. REJ: I'm Robert Rej, Director of Clinical Chemistry and Hematology at the New York State Department of Health. I'm a former member of this panel, and I'm a temporary voting member to this panel today.
DR. EVERETT: I'm James Everett. I'm Medical Director of Madison Memorial Health Care in Madison, Florida.

DR. MANNO: I'm Barbara Manno. I'm Professor of Psychiatry at Louisiana State University Health Sciences Center in Shreveport, Louisiana. And I'm a toxicologist and I'm a voting member of the panel.

DR. DOUMAS: Basil Doumas, Professor Emeritus, Medical College of Wisconsin, in pathology.

DR. JANOSKY: Janine Janosky from the University of Pittsburgh in the School of Medicine. I'm a biostatistician. I'm a voting member of the Dental Products Panel.

DR. LEWIS: I'm Sherwood Lewis. I'm the Director of Toxicology in the Office of the Chief Medical Examiner, the State of Connecticut. I'm a voting member of the panel.

MS. KRUGER: I'm Davida Kruger. I'm a certified nurse practitioner from Henry Foote Health Systems in Detroit in the area of diabetes, and I am the consumer representative on this panel. Thank you.
DR. FLOYD: Alton Floyd. I'm the industry representative for the panel today sitting in. And I have my own consulting company, Trigon Technology.

DR. GUTMAN: I'm Steve Gutman, and I'm the Director of the Division of Clinical Laboratory Devices.

DR. ROSENBLOOM: I'm Arlan Rosenbloom, Professor Emeritus of pediatrics, pediatric endocrinologist at the University of Florida, and Director of the Children's Medical Services Center.

DR. CLEMENT: Steve Clement here in D.C., Associate Professor, Georgetown University, and Director of the Georgetown Diabetes Center.

DR. KIMBERLY: Mary Kimberly from the Centers for Disease Control and Prevention. I'm Coordinator of the Cholesterol Reference Method Lab Network, and I'm here as a guest today.

DR. RIFAI: I'm Nader Rifai. I'm Associate Professor at Harvard Medical School and the Director of Clinical Chemistry at Children's Hospital.

CHAIRMAN NIPPER: And I'm Henry Nipper. I'm Dean of Admissions at Crane University School of
Medicine, Associate Professor of Pathology and Associate Director of Clinical Chemistry and Toxicology at St. Joseph Hospital in Omaha. And I’m Chair of the panel, except Veronica runs things.

(Laughter.)

We all know that.

MS. CALVIN: Thank you. I will now read the conflict of interest statement.

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

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

We would like to note for the record that the agency took into consideration matters concerning Drs. Martin Kroll, Nader Rifai, Arlan Rosenbloom, Basil Doumas, and Ms. Davida Kruger. These panelists reported current and/or past interest in firms at issue, but not in matters related to what is being discussed today.

Since these matters are not related to the specific issues of this meeting, the agency has determined that they may participate fully in today’s deliberations.

The agency would also like to note for the record that Dr. Henry Ginsberg, who is the guest speaker for today, has acknowledged previous interest in firms at issue.

In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participant should excuse him or herself from such involvement, and the exclusion will be noted for the record.
With respect to all other participants, we ask, in the interest of fairness, that all persons making statements or presentations disclose any current or previous financial involvement with any firm whose products they may wish to comment upon.

Thank you. I’ll turn the meeting back over to Dr. Nipper.

CHAIRMAN NIPPER: Thank you, Ms. Calvin.

Before we begin the open public hearing, we’re going to hear about Y2K from Dr. David Brown from the Office of Science and Technology. And I believe that this handout is from you, and a nice folder.

DR. BROWN: Correct. I’m happy to be able to provide that. We have some extra copies over there if you need one.

I’d like to give a very brief presentation about our activities in the area of Y2K. I think that you are fortunate in that I guess you haven’t had a meeting in some time perhaps because we are almost at the Y2K before you are subjected to the presentation.

And I think it’s just about too late probably for...
anything to be done, but at least you can be acquainted with some of the --

(Laughter.)

-- things which we have been doing.

I think we have been concerned about this for some time. We know that there has been a lot of alarm raised. And, in fact, I think one of the major purposes behind our work in this area is that, dating back, say, to 1996, we had quite a few dire predictions made. And so we wanted to see, is there a problem? What do we need to do? And perhaps we are able to, in some way, reassure the public if there are not going to be these dire consequences.

Of course, our efforts will probably be more than overwhelmed by what I am informed is an NBC movie as a Y2K catastrophe movie, which will be shown shortly. However, we will still go ahead.

Indeed, we are told that most of our PCs will be unreliable, told that all of our health care systems will be failing to work, our medical devices will be non-functional. I think everyone is aware of the basic problem, of course, that back when some of
us were programmers there was a severe shortage of space, really.

    I think that's the basic problem. When you are doing with 80-column cards to input data, you just used two of those columns for the year, and certainly a computer program could be confused between 1900 and 2000, if they just ran across 00.

    And for those of us who have done more programming than that, we are aware that computer programs can become more confused than just that particular ambiguity, by encountering 00 if their programmer was not allowing for that eventuality.

    Well, where can this come up? Certainly, there are microprocessors, PC-controlled products, more and more all the time, that we are concerned not only with some of the direct medical devices but also the laboratory equipment, because that certainly applies to the products that are reviewed by this panel in particular.

    But there are many software applications, device interfaces to databases and recordkeeping systems, and this problem of embedded chips, which
even the manufacturers of devices are not thoroughly
cognizant of, but are embedded in the devices fairly
deeply, and then are used for dates and displays and
recording.

Well, certainly, there is a reason to
consider whether or not some of these things could
have really bad consequences when they are
misprogrammed. And our definition of year 2000
compliance has tended to be pretty broad.

We're just not saying, is there going to
be a problem when the clocks ticks over on midnight on
December 31st; but the question about 9/9/99, was that
going to be a major problem; the question about leap
year in the year 2000, since there will be a leap year
and normally in those years divisible by four there is
not one, has that been taken care of.

So we want systems to be year 2000
compliant. On the other hand, we want to see what is
the magnitude of any hazards which may arise.
Certainly, as far as this panel and all of our other
panels, and elsewhere in the medical community, we are
always interested in knowing what insights you may
have into the problem, as your facilities have checked out your Y2K readiness.

Well, I think the primary message of this presentation is the primary thing which we have accomplished -- and I think it's a major accomplishment -- that we do have an FDA product database. This is accessible through the regular FDA site, www.fda.gov. That's the easy thing to remember, and from there you can, of course, link to the year 2000 area of the web site and find out a lot about the status of a lot of medical devices, because I think our primary accomplishment has been to work with manufacturers to find out -- to have them post information about their devices.

Well, let me step back a minute. We have concerns of three kinds. First, how about the Center's systems? Certainly, we use a lot of computers inside CDRH, and we had to make sure that our own systems would be Y2K compliant. And we are assured by our computer staff that, indeed, that is the case. We've gone to great lengths to try to ensure that that is the case.
The second item is, what about the medical devices which we regulate? Our first activity was to send out notifications to manufacturers so that we could be sure that they really were cognizant of the potential for that problem, and of our interest in their taking steps to address it.

The second was to do something very concrete, to put up this database of biomedical devices, where manufacturers have submitted information which we have put up, or they have submitted their own URLs which link to our database, so that people can see what potential problems there are with their medical devices. And I think that has been a worthwhile effort as clinical facilities have used that quite a bit to examine the Y2K compliance of the devices which they use.

And the good news in that effort was we have found that although there are a fair number of non-compliant devices, most of the problems are being addressed, and most of the problems are of a fairly minor nature.

First, we'll note a couple of pages from
the web site, so that you can be familiar with it. We are talking about biomedical equipment, not just medical devices, and also laboratory equipment and other types of equipment. And just note that there are various search capabilities to try and make this database user-friendly. You really have to get up on that database yourself to check that out more thoroughly.

What are the kinds of answers which we have discovered? Well, we have about 693 manufacturers who have reported that they do have non-compliant products, 345 of these specifically on our database and 348 of these providing their own links to their own web sites.

So, indeed, there are problems. We are trying to get manufacturers to address these, and most of these are being addressed. The good news, however, was that most of these have been found to have a very limited impact, mainly the question of -- in fact, mainly the question -- a matter of printing out incorrect dates, for example.

But some of these -- for example, with
radiation therapy equipment and the use of radionuclides -- have to do with miscalculations which could have had serious consequences.

The kinds of activities which we have been involved in -- letters to manufacturers, guidances to manufacturers, establishment of the database which I have just mentioned on our website -- but we have also gone beyond that to try to monitor and assess the performance of the manufacturers in addressing these problems.

In fact, the latest thing we have been involved in is a major contract with Battelle to go out and look at the -- what we refer to as potentially high-risk devices, to really actually go to manufacturers' facilities and check to make sure that their statements about their -- the way in which they have addressed these questions are, indeed, correct. And, indeed, we have found, with an extremely small number of exceptions, that that is the case.

In just about conclusion, I would only draw your attention to the fact that further questions about Y2K could be addressed to the panel Executive
Secretary, or to the person who really is in charge within our Center of all Y2K matters, Tom Shope. And here is the contact information for Dr. Shope.

