

UNITED STATES OF AMERICA

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DEPARTMENT OF HEALTH AND HUMAN SERVICES -3 P236

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FOOD AND DRUG ADMINISTRATION

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CLINICAL CHEMISTRY AND CLINICAL
TOXICOLOGY DEVICES PANEL

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MEETING

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THURSDAY,
OCTOBER 28, 1999

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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

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P-R-O-C-E-E-D-I-N-G-S

(9:12 a.m.)

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

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1 brief summary minutes of the last panel meeting.

2 The Clinical Chemistry and Clinical
3 Toxicology Devices Panel last met on February 26,
4 1999, to discuss a pre-market approval application for
5 the continuous glucose monitoring system presented by
6 Minimed, Incorporated. The panel unanimously
7 recommended approval of the PMA subject to the
8 following conditions: submission of additional data
9 regarding interference, validation of the calibration
10 algorithm, and use in some patient groups not
11 previously selected for the study, and labeling
12 changes. On June 15, 1999, the device was granted
13 full approval to the market.

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

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1 of his highlights.

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

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

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

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

18 DR. REJ: I'm Robert Rej, Director of
19 Clinical Chemistry and Hematology at the New York
20 State Department of Health. I'm a former member of
21 this panel, and I'm a temporary voting member to this
22 panel today.

1 DR. EVERETT: I'm James Everett. I'm
2 Medical Director of Madison Memorial Health Care in
3 Madison, Florida.

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

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

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

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

19 MS. KRUGER: I'm Davida Kruger. I'm a
20 certified nurse practitioner from Henry Foote Health
21 Systems in Detroit in the area of diabetes, and I am
22 the consumer representative on this panel. Thank you.

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1 DR. FLOYD: Alton Floyd. I'm the industry
2 representative for the panel today sitting in. And I
3 have my own consulting company, Trigon Technology.

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

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

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

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

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

21 CHAIRMAN NIPPER: And I'm Henry Nipper.
22 I'm Dean of Admissions at Crane University School of

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1 Medicine, Associate Professor of Pathology and
2 Associate Director of Clinical Chemistry and
3 Toxicology at St. Joseph Hospital in Omaha. And I'm
4 Chair of the panel, except Veronica runs things.

5 (Laughter.)

6 We all know that.

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

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

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

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1 best interest of the government.

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

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

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

17 In the event that the discussions involve
18 any other products or firms not already on the agenda
19 for which an FDA participant has a financial interest,
20 the participant should excuse him or herself from such
21 involvement, and the exclusion will be noted for the
22 record.

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

6 Thank you. I'll turn the meeting back
7 over to Dr. Nipper.

8 CHAIRMAN NIPPER: Thank you, Ms. Calvin.

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

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

17 I'd like to give a very brief presentation
18 about our activities in the area of Y2K. I think that
19 you are fortunate in that I guess you haven't had a
20 meeting in some time perhaps because we are almost at
21 the Y2K before you are subjected to the presentation.
22 And I think it's just about too late probably for

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1 anything to be done, but at least you can be
2 acquainted with some of the --

3 (Laughter.)

4 -- things which we have been doing.

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

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

18 Indeed, we are told that most of our PCs
19 will be unreliable, told that all of our health care
20 systems will be failing to work, our medical devices
21 will be non-functional. I think everyone is aware of
22 the basic problem, of course, that back when some of

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1 us were programmers there was a severe shortage of
2 space, really.

3 I think that's the basic problem. When
4 you are doing with 80-column cards to input data, you
5 just used two of those columns for the year, and
6 certainly a computer program could be confused between
7 1900 and 2000, if they just ran across 00.

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

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

20 But there are many software applications,
21 device interfaces to databases and recordkeeping
22 systems, and this problem of embedded chips, which

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1 even the manufacturers of devices are not thoroughly
2 cognizant of, but are embedded in the devices fairly
3 deeply, and then are used for dates and displays and
4 recording.

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

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

17 So we want systems to be year 2000
18 compliant. On the other hand, we want to see what is
19 the magnitude of any hazards which may arise.
20 Certainly, as far as this panel and all of our other
21 panels, and elsewhere in the medical community, we are
22 always interested in knowing what insights you may

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1 have into the problem, as your facilities have checked
2 out your Y2K readiness.