The only thing I will append to this is that FDA and, of course, CDRH in feeding into the FDA effort will be operating an emergency operations center as the date rolls over into the next millennium. And we have established a procedure to supplement, which, of course, that procedure which we've had all along to -- when we find out that there are problems with medical devices.

So that if we do find out that problems are arising, and the year rolls over, we will be able to address those. And this is an addition part of that larger effort being led by John Tuskimen, who is to set up an emergency response center in downtown D.C. for the interest of all of the various sectors of the nation's economy, for obviously no matter how good a job we do with medical devices, if there isn't any electric power or water, then, of course, we'd be in very serious problem. But I think that those things are being addressed.
So that is the conclusion of this presentation. I'd be happy to answer any questions. And, again, there are some handouts that are available in the corner of the room.

CHAIRMAN NIPPER: Thank you, Dr. Brown.

Does anyone have questions?

DR. RIFAI: What kind of information are companies providing the FDA for the FDA? Is it just a letter indicating that they believe they are now Y2K compliant, or they are providing evidence indicating that they are compliant?

DR. BROWN: The information that they are providing is, one, that their products don’t involve a date; two, that they are Y2K compliant; or, three, if they have a problem product, then the nature of that problem, what they are trying to do about it.

Now, you are correct -- this is, as with almost everything we do, a self-certification by the manufacturer. That’s why we have gone out with these potentially high-risk devices to actually send inspection teams into manufacturers’ facilities to do a survey which is a spot check, but a survey to make
sure that there is a basis for what they are telling us, and that they have, indeed, carried out the tests which they have said they have done.

Okay? Well, thank you.

CHAIRMAN NIPPER: Thank you. No other questions?

Well, thank you very much, Dr. Brown, for your presentation.

At this time, we are a little bit ahead of schedule, but I would like to move ahead so that we have as much time as we need for the panel to deliberate, ask questions, and so forth.

So at this point, I would like to open the meeting for an open public hearing. We are not aware of anyone who has requested time to address the panel and present information relevant to the agenda, but interested persons may so state at this point.

If there is a speaker, the speaker is asked to state whether or not they have any financial involvement with the manufacturer of the product being discussed or with their competitors. Seeing no one who wishes to address the panel, I think at this time.
if the sponsor is ready we should move ahead with the sponsor presentation.

Polymer Technology Systems has indicated that three individuals will present to the panel -- Mr. Jim Connolly, the President; Dr. Sunil Anaokar; and Dr. Mark Deeg.

And, Mr. Connolly, the floor is yours to address the panel or to ask your associates to participate.

We're going to move that overhead projector, if you will just wait for a second. We're just going to set it down so we can see across the room.

MR. CONNOLLY: Thank you. The fact that we are a technology-driven company is proof -- now we have another problem with some technology, which we will fix here in just a moment, like the rest of them.

The first dry chemistries that I'm aware of were about 300 B.C., done by obviously a Greek person of some kind. So the things that we're talking about today have come a long way since then.

I wanted to give you some of our
background and some of our thinking as we repair our presentation here. The first dry chemistries I saw were in the clinical laboratory -- not in the laboratory but in an emergency room I think about 1973 or '74, and working in a clinical chemistry department where samples are handled and processes are in place, and people are trained versus going down to an emergency room one day and seeing a slender piece of material with some blood applied to it going into a small instrument and giving an answer that no one believes.

Certainly, as a laboratorian, I thought it was interesting, but certainly not the real deal, as we called it. That was a few years ago.

I think it's interesting now that we're on the other side of the table trying to sell these pieces of paper as the real deal, and the changes that have occurred over the past 25 years, and particularly the last five years.

I'd read from my notes, but if you know John and Margo and I, we all have something in common -- it's our handwriting, which is a struggle. That's
why we need these slides as quick as we can.

Now, we founded this company in 1992, as a result of a meeting with Charlie Suther, which I believe one of our panel members knows here, a fellow that has been active in diabetes back in the Ames Company before it was Miles/Bayer, later on Boehringer Mannheim, and then to Medisense, along with a fellow by the name of Dr. Tony Gatto.

And I was at dinner one night and someone decided what the world needed was a device that people could use at home to manage the complications of diabetes. And we started talking about diabetes and cholesterol issues, which were the thing of the day in the late '80s, early '80s. And that was truly the genesis of the company.

So the company's package is just as it says. It's a multi-test menu. It used to be called an MTM device. It is no longer. It is the BioScanner 2000. But it is a small device that does many tests.

And the goal, as I stated earlier, was to bring back the quality or to make sure the quality was in the product that clinical laboratories are used to
using but in a package that could go to the consumer and also go through clear waiver things to put it in places where people didn’t have access to rapid testing; therefore, quick response and care of patients.

So when you see the device -- I’m not sure if there’s one here today. We’ve got some pictures of one. When you see the device, it’ll look like a glucometer. I hope I’m not abusing their trademark. I didn’t see them as guests here. But it is not a glucose meter. Let me do it like that.

This is a true five-wavelength, two-angle spectrophotometer. It just happens to be small. We made it small so it could be used in personal use, carried with you. It’s battery-powered. The multiple wavelengths are there for a number of reasons, to make development of the chemistries, the broad spectrum of tests that we wanted, easier for the chemist. In other words, they’re not locked into a particular wavelength or measurement algorithm.

And the company is focused on diabetes disease management, to provide tools for the diabetic
to manage his disease, and share information with his caregiver, and also a tool for the caregiver to use. But the focus is not on the daily glucose measurement because most diabetics don’t die from high glucoses at the moment; rather, the complications.

So, thus, the emphasis on the lipids and the one we speak about today, triglyceride. But it’s using these all together. We think there is controversy about triglycerides, as well as a number of other things. But for sure, when used with other tests, they definitely provide a utility for CHD. When used independently with women at higher risk, and particularly when used with diabetics, they make quite a contribution.

So rather than focus on the controversy and go to all of the papers that depended -- as an independent risk factor -- some people much more capable than I will talk about that -- we’d rather focus on the relationship of triglycerides and the other lipids to diabetes for -- so I’d like to call it a half-full glass of water.

Just a quick background. There’s 200,000
that die from diabetes. You can go right through these. Eighty percent of them die from cardiovascular disease, half of Type 2s are discovered after their first heart attack, number one cause of blindness in the U.S., number one cause of non-traumatic amputations, number one cause of kidney failure, third of the dialysis patients in the U.S. are diabetics, 25 percent of the people that die from heart attacks are diabetics. So the relationship is very clear here.

This is the package or the menu that we talked about. We began with a test to make the regulatory process as straightforward as possible, beginning with a test that had a lot of background glucose, getting into a little bit more controversial things, and then as we go down the line even more controversial. But you can see all of the tests definitely have a relationship to diabetes.

Obviously, the lipids, ketones, outside the lipid arena, but again used in areas where diabetics are sick, and the gold standard for measuring compliance A1C. We, by luck or by gosh or by circumstance, ended up that the panel with
triglycerides. I think it could have just as well
been a different test, one of these other tests that
ended here, and there are more to come after this.
Micro albumin is not on here, but, again, it's more
tests in that same arena.

This is where they're at approval-wise.
There are six approvals. We are waiting for some
other approvals, and today, obviously, there are some
questions about triglycerides, and these submissions
are just around the corner for us.

So you can see where the company is going,
and I think it's pretty clear why we're headed in that
direction -- to provide a utility to the patient and
the caregiver that does not exist today, with the same
kind of capability information they'd receive from the
hospital.

There's a lot of crossover between this
thing. When we first got started, it was strictly
diabetics, and there has been a lot of interest in our
products to be used in areas outside diabetes because
of the lipid things and cardiovascular disease. And
we are hoping to address that market through the
consumer approval of our products, which leads to an
easier CLIA path, which gets us into the physician's
office and into some of the screening areas.

So we have 30 percent of the population.
Most of the experts here know these facts to be so.
A lot of them at risk for CAD, and a bunch of these
people are insulin-resistant or early Type 2
diabetics.

I'm just going to go over this briefly
because there are people here to do a better job of
this than I. But it's early onset, and it's around
for a long time before it's detected. The impacts are
there for quite a while. I believe about half of
this, half of the Type 2s, are discovered after their
first heart attack.

And there is this dyslipidemic thing,
which seems to be common, which has been published by
guys like Reaven, Grundy, Hafner, and so forth, with
the elevated triglycerides and the decreased HDL.
Again, used in combination, markers for CAD, as well
as some possible indications or -- what is that word?
It's not diagnostic. About Type 2 diabetes.
Next slide?

We took a couple of quotes here, which someone else will explain. The part I like about this, that some of these standards -- this published work has a big thing here and what -- a big impact on what we’re trying to do here. And that is that these tools sometimes are not there, or maybe the educational process is not there.

But a lot of people that are dyslipidemic in this area were not aware of this, and very few of them are receiving treatment. So this is one of the tools that we hope to provide -- a knowledge device.

Same thing. Elevated triglycerides and decreased HDL issues, and coronary heart disease -- well published, well documented. We have a handout here today with several references talking about this and the authors. We’ll make those available as soon as I finish here.

And the conclusion -- optimal care should be taken -- taking care of these people that are dyslipidemic, particularly those on insulin.

And my favorite, especially for today,
this study, which we all know very well, most of us
know very well, that are in this area anyway, that
triglycerides levels were a better predictor of
outcome than cholesterol levels. And there is a
BioScanner 2000, which used to be the MTM, about the
size of a package of cigarettes.

There is a bunch of them. We can just go
right through these. Half of them, the Type 2 is
diagnosed; the other half we believe are undiagnosed
-- cost a bunch of money.

There's one more.

So any impact on this quality of life,
reduction of cost, more responsive, more effective,
kind of things we think would make a huge impact in
diabetes.

My history with dry chemistry began when
I was in school with early test type things from
Lilly, later on the Ames Miles/Bayer product referred
to. Boehringer got in with a product, B.G., if any of
you remember it -- a major milestone in diabetes --
and Lifescan in 1985 with a much easier to use device.

And, to me, a company that came out with
the proof that you can really do quantitative measurements accurately, not using necessarily paper chemistry but certainly some of the sophisticated membranes that came into being in the mid '80s; and now I think a culmination of that, of using the materials, putting them together, and coming up with a system that does perform to the standards that we'll show you today.

Does anyone know who Nicholas Culpeper was? I didn't. I thought he was a guy down the hall that did most of the copy repair. He translated, in his day, a lot of the medical information that was in different languages into English to be used by the English.

I think -- I certainly don't draw any parallels between our accomplishments and his in bringing medicine to everyone, but it certainly was a big change to take some of the mystery out of medicine, or the relationship between physicians and patients, and make it something where the patients are more involved now. And I think patients are getting more involved for a lot of reasons.

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One, health care and access to it has certainly changed, and the 'net has certainly made a lot of information available to people that wasn’t there earlier. So I think this is one of the things we’d like to draw an analogy to.

There is a big change in patient access to care. Products like ours are going to provide more information, more utility, for the patient and for the physician. And I’ve never had hair that long.

That’s it.

We’ve got a short three-minute presentation to show you what the product is.

(Whereupon, a portion of the video was shown.)

That micro albumin is the one that’s used in England. But I think you get the picture here. It’s a single instrument with different test strips that are inserted into it with a small blood sample, a very small blood sample, some as small as five microliters.

Results are usually in less than a minute.

Later on, some tests will be combined together in
logical panels like cholesterol, HDL, a direct LDL. But, again, it’s all focused on the diabetic with a single instrument, with a lot of capabilities.

And I think there’s one more part to this.

(Whereupon, the remainder of the video was shown.)

I was just checking on the A/V guy to see if he had it right.

The rest of this information is going to be presented -- an overview -- mine was the overview, the introduction of the company. And I’m not sure how the data has been presented. There are four people here to present the data and the nature of diabetes, and I’m not sure who comes up next.

Dr. Mark Deeg is an endocrinologist at the University of Indiana, and he is going to help us out here.

DR. DEEG: Thank you, Jim.

As he said, my name is Mark Deeg. I’m an endocrinologist at Indiana University. I conduct basic research on HDL metabolism, and clinically I’m the Director of the Cardiology Clinic at what I call...
the Indiana Vascular Disease Center, otherwise known as the Roudebush VA, which has -- veterans have a lot of cardiac disease.

I serve as a consultant for TPTS, in terms of the clinical utility of the various tests, and they have asked me today to talk a little bit about what it really means when you measure someone’s triglycerides.

Personally, I’m actually delighted that you invited Dr. Ginsberg here. He is one of the -- as Ms. Calvin indicated, he’s one of the foremost experts in the country with respect to lipids and what they mean.

You can leave the lights up.

I’m going to throw around a few numbers, and let me just sort of introduce a little bit about triglycerides and what some of these numbers might mean. Let me just give you just a little bit of background.

First of all, in the last national population survey, the median triglycerides for women was about 88 milligrams per deciliter. This just gives you an idea of where the country stands. For
men, it’s about 112. Okay.

In 1993, the NCEP classified triglycerides as such. They said less than 200 was considered normal, 200 to 400 was borderline, greater than 400 to 1,000 was high, and greater than 1,000 was considered very high. Sort of an interesting scale.

Now, triglycerides actually are quite common. So this is 88 for women, 112 for men, less than 200 -- it’s 200, 400 -- 400 to 1,000, and greater than 1,000. Now, triglycerides actually are a fairly common problem in the United States. On average, about five to 10 percent of the population fit into this category of Americans.

Now, if you live in Indiana, like I do, which is one of the heaviest states in the country, there is actually more like 10 to 20 percent of the Indiana population fit into this category.

The major focus is triglycerides, and some of the controversy, is their role in cardiovascular disease, in predicting cardiovascular disease. The one complication that I’m not going to talk about, which is actually quite important, that people in this
category -- high-risk for what’s called pancreatitis. And it’s a potentially big problem in our diabetics, but we’re not going to talk about this class of people.

Lights, please.

So what I want to talk about for the next 20 minutes or so is, what does it mean to me as a practicing physician when I measure someone’s triglycerides? And what does it mean to the patients, and what do I tell them?

Next slide.

What I want to talk about -- I’ve outlined here -- is these five things, and some of these things I’m sure Dr. Ginsberg will touch on. We’ll talk a little bit about the ugly details of triglyceride metabolism.

And the reason I throw that up there is because if you really want to understand what happens when you really measure triglycerides, you need to understand what this is or how -- where triglycerides come from and where they go to, discuss the controversial issue about triglycerides as an
independent risk factor for coronary artery disease, triglycerides as a synergistic risk factor, triglycerides as a metabolic marker for other syndromes.

Now we’re getting a little bit of clinical trials about what happens when we treat people for their triglycerides. Basically, fat flows around in our blood as balls of grease. This is just a cut view of a ball of grease that consists of various fats, which include cholesterols and triglycerides and various proteins.

There’s a whole bunch of these different balls of grease with different names, the largest being chylomicrons, VLDL, very low dense type of proteins, IDL, intermediate dense, the bad guys -- that is, LDL cholesterol -- and the good guys, HDL cholesterol, which we refer to as happy healthy.

Next slide.

If you had bacon and eggs for breakfast, this is what’s happening. You consume that dietary fat. It’s absorbed into the intestine and forms what’s called chylomicrons. These chylomicrons are
the largest particles that are very triglyceride rich. Okay?

These chylomicrons are then broken down through an enzymatic action to remnants, which are then broken up into the liver. The liver can then reprocess this fat and these triglycerides into another particle that I call VLDL.

These also are triglyceride rich. These are also broken down further, and by the same mechanisms, into remnants, some of which are called IDL. And there are a number of particles in between this. This is sort of simplified. It's even more complicated than this.

Now, one of the important points about triglycerides and what makes it so difficult as triglycerides as risk factors is that it's metabolically linked with all of these other lipoproteins. So, for example, as these VLDL particles are broken down into IDL, some of the constituents end up in HDL. Hence, this interrelationship between triglycerides and HDL. We'll talk about that some more.
These remnants can be further broken down into LDL -- again, the bad guy in terms of the, you know, very well-established risk factor for coronary artery disease. The LDL can either go back to the liver or deliver its cholesterol elsewhere. Other remnants can be taken back into the liver.

So to borrow a phrase actually from Dr. Ginsberg in one of his editorials a couple of years back, is when you ask the question, what does triglycerides mean, are triglycerides a risk factor, his answer was, it's a simple question but a very complicated answer.

But the point I want to make in this presentation is that even though scientifically it's complicated, it's still very clinically useful for the physician as well as for the patient.

Whoa.

(Laughter.)

Let’s talk about this issue. For a long time, triglycerides as an independent risk factor of coronary artery disease has been controversial. And let me just visit that issue a little bit. And why
has that been difficult?

    Well, part of it has to do with that the
daily variation of measuring someone's fasting
triglycerides is actually quite high compared to other
particles in the blood. For example, your daily
variation in triglycerides can be upward of 20
percent; whereas, for LDL cholesterol, it can anywhere
from five to 10 percent.

    As I alluded to, when you measure
triglycerides, there's a lot of different particles in
blood that have triglycerides, and you're not really
sure which one you're measuring. And what I didn't
emphasize is that those are remnants I talked about --
those broken down particles -- at least scientifically
appear to be atherogenic. And that's actually what we
may be measuring when we're measuring triglycerides,
looking at those things.

    The issue of an independent risk factor as
very -- a synergistic factor we'll talk a little bit
about.

    And, finally, sort of the bread and butter
of the clinical evidence based medicine just hasn't
been there for triglycerides. We're beginning to see
that now, and we'll see further trials in the next few
years. But it's not here yet.

Next?

Some more recent data addressing the issue
of triglycerides as an independent risk factor are now
really coming forth that, indeed, triglycerides are an
independent risk factor for men. And that has been
the most difficult group to show this.

This is a particular study called the
Copenhagen Male Study, with about 3,000 men, who
measured their triglycerides and a whole bunch of
other things, including body mass. And what was
unique about this study, they actually took into
account dietary alcohol.