3 Well, I think the primary message of this
4 presentation is the primary thing which we have
5 accomplished -- and I think it's a major
6 accomplishment -- that we do have an FDA product
7 database. This is accessible through the regular FDA
8 site, www.fda.gov. That's the easy thing to remember,
9 and from there you can, of course, link to the year
10 2000 area of the web site and find out a lot about the
11 status of a lot of medical devices, because I think
12 our primary accomplishment has been to work with
13 manufacturers to find out -- to have them post
14 information about their devices.

15 Well, let me step back a minute. We have
16 concerns of three kinds. First, how about the
17 Center's systems? Certainly, we use a lot of
18 computers inside CDRH, and we had to make sure that
19 our own systems would be Y2K compliant. And we are
20 assured by our computer staff that, indeed, that is
21 the case. We've gone to great lengths to try to
22 ensure that that is the case.

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1 The second item is, what about the medical
2 devices which we regulate? Our first activity was to
3 send out notifications to manufacturers so that we
4 could be sure that they really were cognizant of the
5 potential for that problem, and of our interest in
6 their taking steps to address it.

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

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

22 First, we'll note a couple of pages from

1 the web site, so that you can be familiar with it. We
2 are talking about biomedical equipment, not just
3 medical devices, and also laboratory equipment and
4 other types of equipment. And just note that there
5 are various search capabilities to try and make this
6 database user-friendly. You really have to get up on
7 that database yourself to check that out more
8 thoroughly.

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

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

22 But some of these -- for example, with

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1 radiation therapy equipment and the use of
2 radionuclides -- have to do with miscalculations which
3 could have had serious consequences.

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

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

20 In just about conclusion, I would only
21 draw your attention to the fact that further questions
22 about Y2K could be addressed to the panel Executive

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1 Secretary, or to the person who really is in charge
2 within our Center of all Y2K matters, Tom Shope. And
3 here is the contact information for Dr. Shope.

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

12 So that if we do find out that problems
13 are arising, and the year rolls over, we will be able
14 to address those. And this is an addition part of
15 that larger effort being led by John Tuskimen, who is
16 to set up an emergency response center in downtown
17 D.C. for the interest of all of the various sectors of
18 the nation's economy, for obviously no matter how good
19 a job we do with medical devices, if there isn't any
20 electric power or water, then, of course, we'd be in
21 very serious problem. But I think that those things
22 are being addressed.

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1 So that is the conclusion of this
2 presentation. I'd be happy to answer any questions.
3 And, again, there are some handouts that are available
4 in the corner of the room.

5 CHAIRMAN NIPPER: Thank you, Dr. Brown.

6 Does anyone have questions?

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

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

17 Now, you are correct -- this is, as with
18 almost everything we do, a self-certification by the
19 manufacturer. That's why we have gone out with these
20 potentially high-risk devices to actually send
21 inspection teams into manufacturers' facilities to do
22 a survey which is a spot check, but a survey to make

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1 sure that there is a basis for what they are telling
2 us, and that they have, indeed, carried out the tests
3 which they have said they have done.

4 Okay? Well, thank you.

5 CHAIRMAN NIPPER: Thank you. No other
6 questions?

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

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

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

18 If there is a speaker, the speaker is
19 asked to state whether or not they have any financial
20 involvement with the manufacturer of the product being
21 discussed or with their competitors. Seeing no one
22 who wishes to address the panel, I think at this time

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1 if the sponsor is ready we should move ahead with the
2 sponsor presentation.

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

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

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

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

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

22 I wanted to give you some of our

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

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

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

20 I'd read from my notes, but if you know
21 John and Margo and I, we all have something in common
22 -- it's our handwriting, which is a struggle. That's

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1 why we need these slides as quick as we can.

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

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

16 So the company's package is just as it
17 says. It's a multi-test menu. It used to be called
18 an MTM device. It is no longer. It is the BioScanner
19 2000. But it is a small device that does many tests.

20 And the goal, as I stated earlier, was to
21 bring back the quality or to make sure the quality was
22 in the product that clinical laboratories are used to

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1 using but in a package that could go to the consumer
2 and also go through clear waiver things to put it in
3 places where people didn't have access to rapid
4 testing; therefore, quick response and care of
5 patients.

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

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

21 And the company is focused on diabetes
22 disease management, to provide tools for the diabetic

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1 to manage his disease, and share information with his
2 caregiver, and also a tool for the caregiver to use.
3 But the focus is not on the daily glucose measurement
4 because most diabetics don't die from high glucoses at
5 the moment; rather, the complications.