And when you adjust the triglyceride
levels for risk, for all of the various things that
can influence triglycerides, what they found, as you
went from the lowest group to the highest group of
triglycerides -- and the cut points here was 100
milligrams per deciliter, 140 milligrams per
deciliter, that as your triglycerides increased, your
risk for a cardiac event went up.

This is just one example of a study. This is a recently published meta-analysis that looked at a whole bunch of population studies, which took into account some 23,000 men. These are the individual studies. This is the summary data -- relative risk for coronary artery disease. This is the risk for each increase of 90 milligrams per deciliter in triglycerides.

So you can see some of the earlier studies where you can see that -- why it was so controversial. It wasn’t much above one. Being above one, obviously, is an increased risk. Some of the later studies began to prove this, and now with the meta-analysis, which basically you combine all of this data. And this data is adjusted for HDL. That, indeed, for men it’s a small -- it’s still a risk factor, albeit small.

Keep going.

However, and I said, this is for men, middle-aged men. Unfortunately, I’m now in that category, having turned 40 this spring.

It’s really been controversial for men.
However, there are other subgroups where triglycerides, as an independent risk factor, is actually much stronger and much more evident. This is illustrated from the Framingham data. This is, again, looking at the relative risk for having a coronary event in men in the orange here at various triglyceride levels, so going from 50, which is actually close to what I would call normal -- and I'm not going to get into that.

But if you had to pick your triglyceride level, you'd want it to be down here -- going up to 400. And you can see there's a small increase, but, again, not very impressive as a risk factor.

However, for women, you can see that in this same range that it's a much better predictor for coronary artery disease. So in post-menopausal women, in this subgroup, triglycerides -- and the studies are all confirming this -- that, indeed, for women, it is a good predictor of coronary artery disease. And, again, this is from the same meta-analysis, and a couple of studies -- this is about 6,500 women -- that for women it was a much better risk factor than it was.
for men.

Next slide.

Well, what about triglycerides as a synergistic risk factor? What about people who have combined dyslipidemia, which is a very common problem, combining it with both high triglycerides and a high LDL? What does this mean for their risk? Let's look at a couple of studies.

This is a study called the PROCAM study -- about 4- or 5,000 men, middle-aged men, followed for eight years, looking at the event rate for coronary artery disease. When they looked at different levels of LDL, going from less than 130 up to 190, triglycerides are low -- let's say less than 200 -- your risk goes up if you have low triglycerides. And, again, this is not unexpected, that if your LDL is higher you have a higher event rate.

However, if you also have high triglycerides, look at your risk factors or the event rates. At any given LDL level, you have at least a twofold or even higher increased risk for coronary artery disease, if you have both high triglycerides.
and high LDL.

Now, what's interesting -- that this particular group, which had the highest event rate, was only five percent of the study population, yet it accounted for 25 percent of the number of events in the whole study. So this particular combination is particularly bad.

Next slide.

Again, this is from the past perspective study that Jim alluded to. Again, they're using triglycerides now less than 123 or greater than 123. And, again, these are sort of numbers that would be considered normal, at least by the old criteria.

And here they're looking at cholesterol rather than LDL, but the same effect -- that if you have higher triglyceride levels, that for any -- for your given cholesterol level you will have a higher risk, a multiplier effect if you will.

Next slide.

Now, this is some interesting data that actually was just down the street at Hopkins by a guy named Mike Miller. And they looked at people -- they
took about 500 men and women who went to the coronary cath lab to have -- so they could look at their coronary arteries and see if they had coronary artery disease, and then followed them for up to 18 years to see who survived and who didn't survive, and based on their triglycerides of being less than 100 or greater than 100.

And, again, this cut point was from the data that I had told you, that this is really the median for the U.S. population -- about 100 for men and women. And that what they found is that people who had triglycerides at the beginning of the study had less than -- triglycerides less than 100 lived longer than those who had triglycerides that were higher.

So the point being from this study is that what we consider high or low may -- one, may vary in different populations, but these absolute numbers I think we may need to consider ratcheting down in terms of what we consider high.

Well, as I alluded to earlier, triglyceride metabolism is quite complicated, and
triglycerides is a risk factor, maybe in addition a marker for the various alterations and metabolism of triglycerides and lipids. This is becoming more and more appreciated as we understand the complexities of triglyceride and lipid metabolism.

When you have high triglycerides, the interplay with all of these other lipoproteins is quite complicated. And what happens is that in association with these high triglycerides there is an increase in these remnants, the chylomicron remnants, which are atherogenic, at least certainly in vitro and animal models; IDL, which, again, another remnant; VLDL remnants. All of these are triglyceride rich. This is what you'll be measuring when you measure triglycerides.

Also, because of the metabolic link with HDL, you have low HDL levels. And also, you have a form of LDL, the bad cholesterol, called small events, which is felt to be particularly nasty or an atherogenic form of LDL. These are all associated with hypertriglyceridemia.

Now, the thing is, what do I mean by
hypertriglyceridemia? Well, it turns out that there have been numerous studies that have shown that certainly when your triglycerides hit 150, or start going higher, you begin to see these metabolic changes.

So when I teach my residents about triglycerides and the clinical chemistry thing says less than 200 being normal, I tell them about these studies that, indeed, certainly in this scenario, when you see low HDL and high triglycerides, there is actually abnormal lipid metabolism and an atherogenic lipid metabolism.

This has been called the atherogenic lipoprotein profile. These things are metabolically intertwined. An important point is that up to about a third of the U.S. population has this metabolic disorder. This is a very common disorder. This is something we’re beginning to appreciate more and more in trying to address how to treat this problem.

Now, the other marker for high triglycerides, as Mr. Connolly was alluding to, was that triglycerides in the insulin-resistant syndrome
are intertwined. The insulin-resistant syndrome again
is very common in the United States, and this syndrome
is associated with many abnormalities that increase
the patient for coronary artery disease.

These include obesity, hypertension, going
on for Type 2 diabetes. There is changes in the
coagulation state, that people tend to be
hypercoagulable, which is part of the events that
occur when you have an acute coronary or heart attack.

And there's also endothelial dysfunction
associated with that -- endothelial cells being the
ones that line the artery wall. And these cells --
it's very important that these cells are happy and
functioning properly. In the insulin-resistant state,
they do not work properly.

Again, also associated with the insulin-
resistant syndrome, and very early in this diagnosis,
are the high TGs, low HDL syndrome -- again, TGs being
over 150 and HDLs being more than 35 for men and 45
for women.

Next slide.

This is a particularly increasing problem
for the United States in terms of coronary artery
disease, and the reason being is we know people with
Type 2 diabetes have an increased -- two- or three-
fold increased risk for coronary artery disease
compared to people who have normal glucose tolerance
-- diabetics, glucose tolerance.

For people with just insulin resistance,
not hypoglycemic, not diabetic, they, too, have this
same two- to four-fold increase in risk of coronary
artery disease.

This is now finally being labeled a
disease, and the reason this is such a big -- and Dr.
Clement will confirm this -- that this insulin-
resistant diabetes is going to be a huge problem for
our country in that currently there are about 16
million Type 2 diabetics, just as many insulin-
resistant patients, and this is going to be a whole
lot worse over the next 20 or 30 years for a number of
reasons.

One is, as a population, we're getting
heavier, which is associated with the insulin
resistance. Another reason is we're getting older.
And that conversion -- becoming insulin-resistant and becoming Type 2 diabetes increases as you get older. So now as the boomers are turning 50, there are 10,000 people turning 50 a year now, and when I turn 50 in 10 --

DR. ROSENBOOM: 10,000 a year?

DR. DEEG: Well, 10,000 a day, and then I represent the peak. In 10 years, it will be closer to 50,000 a day will be turning 50. This will become a huge, huge, huge problem.

Next slide.

As I mentioned, the combined dyslipidemia, which is a particularly nasty lipid profile to have in terms of risk, is very common in diabetics. This is some data from the NHANES population, looking at triglycerides in diabetics that about half -- a little more than half have triglycerides less than 200, a third have 200 to 400, and 10 percent have greater than 400.

Now, the thing I want to, again, reemphasize is that diabetics are at increased risk for pancreatitis, particularly if they have diabetes
along with a genetic disorder. Again, these are triglycerides in the 1,000 range.

Next slide.

Jim alluded to this -- that diabetes is a very nasty risk factor for coronary artery disease, that if you have diabetes you are more than likely going to die from an atherosclerotic event -- heart attack or stroke.

These account for most complications. And of concern to me as a practitioner is that at the time of diagnosis -- and this is one of the arguments for early diagnosis as well as, you know, looking for people with insulin resistance -- as many as half the patients at the time of diagnosis already have coronary artery disease. We missed the boat. The horses are out of the barn.

What are some of the clinical trials that can help us decide if treating triglycerides are important or not? There has not been a trial directly aimed at answering that question. Part of the reason is that it's just difficult to do because of the inner metabolic connections between those lipoproteins.
Part of it is that, again, because of the controversy about triglycerides as a risk factor. But there is some data that suggests that treating these people gives them clinical benefit. And let me show you data from a couple of trials.