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

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

22 Just a quick background. There's 200,000

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1 that die from diabetes. You can go right through
2 these. Eighty percent of them die from cardiovascular
3 disease, half of Type 2s are discovered after their
4 first heart attack, number one cause of blindness in
5 the U.S., number one cause of non-traumatic
6 amputations, number one cause of kidney failure, third
7 of the dialysis patients in the U.S. are diabetics, 25
8 percent of the people that die from heart attacks are
9 diabetics. So the relationship is very clear here.

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

18 Obviously, the lipids, ketones, outside
19 the lipid arena, but again used in areas where
20 diabetics are sick, and the gold standard for
21 measuring compliance A1C. We, by luck or by gosh or
22 by circumstance, ended up that the panel with

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1 triglycerides. I think it could have just as well
2 been a different test, one of these other tests that
3 ended here, and there are more to come after this.
4 Micro albumin is not on here, but, again, it's more
5 tests in that same arena.

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

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

17 There's a lot of crossover between this
18 thing. When we first got started, it was strictly
19 diabetics, and there has been a lot of interest in our
20 products to be used in areas outside diabetes because
21 of the lipid things and cardiovascular disease. And
22 we are hoping to address that market through the

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1 consumer approval of our products, which leads to an
2 easier CLIA path, which gets us into the physician's
3 office and into some of the screening areas.

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

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

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

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1 Next slide?

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

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

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

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

22 And my favorite, especially for today,

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1 this study, which we all know very well, most of us
2 know very well, that are in this area anyway, that
3 triglycerides levels were a better predictor of
4 outcome than cholesterol levels. And there is a
5 BioScanner 2000, which used to be the MTM, about the
6 size of a package of cigarettes.

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

11 There's one more.

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

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

22 And, to me, a company that came out with

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

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

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

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

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

10 That's it.

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

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

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

21 Results are usually in less than a minute.
22 Later on, some tests will be combined together in

1 logical panels like cholesterol, HDL, a direct LDL.
2 But, again, it's all focused on the diabetic with a
3 single instrument, with a lot of capabilities.

4 And I think there's one more part to this.
5 (Whereupon, the remainder of the video
6 was shown.)

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

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

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

18 DR. DEEG: Thank you, Jim.

19 As he said, my name is Mark Deeg. I'm an
20 endocrinologist at Indiana University. I conduct
21 basic research on HDL metabolism, and clinically I'm
22 the Director of the Cardiology Clinic at what I call

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1 the Indiana Vascular Disease Center, otherwise known
2 as the Roudebush VA, which has -- veterans have a lot
3 of cardiac disease.

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

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

13 You can leave the lights up.

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

19 First of all, in the last national
20 population survey, the median triglycerides for women
21 was about 88 milligrams per deciliter. This just
22 gives you an idea of where the country stands. For

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1 men, it's about 112. Okay.

2 In 1993, the NCEP classified triglycerides
3 as such. They said less than 200 was considered
4 normal, 200 to 400 was borderline, greater than 400 to
5 1,000 was high, and greater than 1,000 was considered
6 very high. Sort of an interesting scale.

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

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

18 The major focus is triglycerides, and some
19 of the controversy, is their role in cardiovascular
20 disease, in predicting cardiovascular disease. The
21 one complication that I'm not going to talk about,
22 which is actually quite important, that people in this

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1 category -- high-risk for what's called pancreatitis.
2 And it's a potentially big problem in our diabetics,
3 but we're not going to talk about this class of
4 people.

5 Lights, please.

6 So what I want to talk about for the next
7 20 minutes or so is, what does it mean to me as a
8 practicing physician when I measure someone's
9 triglycerides? And what does it mean to the patients,
10 and what do I tell them?

11 Next slide.

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

17 And the reason I throw that up there is
18 because if you really want to understand what happens
19 when you really measure triglycerides, you need to
20 understand what this is or how -- where triglycerides
21 come from and where they go to, discuss the
22 controversial issue about triglycerides as an

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1 independent risk factor for coronary artery disease,
2 triglycerides as a synergistic risk factor,
3 triglycerides as a metabolic marker for other
4 syndromes.

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

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

18 Next slide.

19 If you had bacon and eggs for breakfast,
20 this is what's happening. You consume that dietary
21 fat. It's absorbed into the intestine and forms
22 what's called chylomicrons. These chylomicrons are

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1 the largest particles that are very triglyceride rich.
2 Okay?

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

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

14 Now, one of the important points about
15 triglycerides and what makes it so difficult as
16 triglycerides as risk factors is that it's
17 metabolically linked with all of these other
18 lipoproteins. So, for example, as these VLDL
19 particles are broken down into IDL, some of the
20 constituents end up in HDL. Hence, this
21 interrelationship between triglycerides and HDL.
22 We'll talk about that some more.

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1 These remnants can be further broken down
2 into LDL -- again, the bad guy in terms of the, you
3 know, very well-established risk factor for coronary
4 artery disease. The LDL can either go back to the
5 liver or deliver its cholesterol elsewhere. Other
6 remnants can be taken back into the liver.

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

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

17 Whoa.

18 (Laughter.)

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

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1 has that been difficult?

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

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

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

21 And, finally, sort of the bread and butter
22 of the clinical evidence based medicine just hasn't

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1 been there for triglycerides. We're beginning to see
2 that now, and we'll see further trials in the next few
3 years. But it's not here yet.

4 Next?

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

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

16 And when you adjust the triglyceride
17 levels for risk, for all of the various things that
18 can influence triglycerides, what they found, as you
19 went from the lowest group to the highest group of
20 triglycerides -- and the cut points here was 100
21 milligrams per deciliter, 140 milligrams per
22 deciliter, that as your triglycerides increased, your

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1 risk for a cardiac event went up.

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

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

18 Keep going.

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

22 It's really been controversial for men.

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

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

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

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1 for men.

2 Next slide.

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

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

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

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1 and high LDL.

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

8 Next slide.

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

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

19 Next slide.

20 Now, this is some interesting data that
21 actually was just down the street at Hopkins by a guy
22 named Mike Miller. And they looked at people -- they

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1 took about 500 men and women who went to the coronary
2 cath lab to have -- so they could look at their
3 coronary arteries and see if they had coronary artery
4 disease, and then followed them for up to 18 years to
5 see who survived and who didn't survive, and based on
6 their triglycerides of being less than 100 or greater
7 than 100.

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

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

21 Well, as I alluded to earlier,
22 triglyceride metabolism is quite complicated, and

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1 triglycerides is a risk factor, maybe in addition a
2 marker for the various alterations and metabolism of
3 triglycerides and lipids. This is becoming more and
4 more appreciated as we understand the complexities of
5 triglyceride and lipid metabolism.

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

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

22 Now, the thing is, what do I mean by

1 hypertriglyceridemia? Well, it turns out that there
2 have been numerous studies that have shown that
3 certainly when your triglycerides hit 150, or start
4 going higher, you begin to see these metabolic
5 changes.

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

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

20 Now, the other marker for high
21 triglycerides, as Mr. Connolly was alluding to, was
22 that triglycerides in the insulin-resistant syndrome

1 are intertwined. The insulin-resistant syndrome again
2 is very common in the United States, and this syndrome
3 is associated with many abnormalities that increase
4 the patient for coronary artery disease.

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

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

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

21 Next slide.

22 This is a particularly increasing problem

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1 for the United States in terms of coronary artery
2 disease, and the reason being is we know people with
3 Type 2 diabetes have an increased -- two- or three-
4 fold increased risk for coronary artery disease
5 compared to people who have normal glucose tolerance
6 -- diabetics, glucose tolerance.

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

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

20 One is, as a population, we're getting
21 heavier, which is associated with the insulin
22 resistance. Another reason is we're getting older.

1 And that conversion -- becoming insulin-resistant and
2 becoming Type 2 diabetes increases as you get older.
3 So now as the boomers are turning 50, there are 10,000
4 people turning 50 a year now, and when I turn 50 in
5 10 --

6 DR. ROSENBLOOM: 10,000 a year?

7 DR. DEEG: Well, 10,000 a day, and then I
8 represent the peak. In 10 years, it will be closer to
9 50,000 a day will be turning 50. This will become a
10 huge, huge, huge problem.

11 Next slide.

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

20 Now, the thing I want to, again,
21 reemphasize is that diabetics are at increased risk
22 for pancreatitis, particularly if they have diabetes

1 along with a genetic disorder. Again, these are
2 triglycerides in the 1,000 range.

3 Next slide.

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

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

17 What are some of the clinical trials that
18 can help us decide if treating triglycerides are
19 important or not? There has not been a trial directly
20 aimed at answering that question. Part of the reason
21 is that it's just difficult to do because of the inner
22 metabolic connections between those lipoproteins.

1 Part of it is that, again, because of the
2 controversy about triglycerides as a risk factor. But
3 there is some data that suggests that treating these
4 people gives them clinical benefit. And let me show
5 you data from a couple of trials.