Next slide.

This is from the Helsinki heart study. This was a study done in the late '80s using a product, Gemfibrozil, primarily as an agent to lower LDL, which it doesn't do very well. But it does lower triglycerides very well.

And what they did is, again, they looked at people who had an LDL-to-HDL ratio of either less than five or greater than five. Okay? So what that means is that these people tend to have either really high LDL levels or low HDL levels. And then when they break it further down where they had low triglycerides or high triglycerides, depending upon -- the cut point was 200.

So in the placebo group here in the sort of green, you can see that the event rate in these groups were pretty similar. But, again, this group
that had the high triglycerides and had this high ratio vis-a-vis high LDL with the low HDL, they had a much higher event rate. Okay? Three- or four-fold greater than these other people.

But when you treated them with Gemfibrozil, you can see there’s a tremendous drop. And as a matter of fact, this group accounted for 80 percent of the trial results.

And what Gemfibrozil does, which I didn’t show you, is lower triglycerides very well. Okay? And, again, this is a group that has elevated triglycerides, again using a more stringent cutoff if you will.

This is a recently published study called the VA HIT trial, which I’m really quite excited about because of the people that they identify. It was about 2,500 patients, again treated with or without Gemfibrozil. Again, what we’re focusing in on was people with low HDLs. HDL, 32; triglycerides only 161; and, interestingly, an LDL of 111. And this is by far the lowest LDL in any major trial that we’ve done to date. Okay?
This is a very typical lipid profile for people with insulin resistance and Type 2 diabetes. These are people with coronary artery disease. And they treated them with Gemfibrozil in order to raise their HDL and lower their triglycerides.

And what they found pharmacologically is what you would expect with this drug -- that actually LDL didn’t change and even went up a little bit, HDL went up -- its final numbers were six percent. This is the preliminary data. Triglycerides went down 25 percent; again, a response you would expect, and, again, going 25 percent from 160.

You had the death rate, the stroke rate -- I’ll call it mortality -- decreased some 25 percent. So this would suggest that, again, it’s a little bit complicated because of the inner mix, but, again this is some data suggesting that treating triglycerides, maybe in conjunction with raising HDL because of the intertwining, was clinically beneficial.

Next slide.

What are some of the current guidelines for triglycerides? These clearly lag behind the LDL
because we lack some of the information. But what is some of the information or guidelines that are out there for physicians?

Again, as I mentioned, the NCEP, in 1993, before a lot of data and many of these things were known, classified normal triglycerides as less than 200. And in certain populations, this may be too high.

Borderline high of 2- to 400, high 400 to a 1,000, and very high being 1,000. The recommendations at that time, in '93, was that people in this group were candidates for therapy, particularly if they had other risk factors for coronary artery disease; for example, diabetes or a family history or genetic disorder in lipid metabolism. That was '93.

Next slide.

Let me -- going on, for diabetics, in 1999, the American Diabetes Association has been a little more aggressive based on some -- not really the data that I showed you, but some of the data with respect to, what should the lipid levels be in
diabetics?

Clearly, a very low LDL level in diabetics, low risk -- HDLs greater than 45, and made it very clear that they wanted to see diabetics with triglycerides less than 200.

Next slide.

So, in summary, is that there is certainly increasing evidence for triglycerides as an increasing independent risk factor for coronary artery disease. The properties are that it is certainly very important in subgroups -- particularly women in diabetics -- as a risk factor. It's a synergistic factor and metabolic marker as well, and that we are now beginning to see some clinical trial data that it's beneficial in certain groups.

And as I said, according to Dr. Ginsberg, it's the complicated answer to a simple question. But it's still a clinical utility.

Let me just show you the next two slides, showing you what triglycerides means to me, as a physician, and what these numbers mean to patients.

For the physician, triglycerides is a very
important component in terms of the global risk assessment. By incorporating triglycerides along with LDL and HDL, you can have a much better idea of what their risk is for coronary artery disease, in terms of predicting disease.

For those who have existing disease, or those who are diabetics, it now becomes a target for therapy in terms of a goal. And this is really based on -- now, this -- you know, do we have the absolute number? Do we know what we need to treat to? No. Okay?

But certainly based on the epidemiological data, some of which I showed you, and some of these other numbers, it certainly seems prudent that we should be addressing triglycerides in these patients. It certainly can help in situations that are not covered by the NCEP guidelines in terms of what to do. For example, a middle-aged man like me, who might have an LDL less than 130, but my triglycerides might be 300.

And, finally, and a very important point for the triglycerides, is that when I see these
numbers, you always to think of, is something else causing this? Do they have diabetes? Do they have hypothyroidism? Maybe it’s their medication? Or is there a genetic disorder? Those are clues that need to tip off the resident.

And, actually, one of my favorite tipoffs for the resident is when the lab results come back, when you’re in the hospital and the lab results come printed out from the lab, and it says they had to spin the sample. That’s usually a good clue that triglycerides are very high, which usually means they are 2,000 or so.

Triglycerides is another number to target. Now, it’s not supposed to be another number to target. It’s another number that they need to know in terms of their risk, and as well as to be aware of.

Measuring triglycerides -- and, again, and all lipids -- is certainly important feedback to them in terms of how they’re responding to the lifestyle changes and how they’re responding to therapy.

And, finally, this feedback is quite important in terms of improving compliance, which is
one of the major difficulties in treating people with lipid disorders because they don’t feel bad unless they have a heart attack.

Next slide.

So with that, I have finished. Thanks.

CHAIRMAN NIPPER: Thank you, Dr. Deeg. I’m sure that we will have questions for you, so stay close.

DR. ANAOKAR: Good morning. I’m Sunil Anaokar with Polymer Technology Systems, and I would like to present to you some specific information on the device that we have, the assay system for measuring triglycerides in whole blood samples.

I would like to present to you how the device works, how it is used, and some specific performance data. And if it is okay with you, Mr. Chairperson, and the rest of the panel, I would like to ask two of my colleagues, two scientists from Polymer Technology Systems, to also present some other information, such as total system error of the system, as well as some information pertaining to the labeling.
Thank you.

First, I would like to present to you the test procedures for the device. You have seen the picture of the device before. To actually use this system is very, very easy, very simple. To use it, all one has to do is first insert the memory chip into the instrument.

The memory chip is a micro chip that has information such as the chemistry that is supposed to be run, the assay, the lot number of the reaction strips, the calibration code for that particular lot, and the expiration date for the lot. That way, if a wrong chemistry is run, a wrong strip is used, or an expired lot or strip is used, then the instrument simply doesn't work.

The instrument is turned on, and the user will check the messages. If the message on the screen says "insert strip," then all one has to do is apply one drop of blood, by finger stick, to the strip, and then insert the strip into the instrument, wait for generally about 60 to 70 seconds, and the results appear on the screen.
The next slide shows how the assay works. It’s an enzymatic assay. The red blood cells are separated from the plasma by a couple of membranes, and the plasma then comes in contact with the reaction membrane, and the reaction membrane has the lipoprotein lipase glycerol-coronase, glycerol phospheroxidase*, ATP, and the chromogens, and the end result of these reactions is the colored product, the intensity which is measured by the instrument, and the intensity of the color is proportional to the concentration of triglycerides in the sample.

I would like to present some performance data now. First, the position -- the position in the hands of the consumer was performed in two different ways.

First, we did a study where three lay users who had never worked in the labs, never had the experience of using any lab devices, were given a total of six different samples. Each user got two samples at two different levels of triglycerides, and they were asked to prepare those blood samples and illustrate 20 times.
And as the percent CV is shown at the bottom of this table, they varied a little bit, but the highest percent CV that they got was 8.8. And please keep in mind that these people had never used any lab device before and had never worked in the laboratory.

The other study was done at three different sites, where 20 lay users participated in the study at each site, and each user was given a total of three different controls who -- that three controls had concentrations -- three different concentrations of triglycerides, and they used the drop method.

They added those controls by putting one drop of the control on the strip, and the -- again, the percent CV is shown here at the bottom of this table.

The linearity of the assay was -- in the lab by lab professionals or lab technicians. Five samples were used. These samples were concentrations that fell within the analytical range of this assay system; that is, between 30 and 500 milligrams per
deciliter. And as you can see, in the data that's shown on the bottom, the regression data, with a slope of 1.0 and coefficient of 0.99, that experiment proved the linearity of the assay quite adequately.

The interference study was then performed, by taking a number of substances and their interferences with this assay system. They are all listed on the left column of this table, and what the right column shows is the highest concentration of these substances where no significant interference was observed. However, this data is included in the package that you received from the FDA.

Interference or any possible influence of cholesterol concentration on the triglyceride measurements was tested by assaying a number of -- actually, 65 samples with different cholesterol concentrations. And the triglyceride concentrations, as assayed in our system, was compared to the triglyceride concentrations assayed in the reference assay. And as you can see, there is no significant bias influenced by cholesterol concentration.

The accuracy of the assay was further
tested by performing a consumer study at nine
different sites with about 382 lay users that
participated in the study. Every user was given the
system, the device, the BioScanner instrument, the
strips, and the memory chip and a lancet device, so
that they could take their own finger stick.