6 Next slide.

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

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

20 So in the placebo group here in the sort
21 of green, you can see that the event rate in these
22 groups were pretty similar. But, again, this group

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1 that had the high triglycerides and had this high
2 ratio vis-a-vis high LDL with the low HDL, they had a
3 much higher event rate. Okay? Three- or four-fold
4 greater than these other people.

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

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

14 This is a recently published study called
15 the VA HIT trial, which I'm really quite excited about
16 because of the people that they identify. It was
17 about 2,500 patients, again treated with or without
18 Gemfibrozil. Again, what we're focusing in on was
19 people with low HDLs. HDL, 32; triglycerides only
20 161; and, interestingly, an LDL of 111. And this is
21 by far the lowest LDL in any major trial that we've
22 done to date. Okay?

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1 This is a very typical lipid profile for
2 people with insulin resistance and Type 2 diabetes.
3 These are people with coronary artery disease. And
4 they treated them with Gemfibrozil in order to raise
5 their HDL and lower their triglycerides.

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

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

20 Next slide.

21 What are some of the current guidelines
22 for triglycerides? These clearly lag behind the LDL

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1 because we lack some of the information. But what is
2 some of the information or guidelines that are out
3 there for physicians?

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

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

17 Next slide.

18 Let me -- going on, for diabetics, in
19 1999, the American Diabetes Association has been a
20 little more aggressive based on some -- not really the
21 data that I showed you, but some of the data with
22 respect to, what should the lipid levels be in

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1 diabetics?

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

6 Next slide.

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

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

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

22 For the physician, triglycerides is a very

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

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

12 But certainly based on the epidemiological
13 data, some of which I showed you, and some of these
14 other numbers, it certainly seems prudent that we
15 should be addressing triglycerides in these patients.
16 It certainly can help in situations that are not
17 covered by the NCEP guidelines in terms of what to do.
18 For example, a middle-aged man like me, who might have
19 an LDL less than 130, but my triglycerides might be
20 300.

21 And, finally, and a very important point
22 for the triglycerides, is that when I see these

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1 numbers, you always to think of, is something else
2 causing this? Do they have diabetes? Do they have
3 hypothyroidism? Maybe it's their medication? Or is
4 there a genetic disorder? Those are clues that need
5 to tip off the resident.

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

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

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

21 And, finally, this feedback is quite
22 important in terms of improving compliance, which is

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1 one of the major difficulties in treating people with
2 lipid disorders because they don't feel bad unless
3 they have a heart attack.

4 Next slide.

5 So with that, I have finished. Thanks.

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

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

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

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1 Thank you.

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

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

16 The instrument is turned on, and the user
17 will check the messages. If the message on the screen
18 says "insert strip," then all one has to do is apply
19 one drop of blood, by finger stick, to the strip, and
20 then insert the strip into the instrument, wait for
21 generally about 60 to 70 seconds, and the results
22 appear on the screen.

1 The next slide shows how the assay works.
2 It's an enzymatic assay. The red blood cells are
3 separated from the plasma by a couple of membranes,
4 and the plasma then comes in contact with the reaction
5 membrane, and the reaction membrane has the
6 lipoprotein lipase glycerol-coronase, glycerol
7 phospheroxidase*, ATP, and the chromagens, and the end
8 result of these reactions is the colored product, the
9 intensity which is measured by the instrument, and the
10 intensity of the color is proportional to the
11 concentration of triglycerides in the sample.

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

16 First, we did a study where three lay
17 users who had never worked in the labs, never had the
18 experience of using any lab devices, were given a
19 total of six different samples. Each user got two
20 samples at two different levels of triglycerides, and
21 they were asked to prepare those blood samples and
22 illustrate 20 times.

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1 And as the percent CV is shown at the
2 bottom of this table, they varied a little bit, but
3 the highest percent CV that they got was 8.8. And
4 please keep in mind that these people had never used
5 any lab device before and had never worked in the
6 laboratory.

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

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

18 The linearity of the assay was -- in the
19 lab by lab professionals or lab technicians. Five
20 samples were used. These samples were concentrations
21 that fell within the analytical range of this assay
22 system; that is, between 30 and 500 milligrams per

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1 deciliter. And as you can see, in the data that's
2 shown on the bottom, the regression data, with a slope
3 of 1.0 and coefficient of 0.99, that experiment proved
4 the linearity of the assay quite adequately.

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

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

22 The accuracy of the assay was further

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1. tested by performing a consumer study at nine
2. different sites with about 382 lay users that
3. participated in the study. Every user was given the
4. system, the device, the BioScanner instrument, the
5. strips, and the memory chip and a lancet device, so
6. that they could take their own finger stick.

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

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

17. The reference assay was then compared to
18. check the validity of the reference method. It was
19. compared to an assay that had been performed in one of
20. the CDC-recommended labs. In our case, it was Pacific
21. Biometrics in Seattle, Washington. It's one of the
22. network labs, the so-called CRMLN or the Cholesterol

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1 Reference Method Laboratory Network.

2 They compared -- they assayed the samples
3 with their method, and when the numbers were compared
4 to the numbers that we got on the Sigma -- with the
5 Sigma reagents, a correlation of 0.98 and a slope of
6 0.94 was obtained.

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

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

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

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1 for the particular sample.

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

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

13 DR. PASQUA: Thanks, Sunil.

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

18 (Laughter.)

19 The total system error, as I'm defining
20 it, is -- as it is commonly defined -- is bias plus
21 two times the standard deviation. It's a good measure
22 of analytical performance in a diagnostic device. And

1 it becomes especially critical as the panel addresses,
2 on one of the questions, whether NCEP standards for
3 laboratory instruments applied to over-the-counter
4 whole blood tests.

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

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

18 The SD from the lay user study was 8.5.
19 I calculated the total system error -- again, bias
20 plus two times SD was 19.9 mils per deciliter. For
21 100, it's 19.9 percent. And that's the way it goes
22 all across.

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1 You note that the higher the reference
2 value goes, it seems like if you calculate it from the
3 regression equation, the more negative the bias
4 becomes. None of the values -- 19.9 percent for 100,
5 23.2 percent for 200, 16.5 percent -- you think it's
6 better than this?

7 (Laughter.)

8 19.9 percent, 23.2 percent, 16.5 percent.
9 Neither meet the 15 percent for the NCEP guidelines,
10 not -- all three of them don't.

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

19 Again, the random error components were
20 the same. Final calculations come to 23.8, 22.5, 14.1
21 percent. None of these point estimates, again, meet
22 the 15 percent requirement that the NCEP has, which is

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1 five percent bias and five percent -- the NCEP
2 recommendation is five percent bias and five percent
3 CV.

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

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

16 The FDA seemed concerned about the
17 confidence intervals around our estimates, especially
18 the SDs. So let me just briefly go -- so what I did
19 for these TSE calculations -- all of these TSE
20 calculations here are calculated from the nominal
21 bias. But what I did was, since I calculated the SDs
22 in mils per deciliter, and I gave the corresponding

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1 percent, I had the lower confidence interval in
2 nominal and the upper 95 percent confidence interval,
3 and I used these to calculate these numbers here.

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

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

20 And that's all I have to say.

21 Margo?

22 CHAIRMAN NIPPER: Before you leave, I want

1 to make sure I have your name correct. Is it P-A-S-Q-
2 U-A? Is that --

3 DR. PASQUA: Yes.

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

6 DR. PASQUA: Dr.

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

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

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

21 Besides the package insert for the strips
22 themselves and the user guide, we will provide a

1 control material. And this is manufactured for us.
2 We don't manufacture our own controls. We will
3 provide a control material to be used with the
4 BioScanner 2000 triglycerides, and this is the package
5 insert for that product.

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

14 And if the FDA has additional
15 recommendations, we would like them to make those
16 additional recommendations because we are very willing
17 to make any changes. And if we misinterpreted any of
18 the suggestions they've made, we're very willing to
19 make any changes to our labeling. So we wanted to
20 make sure that we went on the record saying that as
21 far as the labeling goes we are very willing to make
22 any requested changes.

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1 Very briefly, hit some of the key items in
2 the package insert, the intended use. This is
3 formatted at a seventh grade level for a home user,
4 describes what, why, who, and when, basically tells
5 them that this measures triglycerides and finger stick
6 blood.

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

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

22 In the performance section, accuracy,

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

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

17 And, finally, before I turn this back over
18 to Jim Connolly, just a summary of our performance.
19 As Manager of Clinical Affairs, it is incumbent upon
20 me to just summarize and let you know that we believe
21 that this product, and based on all of the studies
22 that we have done, and the information that we have

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1 provided, the performance studies, show this product
2 to be safe, effective, and substantially equivalent to
3 a predicate device.