They were only given that written
procedure for the -- for performing the finger sticks
as well as performing the assay. No other
instructions were given, and they performed their own
assay.

And the readings that we received on the
BioScanner system were compared to our in-house
reference assay, which is a reagent system from Sigma
Diagnostics, which is the reagent for automated lab
analyzers.

The reference assay was then compared to
check the validity of the reference method. It was
compared to an assay that had been performed in one of
the CDC-recommended labs. In our case, it was Pacific
Biometrics in Seattle, Washington. It’s one of the
network labs, the so-called CRMLN or the Cholesterol
Reference Method Laboratory Network.

They compared -- they assayed the samples with their method, and when the numbers were compared to the numbers that we got on the Sigma -- with the Sigma reagents, a correlation of 0.98 and a slope of 0.94 was obtained.

Then we compared the assay of the -- of the CRMLN lab was as the results we had from the other system that the consumer got directly. And we had a correlation of 0.93 with a slope of 0.85.

Since the finger stick blood drops can vary in volume, we did a volume study where we looked at volumes of the whole blood from a patient that were added to the strip. And as you can see in the table, we don't see any significant difference between 15 microliters of blood and up to 30 microliters of blood.

And, finally, hematocrit values varied from patient to patient. We did a study -- a hematocrit study looking at blood samples for different hematocrits, the same blood sample but different hematocrits. The hematocrit was adjusted
for the particular sample.

We took two samples with two different levels of triglycerides, and they were tested by the reference assay, and then on the BioScanner. And as you can see, the values did not change very much between 30 to about 50 percent hematocrit. Above 50 percent, they drop considerably.

So, at this point, we will glad to answer any questions, or during the question and answer period. But at this point I would like to introduce to you Dr. John Pasqua, who is the manager and senior scientist in our R&D group.

DR. PASQUA: Thanks, Sunil.

Well, it's getting late in the presentation, so there's nothing to energize an audience better than a good discussion of total system error.

(Laughter.)

The total system error, as I'm defining it, is -- as it is commonly defined -- is bias plus two times the standard deviation. It's a good measure of analytical performance in a diagnostic device. And
it becomes especially critical as the panel addresses, on one of the questions, whether NCEP standards for laboratory instruments applied to over-the-counter whole blood tests.

The first -- the top table -- well, first, let me say that the random error component of all these, of all the system error calculations, are derived from the lay user study, where three users each had three blood samples, N of 20, and different instruments. And that's how they got the CV percent.

The bias I calculated two different ways -- commonly, the first table, the top table, that was calculated from a regression equation versus our reference method. Simply plugged in the reference value into the regression equation, let's look at 100, got 97. The bias was minus 2.8. There are some rounding issues there.

The SD from the lay user study was 8.5. I calculated the total system error -- again, bias plus two times SD was 19.9 mils per deciliter. For 100, it's 19.9 percent. And that's the way it goes all across.
You note that the higher the reference value goes, it seems like if you calculate it from the regression equation, the more negative the bias becomes. None of the values -- 19.9 percent for 100, 23.2 percent for 200, 16.5 percent -- you think it's better than this?

(Laughter.)

19.9 percent, 23.2 percent, 16.5 percent. Neither meet the 15 percent for the NCEP guidelines, not -- all three of them don't.

The way -- another way to calculate the bias was from the surrounding data points. I got this recommendation from actually John Dawson, a statistician for the FDA. He thought -- for example, for 200, I took the point with the reference value from 190 to 290 mils per deciliter, calculated the bias, and took the average of the bias. And the average bias for 200 was minus 10.

Again, the random error components were the same. Final calculations come to 23.8, 22.5, 14.1 percent. None of these point estimates, again, meet the 15 percent requirement that the NCEP has, which is
five percent bias and five percent -- the NCEP recommendation is five percent bias and five percent CV.

But it’s interesting to note that the bias calculated from the surrounding points doesn’t go up as steeply as the regression. And I kind of favor this approach. This is real. This is more predicted. I think this is more representative of the true bias in that area, although, I’ve got to admit, for 400, there were only five points.

Here is -- I just want to show you how I calculated the bias by the surrounding points. Between 95 and 105, for the 100 sample; 190 and 210 for the 200; 381 to 413 for the 400; and 23, 17, and 5. And here are the biases calculated from that.

The FDA seemed concerned about the confidence intervals around our estimates, especially the SDs. So let me just briefly go -- so what I did for these TSE calculations -- all of these TSE calculations here are calculated from the nominal bias. But what I did was, since I calculated the SDs in mils per deciliter, and I gave the corresponding
percent, I had the lower confidence interval in nominal and the upper 95 percent confidence interval, and I used these to calculate these numbers here.

And, again, against the NCEP standards, even the lowest -- if we use the lowest estimate of that SD, 21.3, 19.8, doesn’t meet 15 percent. At the high level, at the 400 level, we do approach the 50 percent sample, be it the low estimate, nominal -- if you use the upper estimate, we don’t make it.

Dr. Anaokar presented a slide the last time showing that we have a negative bias against the CRMLN reference method, and we just want to propose -- we -- that’s fairly easy to remedy. We can either switch the CRMLN reference method in our own lab. We can have them target -- we can calibrate the serum, having the CRMLN lab assign values to it by running their method, or we can do both. And that’s just something that we’re very willing to do if the panel decides it would be in our best interest.

And that’s all I have to say.

Margo?

CHAIRMAN NIPPER: Before you leave, I want
to make sure I have your name correct. Is it P-A-S-Q-U-A? Is that --

DR. PASQUA: Yes.

CHAIRMAN NIPPER: -- the spelling? Is it Dr. or Mr.?  

DR. PASQUA: Dr.

CHAIRMAN NIPPER: Dr. Thank you, Dr. Pasqua.

MS. ENRIGHT: I'm Margo Enright. I'm the Manager of Clinical Affairs for Polymer Technology Systems, and I'm just briefly going to go over the labeling that we have presented for this product, for the BioScanner triglycerides.

Besides a user guide for the BioScanner itself, we have, of course, a package insert that goes through and has all of the key elements that are required for a package insert, giving instructions on how not only to run the test but also describing our performance. And I'm going to specifically take a look at some of these items.

Besides the package insert for the strips themselves and the user guide, we will provide a
control material. And this is manufactured for us. We don't manufacture our own controls. We will provide a control material to be used with the BioScanner 2000 triglycerides, and this is the package insert for that product.

So, briefly reviewing the labeling for this triglycerides product, just to give you a little history, there have been several iterations of this labeling. Our first submission to the FDA for the OTC triglycerides product was December 30, 1998. And we followed all of the FDA recommendations with respect to product labeling. We have reformatted and revised for input from the FDA.

And if the FDA has additional recommendations, we would like them to make those additional recommendations because we are very willing to make any changes. And if we misinterpreted any of the suggestions they've made, we're very willing to make any changes to our labeling. So we wanted to make sure that we went on the record saying that as far as the labeling goes we are very willing to make any requested changes.
Very briefly, hit some of the key items in the package insert, the intended use. This is formatted at a seventh grade level for a home user, describes what, why, who, and when, basically tells them that this measures triglycerides and finger stick blood.

As you may note, what's in bold we very carefully note to the consumer that they need to consult their health care provider for use of the device. Also, use of this test may give you an early warning that you should see your health care professional. Those are real critical pieces of the labeling.

Expected values -- we use the NCEP expected values recommendations, again, with the caveat in bold at the end. If your triglycerides result is above 200 milligrams per deciliter, you should contact a physician and follow your physician's advice. We try and make it very clear that this is not to be used as a substitute for seeing your physician.

In the performance section, accuracy,
there was an issue that as far as how we reported the accuracy, and we look to the FDA to make a recommendation. And maybe their statistician can help us in terms of we added the additional line, "The result of these studies shows that the BioScanner test system compares well to the laboratory instrument and can be run by a consumer or a layperson in their own home with accurate results 95 percent of the time."

If we can get some help from the -- suggestion from the FDA as far as how to calculate that. There was an issue regarding that. But we will follow the guidelines that the FDA gives us on calculating that accuracy because there are -- as you know, just like total system error, there are a number of ways to calculate accuracy. So we will report as the FDA would like us to report.

And, finally, before I turn this back over to Jim Connolly, just a summary of our performance. As Manager of Clinical Affairs, it is incumbent upon me to just summarize and let you know that we believe that this product, and based on all of the studies that we have done, and the information that we have
provided, the performance studies, show this product to be safe, effective, and substantially equivalent to a predicate device.

I’ll now give this back to Jim Connolly to summarize.

MR. CONNOLLY: Thank you, Margo.

Could we turn the lights back on? I have to read my own writing.

I had a lot of great ideas. There are some compelling statements here. But I think I’d rather just -- after looking at some of the data, I think part of the things that are missing, especially when we get more significant figures, or words such as "clinical utility" or "clinical significance," and I think it’s interesting that the higher the triglycerides went the better the performance seemed to be. I don’t know whether it was because of low numbers or the math, but the point was that around some of the critical areas there were some numbers there.

I don’t think I want to defend the lack of performance, but I think whether someone has got a 50
triglyceride or a 75 triglyceride, that's not near as important as if they have one over 400, or certainly over 200.

I've got eight minutes to do this, but I don't think it's worth eight minutes to go through this thing. But we think we provide a product for the patient and for the physician to be used in these risk factors. And in Dr. Ginsberg's paper, I also liked the -- or liked or thought about the ending of the paper, about has the question been answered, or is it there yet?

And if you combine that with the words that are in the FDA document at the end of the presentation today, as to risk versus benefit, I think the benefits here are enormous, particularly in the diabetics and in women. And I think there is certainly, from Dr. Deeg's presentation, a lot to be said about the general public, the non-diabetic folks.

So I think -- I'm not sure what the risks are of having this product on the market. I think the risks of not having it on the market to those that are at risk -- little overusage of that word -- are pretty
dramatic.

As to the jury's out -- I mean, we hear a lot of that thing about the jury being out on triglycerides. Is it real or is it not? Papers -- some say they are; some say that it isn't. But, again, I think the benefits of the product in giving the patient access to some care and the physician and the patient -- when the tests are performed right there, to do the consultation, and not going back to our old system of drawing blood samples, sending it out to a lab, a couple of days later, questionable thing, the patient was not contacted, or our current health care system really doesn't provide a system to encourage the patient to -- it should be the physician -- to follow up on things like this. It just takes more time.

If I fell on that box, it would be a heck of a conclusion.

(Laughter.)

So let me take to the last part of my notes before I fall down here. You know, these values actually do address the major costs in health care --
diabetes and cardiovascular disease. Any impact we can have on probably the bulk of our dollars -- that is, greater than probably 70 percent of the total dollars spent in the U.S. are on these two diseases.

So I think any impact that we can have on these two diseases is certainly worth looking at. And I think it's definitely beneficial, and I'm a little at loss as to what the risk could be.

What did I leave out, Sunil?

We have a little note to end this with. I got interested in dyslipidemia because, of all people, I became insulin-resistant shortly after this prolonged approval process. I don't know if they're related, but --

(Laughter.)

-- I now have a genuine interest in insulin-resistance, particularly in high triglycerides and low HDLs.

As you know, we also had a hemoglobin A1C product that's about to come to the FDA. I can tell you, nine years ago, when I was working on a somewhat similar project, one day a week we would take a
scientist to lunch or to dinner just to kind of keep the company warm and close. We’ve always worked, since our large company affairs, with small companies.

And in small companies you use a lot of your own blood. So not only do people know a lot about you in a small company because they see you every day -- it’s pretty hard to hide your warts -- you also find out a lot about your lipids.

As a medical technologist, I’ve seen a couple thousand or so serum samples sitting in racks, and, in 1989, I saw some of my own and couldn’t believe it. I did some of the original Peculan-David enzymatic triglyceride work back in the ’70s, and I know my triglycerides are around 70.

But at age -- at an older age --

(Laughter.)

-- it’s about 500. So I just assumed that Chinese restaurant I’ve taken this scientist to was the issue. Everything else about me was normal. I dieted a little bit, drank three gallons of water, took another measurement, and sure enough I got it to half what it was. So, therefore, it wasn’t a problem.
until about nine years later.

I've always had a low HDL, so I'm genetically absolutely fit for this thing. HDL at 35, 34 -- and do I know that's the correct number? Yes, because I've had it run hundreds, if not thousands, of times. Now I've got an HDL of 25, a triglyceride of -- in the hundreds, certainly above 400 milligrams, and I've become insulin-resistant. Now I'm a proud supporter of Bristol-Meyers-Squibb.

But this thing could have been intervened with, as in many people, nine years ago when there was an indication there that something was awry, as Dr. Deeg mentioned. So I think the use of this thing in coronary artery disease is -- if it's a question, I think it's a mute question, about risk and benefit.

And the use of diabetes -- I think there's no question about people who are at these high risks that need to monitor their therapy, their diet, their exercise, and their medications. Triglycerides is one of the best ways to do it.

And I think there's absolutely no question about triglycerides being used with our other
approvals that we're patiently waiting for in HDL that would be even of more impact on this diagnosis of coronary heart disease and some of the assessments used to determine if someone is becoming dyslipidemic, and I won't say the other word. But it certainly has impact outside of cardiovascular disease.

So I think this panel should obviously approve this and make the right recommendation, so we can get this product into the market and make an impact for those people that are in this drug situation right now with cardiovascular disease and those diabetics who are consuming a vast amount of our physician's time and our health care dollars.

Thank you.

CHAIRMAN NIPPER: Thank you, Mr. Connolly, and I appreciate the presentations made by the other members of your company and other presenters.

I'd like to mention to the panel a couple of housekeeping items. One that I continually am reminded of by FDA staff, and I thought of this on my own, so I must be getting the message, is that considerations of cost are beyond the scope of the
panel's deliberations.

We are always interested -- I'm sure that all of us as individuals are interested to hear these from time to time. But in dealing with this device, we confine ourselves to the FDA's mission in this area.

The second thing that I wanted to just call attention to the panel is that I was -- I remarked that at the end we will be making some final recommendations. That's different than a vote. And so I think that as we begin to formulate our questions, to direct our questions to the sponsor and to the FDA presenters, we will be thinking in terms of recommendations as opposed to an up and down vote at the end.

MR. CONNOLLY: Dr. Nipper, may I have a moment, please?

CHAIRMAN NIPPER: Yes.

MR. CONNOLLY: If the costs are not to be considered in this product, then I think I need to emphasize quality of life and lack of death as being major points in helping diagnose these diseases.
CHAIRMAN NIPPER: Thank you. Safety and effectiveness is a good guideline there. It’s not that we’re not interested in cost, but I think the FDA is not allowed to bring cost effectiveness or cost of treatment, either high or low, into the decision about safety and effectiveness.

At this point, we are a few minutes ahead of schedule, so I’d like to use the time to add to the question and answer period. And I think that if the committee is -- is the panel is willing, what we’ll do is try to go around the room and allow individuals to -- are you motioning to me, sir? Okay.

We will allow individual members of the panel to ask questions of the presenters. I’m going to ask one question, and then I’ll let Dr. Rifai pick up from me.

The first -- the question that I had for Dr. Deeg is I think a rather simple one. And you can approach the microphone, so you can be on the record. Dr. Deeg, in the clinical studies that you cited in your presentation, I notice the word "non-fasting" appeared many times. Were there any of the clinical
studies that you cited in which the triglyceride data were -- I’m sorry, I started to say fasting -- were there any studies in which the triglyceride data obtained was non-fasting or were the subjects fasting for the data?

DR. DEEG: The studies I cited were all for fasting. I’ll just add in a point about -- an issue about non-fasting triglycerides and post-prandial dyslipidemia -- is appearing to be a very important predictor for coronary artery disease at this point.

CHAIRMAN NIPPER: Okay. But you didn’t cite any studies to --

DR. DEEG: Correct.

CHAIRMAN NIPPER: -- show -- to support that theory today.

DR. DEEG: Well, no, I have a slide I could show you quick. Would you like to see it?

CHAIRMAN NIPPER: Why don’t we go around the room, and then if we have a little time left -- because I know that the panel probably has a lot more questions. We’ll have time for deliberation about
Dr. Rifai?

DR. RIFAI: I just have also a few short questions for Dr. Deeg. Forgive me if they are naive.

How often do you see your patients?

DR. DEEG: How often do I see my patients?

DR. RIFAI: Yes.

DR. DEEG: Typically, diabetics I see about every four months.

DR. RIFAI: What do you order --

DR. DEEG: What do I order?

DR. RIFAI: -- in terms of lab tests every time you see them?

DR. DEEG: For diabetics, I order a hemoglobin A1C for glycemic control; I now order a lipid panel every time.

DR. RIFAI: And you think more frequent measurement of lipid -- of triglyceride per se is valuable?

DR. DEEG: Certainly, in the initial management of the patients, more frequent -- as you are fine-tuning their therapy and getting to your
goals, and things of that nature. Once you have attained your goals, then you can cut back a little bit on the frequency.

DR. RIFAI: And at which level do you consider treatment? Let's say just -- you have increased cholesterol. At which level do you intervene?

DR. DEEG: Well, for diabetics, because the risk for coronary artery disease is so high, I'm very aggressive, and the ADA is, you know, consistent with this in terms of treating their cholesterol levels and their triglycerides.

So the ADA is recommending that LDL cholesterol be 100 for all diabetics, and that's in part because their risk is so high. The triglycerides, again, along the ADA guidelines, try and keep them certainly less than 200, sometimes even lower than that.

DR. RIFAI: Thank you.

DR. KIMBERLY: I have some questions for Dr. Anaokar regarding the comparison with CRMLN laboratory. How were the samples collected for the --
that were sent to the network laboratory for the CRMLN laboratory? And also, what type of pre-analytical considerations were taken as far as the patient or the layperson as far as collecting the finger stick and assuming the serum sample?