4 I'll now give this back to Jim Connolly to
5 summarize.

6 MR. CONNOLLY: Thank you, Margo.

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

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

21 I don't think I want to defend the lack of
22 performance, but I think whether someone has got a 50

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1 triglyceride or a 75 triglyceride, that's not near as
2 important as if they have one over 400, or certainly
3 over 200.

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

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

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

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1 dramatic.

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

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

19 (Laughter.)

20 So let me take to the last part of my
21 notes before I fall down here. You know, these values
22 actually do address the major costs in health care --

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1 diabetes and cardiovascular disease. Any impact we
2 can have on probably the bulk of our dollars -- that
3 is, greater than probably 70 percent of the total
4 dollars spent in the U.S. are on these two diseases.

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

9 What did I leave out, Sunil?

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

15 (Laughter.)

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

19 As you know, we also had a hemoglobin A1C
20 product that's about to come to the FDA. I can tell
21 you, nine years ago, when I was working on a somewhat
22 similar project, one day a week we would take a

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1 scientist to lunch or to dinner just to kind of keep
2 the company warm and close. We've always worked,
3 since our large company affairs, with small companies.

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

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

15 But at age -- at an older age --

16 (Laughter.)

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

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1 until about nine years later.

2 I've always had a low HDL, so I'm
3 genetically absolutely fit for this thing. HDL at 35,
4 34 -- and do I know that's the correct number? Yes,
5 because I've had it run hundreds, if not thousands, of
6 times. Now I've got an HDL of 25, a triglyceride of
7 -- in the hundreds, certainly above 400 milligrams,
8 and I've become insulin-resistant. Now I'm a proud
9 supporter of Bristol-Meyers-Squibb.

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

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

21 And I think there's absolutely no question
22 about triglycerides being used with our other

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1 approvals that we're patiently waiting for in HDL that
2 would be even of more impact on this diagnosis of
3 coronary heart disease and some of the assessments
4 used to determine if someone is becoming dyslipidemic,
5 and I won't say the other word. But it certainly has
6 impact outside of cardiovascular disease.

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

14 Thank you.

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

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

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1 panel's deliberations.

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

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

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

18 CHAIRMAN NIPPER: Yes.

19 MR. CONNOLLY: If the costs are not to be
20 considered in this product, then I think I need to
21 emphasize quality of life and lack of death as being
22 major points in helping diagnose these diseases.

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1 CHAIRMAN NIPPER: Thank you. Safety and
2 effectiveness is a good guideline there. It's not
3 that we're not interested in cost, but I think the FDA
4 is not allowed to bring cost effectiveness or cost of
5 treatment, either high or low, into the decision about
6 safety and effectiveness.

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

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

17 The first -- the question that I had for
18 Dr. Deeg is I think a rather simple one. And you can
19 approach the microphone, so you can be on the record.
20 Dr. Deeg, in the clinical studies that you cited in
21 your presentation, I notice the word "non-fasting"
22 appeared many times. Were there any of the clinical

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1 studies that you cited in which the triglyceride data
2 were -- I'm sorry, I started to say fasting -- were
3 there any studies in which the triglyceride data
4 obtained was non-fasting or were the subjects fasting
5 for the data?

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

12 CHAIRMAN NIPPER: Okay. But you didn't
13 cite any studies to --

14 DR. DEEG: Correct.

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

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

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

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1 that.

2 Dr. Rifai?

3 DR. RIFAI: I just have also a few short
4 questions for Dr. Deeg. Forgive me if they are naive.
5 How often do you see your patients?

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

7 DR. RIFAI: Yes.

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

10 DR. RIFAI: What do you order --

11 DR. DEEG: What do I order?

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

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

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

20 DR. DEEG: Certainly, in the initial
21 management of the patients, more frequent -- as you
22 are fine-tuning their therapy and getting to your

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1 goals, and things of that nature. Once you have
2 attained your goals, then you can cut back a little
3 bit on the frequency.

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

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

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

19 DR. RIFAI: Thank you.

20 DR. KIMBERLY: I have some questions for
21 Dr. Anaokar regarding the comparison with CRMLN
22 laboratory. How were the samples collected for the --

1 that were sent to the network laboratory for the CRMLN
2 laboratory? And also, what type of pre-analytical
3 considerations were taken as far as the patient or the
4 layperson as far as collecting the finger stick and
5 assuming the serum sample?

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

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

20 MS. ENRIGHT: Yes. The patient finger
21 stick results were run at the same time, within the --
22 the draw was either prior to the finger stick or after

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1 the finger stick, depending on the number of
2 laypersons that we had available. But waiting -- so
3 that was just a logistical thing. But within 10
4 minutes of each other, so they were drawn at the same
5 time.

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

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

16 The lay users themselves were given
17 written instructions on how to perform the testing.
18 And if there was any variation, it was due to the lay
19 user's use. The professional -- in a professional
20 result on the BioScanner, the finger stick was
21 compared to the lay users. And differences between
22 the lay user and the professional results may have had

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1 a little bit to do with the fact that many of the lay
2 users that we used had absolutely no experience doing
3 a finger stick. But they were not in any way coached.
4 They were just given written instructions.

5 DR. KIMBERLY: Okay. Thank you.

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

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

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

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

21 (Laughter.)

22 One which is very true is that probably

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1 the majority of the people using this product are
2 going to be diabetics who currently know how to do
3 finger sticks. They're going to get better results.
4 It's my feeling that those results would meet the
5 guidelines.

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

14 So it's -- I think it's a monumental fact
15 that we got the kind of answer that we did, assuming
16 that probably 95 percent of these patients had never
17 done a finger stick before. So in that case, I think
18 they are probably not going to be the users of the
19 product, but to hold us to, you know, totally unknown
20 people, to NCEP guidelines that were developed for
21 large analyzers with incredible performance on CVs,
22 using serum. None of them use whole blood, so there

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1 really are no standards for whole blood.

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

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

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

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

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

19 MR. CONNOLLY: Without a panel.

20 DR. CLEMENT: I'm still looking for a
21 number, I mean, compared to -- like, for example, if
22 we compare it to another reference method, such as

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1 serum, which you've done in your case.

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

4 DR. CLEMENT: Right.

5 MR. CONNOLLY: Non-testers?

6 DR. CLEMENT: Right.

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

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

19 (Laughter.)

20 -- untrained people.

21 DR. GUTMAN: Let me just correct the
22 record. It is true that the cholesterol product did

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1 not meet NCEP guidelines, but it was off by about two
2 percent. It was in the ballpark. There was a lot of
3 discussion about that product. And, in fact, in the
4 labeling of that product, the cut points were set so
5 that the signal was actually below the traditional
6 cutoffs.

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

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

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

20 MR. CONNOLLY: Yes.

21 CHAIRMAN NIPPER: Which question are you
22 answering?

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1 MR. CONNOLLY: I'm answering the question
2 about the cholesterol product that did not meet the
3 NCEP guidelines.

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

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

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

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

22 Dr. Rosenbloom?

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1 Were you finished?

2 DR. CLEMENT: Yes, I'm done.

3 CHAIRMAN NIPPER: Dr. Rosenbloom?

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

13 And that seems a rather dramatic
14 recommendation, which is only supported by the
15 statement of Dr. Naito, who is the Chief of Clinical
16 Chemistry at the VA in Cleveland. And I wondered if
17 there was -- and it's not in keeping with the American
18 Diabetes Association recommendations which are that
19 adult patients with diabetes should be tested annually
20 for lipid disorders, with fasting serum cholesterol,
21 triglyceride, HDL cholesterol, and calculated LDL
22 cholesterol.

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1 And then, if the values fall in the lower
2 risk levels, assessment may be repeated every two
3 years. Tests resulting in borderline or abnormal
4 values should be repeated for confirmation. Tests
5 resulting in abnormal values requiring institutional
6 therapy should be repeated following the NCEP
7 recommendations, and lipid values should be
8 reevaluated following a macrovascular event.

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

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

20 MS. ENRIGHT: In our initial labeling, we
21 did not address the issue of how often these tests
22 should be used. But one of the FDA requests was to

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1 add that information to the package insert. And what
2 we did is we consulted. We were told that we had to
3 consult with an expert in the area in this. And as
4 you alluded to, this suggestion came from Dr. Herb
5 Naito from the VA Medical Center in Cleveland. And we
6 are certainly open to making changes in the labeling
7 that address this.

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

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

19 And as we all know, when you take this
20 drug, there is no -- you don't feel any better, so
21 there is really no reason to comply. It's a very
22 expensive drug. A lot of diabetics don't have health

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1 insurance, and to buy another \$2,000 a year worth of
2 statins, or whatever, is a burden there.

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

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

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

14 DR. ROSENBLOOM: And --

15 MR. CONNOLLY: We're willing to make
16 changes.

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

20 CHAIRMAN NIPPER: Thank you, Dr.
21 Rosenbloom.

22 Dr. Floyd?