MS. ENRIGHT: Dr. Kimberly, Dr. Anaokar has asked me to answer your question. As far as the samples for the CRMLN laboratory analysis, the samples were collected -- both finger stick samples were performed by a professional on the BioScanner as well as the lay user themselves on the BioScanner. And we drew venous samples and collected serum samples, which were then frozen for the CRMLN labs procedure and shipped to the CRMLN lab on dry ice.

DR. KIMBERLY: Okay. What type of pre-analytical considerations did you -- were all of the patients seated? I mean, so that they were all -- I mean, so that the samples were all drawn -- were they all drawn in the same timeframe?

MS. ENRIGHT: Yes. The patient finger stick results were run at the same time, within the -- the draw was either prior to the finger stick or after
the finger stick, depending on the number of
laypersons that we had available. But waiting -- so
that was just a logistical thing. But within 10
minutes of each other, so they were drawn at the same
time.

DR. KIMBERLY: Were they seated during
that whole time? Were they in the same posture? I
mean, the NCEP makes recommendations regarding how the
patient should be treated beforehand.

MS. ENRIGHT: Right. Right. We did -- we
did follow -- and I think there are some guidelines in
the -- there are some NCEP guidelines for finger stick
technique, which is that -- those guidelines were
provided to all of the persons involved in doing the
finger sticks in our clinical trials of professionals.

The lay users themselves were given
written instructions on how to perform the testing.
And if there was any variation, it was due to the lay
user's use. The professional -- in a professional
result on the BioScanner, the finger stick was
compared to the lay users. And differences between
the lay user and the professional results may have had
a little bit to do with the fact that many of the lay users that we used had absolutely no experience doing a finger stick. But they were not in any way coached. They were just given written instructions.

DR. KIMBERLY: Okay. Thank you.

DR. CLEMENT: Steve Clement. I'm not quite sure who to address this question to. The sponsors maybe -- select the person.

The way I look at this data is the sponsor is asking the FDA to set up a different standard for accuracy, total system error if you will, with the increased benefit that this is something that is going to have better access for the patient, which I think is, you know, a very good cause.

. From the sponsor's point of view, what would you consider a standard error that's valuable to the patient? Or total system error. Excuse me.

MR. CONNOLLY: I think there's a couple of answers, and I grabbed it quick before -- someone else may want to get in line.

(Laughter.)

One which is very true is that probably
the majority of the people using this product are going to be diabetics who currently know how to do finger sticks. They're going to get better results. It's my feeling that those results would meet the guidelines.

I only had 15 minutes to put this together. I think that when you go to the general public and patients where -- we go to several different places to get people involved in this thing, and it's difficult for people who have never done finger sticks. And, as you know, there has never been a market for a product for a finger stick other than glucose.

So it's -- I think it's a monumental fact that we got the kind of answer that we did, assuming that probably 95 percent of these patients had never done a finger stick before. So in that case, I think they are probably not going to be the users of the product, but to hold us to, you know, totally unknown people, to NCEP guidelines that were developed for large analyzers with incredible performance on CVs, using serum. None of them use whole blood, so there
really are no standards for whole blood.

DR. ANAOKAR: That is absolutely right. We did check for any guidelines. We looked for guidelines for whole blood that NCEP may have. We found out that there are none. I even checked with Dr. Naito, and he said there are none.

There is a precedent, though. There is a product on the market. It's been on the market for some time for cholesterol, and that does not meet NCEP guidelines for either the total system error or the position. And it is a whole blood product.

Actually, the total system error on that product is more than twice what is recommended by NCEP.

MR. CONNOLLY: And that product was approved by the FDA.

DR. ANAOKAR: It is approved by FDA. It's been on the market for over-the-counter use.

MR. CONNOLLY: Without a panel.

DR. CLEMENT: I'm still looking for a number, I mean, compared to -- like, for example, if we compare it to another reference method, such as
serum, which you’ve done in your case.

MR. CONNOLLY: Do you mean, what do we think the number should be for whole blood?

DR. CLEMENT: Right.

MR. CONNOLLY: Non-testers?

DR. CLEMENT: Right.

MR. CONNOLLY: I don’t think I know. I think it is a number in the high range. With untrained people, with a 15 or a 14-point something or other CV, which met the goal, and a CV of 5.06 -- .06 outside the goal -- I think on an unmeasured sample, on an untrained person, that’s incredible, because there are many products, as the cholesterol we just mentioned, are approved that came nowhere close to that.

So what’s the number? What was our number, 22? 22, I think would be the right number for whole blood --

(Laughter.)

-- untrained people.

DR. GUTMAN: Let me just correct the record. It is true that the cholesterol product did
not meet NCEP guidelines, but it was off by about two percent. It was in the ballpark. There was a lot of discussion about that product. And, in fact, in the labeling of that product, the cut points were set so that the signal was actually below the traditional cutoffs.

The signals were set at 190 and 230 rather than at 200 and 240, so that the error in the system would be towards false positives and people would be driven in to see their doctors more often than not, the notion being it wouldn’t be terribly harmful to see your doctor an extra time. It actually probably isn’t terribly harmful on a single occasion to miss your cholesterol either, since there is no immediate adverse negative impact.

But there was an error, but it wasn’t off by a factor of two. It was about two percent.

CHAIRMAN NIPPER: Are you answering a question here, Mr. Connolly?

MR. CONNOLLY: Yes.

CHAIRMAN NIPPER: Which question are you answering?
MR. CONNOLLY: I'm answering the question about the cholesterol product that did not meet the NCEP guidelines.

CHAIRMAN NIPPER: I don't believe anybody asked that question. Does someone want to ask that question, so he can present this information? I believe the sponsor brought up that topic. And I don't want to be contentious here, but we have only a limited time for committee deliberation. And if the committee is willing to hear that, if the panel is willing to hear that, then I'm -- this information -- I am willing to present it.

But I'd like to get around the room before we break, if we could.

DR. ROSENBLOOM: Yes. And then let's see if we've got --

CHAIRMAN NIPPER: Yes, let's see if we have time, Mr. Connolly. I apologize for cutting you off. I don't mean to remove that information from the table if you want to present it. We may have time later today.

Dr. Rosenbloom?
Were you finished?

DR. CLEMENT: Yes, I'm done.

CHAIRMAN NIPPER: Dr. Rosenbloom?

DR. ROSENBLOOM: I had some question about labeling, if there was any operational research or any opinion to support the recommendation in the labeling for over-the-counter use that the testing be done two to three times per year, and it doesn't say in whom. That means in everybody, even us young middle-aged folks, who have no other risk factors. And at least monthly in those with diabetes and in the post-menopausal state.

And that seems a rather dramatic recommendation, which is only supported by the statement of Dr. Naito, who is the Chief of Clinical Chemistry at the VA in Cleveland. And I wondered if there was -- and it's not in keeping with the American Diabetes Association recommendations which are that adult patients with diabetes should be tested annually for lipid disorders, with fasting serum cholesterol, triglyceride, HDL cholesterol, and calculated LDL cholesterol.
And then, if the values fall in the lower risk levels, assessment may be repeated every two years. Tests resulting in borderline or abnormal values should be repeated for confirmation. Tests resulting in abnormal values requiring institutional therapy should be repeated following the NCEP recommendations, and lipid values should be reevaluated following a macrovascular event.

And then it goes on to talk about following the National Cholesterol Education Program recommendations for children and adolescents.

So my question is: what is the clinical practice, background, clinical experience, or operational research on which these recommendations which would be promulgated to the general public -- that virtually anyone should be tested two to three times per year, and that people with diabetes and in the post-menopausal state should be tested monthly without any qualifications?

MS. ENRIGHT: In our initial labeling, we did not address the issue of how often these tests should be used. But one of the FDA requests was to
add that information to the package insert. And what we did is we consulted. We were told that we had to consult with an expert in the area in this. And as you alluded to, this suggestion came from Dr. Herb Naito from the VA Medical Center in Cleveland. And we are certainly open to making changes in the labeling that address this.

Initially, we did not make a recommendation on labeling. So we are open to your suggestions on what we should recommend in the labeling.

MR. CONNOLLY: I think there's an issue with compliance that we've tried to address. We understand from several of the people that supply lipid-lowering drugs that approximately 75 percent of those people are off those drugs in nine months. We think monitoring more often would keep the patient more compliant and on a drug.

And as we all know, when you take this drug, there is no -- you don't feel any better, so there is really no reason to comply. It's a very expensive drug. A lot of diabetics don't have health
insurance, and to buy another $2,000 a year worth of statins, or whatever, is a burden there.

But the compliance issue I think should be the driving fact in how often they should test. Whatever it takes to keep them on therapy.

DR. ROSENBLOOM: That’s a very qualified -- that’s far more qualified than is in the labeling. What you are addressing is far more qualified. In the labeling, it just says if you have diabetes you should test every month, or if you’re post-menopausal.

MR. CONNOLLY: We are -- as Margo suggested earlier, we are happy to -- we would change the label appropriately.

DR. ROSENBLOOM: And --

MR. CONNOLLY: We’re willing to make changes.

DR. ROSENBLOOM: And, of course, the ADA guidelines are very specific and based on expert opinion. That was my question.

CHAIRMAN NIPPER: Thank you, Dr. Rosenbloom.

Dr. Floyd?