1 DR. FLOYD: I don't have too many specific
2 questions, but one I will address -- there has been a
3 lot of data presented to show how variable this test
4 is in the hands of consumers. There are two issues
5 that pop into my mind immediately when I see that kind
6 of data. One is, how much variability is in the
7 device the consumers handle? I didn't see any of that
8 presented.
9 And the second is, what accounts for the
10 variability in the hands of consumers? There was an
11 allusion here earlier, although it wasn't addressed
12 specifically, that the differences in hematocrit make
13 a difference in the values that are obtained. I'd
14 really like to see some data on how that's addressed.
15 Does that relate to the volume of plasma that's
16 actually available to the chemistry to react? And is
17 that accounting for the variability?
18 So there are a number of those specific
19 issues I'd like to see a little bit more data on, just
20 so I could understand where the variability in the
21 test is coming from.
22 CHAIRMAN NIPPER: Thank you, Dr. Floyd.

1 Ms. Kruger?

2 MS. KRUGER: I have some specific

3 questions about the users. I heard studies about

4 pipatsin controlled, and then I heard about a 382-

5 patient study, and I made the assumption that is the

6 one that was both lay people as well as health care

7 providers doing that test. Is that correct?

8 MS. ENRIGHT: The data that we presented

9 was --

10 CHAIRMAN NIPPER: Would you speak into the

11 microphone, please?

12 MS. ENRIGHT: Sorry.

13 CHAIRMAN NIPPER: Thank you.

14 MS. ENRIGHT: The data that we presented

15 was only the consumer data. We also did, in

16 conjunction with that, do a professional study.

17 MS. KRUGER: And how many consumers were

18 there that used the device? How many consumers? Was

19 it 382?

20 MS. ENRIGHT: 382.

21 MS. KRUGER: And these consumers actually

22 used their own finger sticks? They poked their own

1 fingers and put it on the drop?

2 MS. ENRIGHT: Yes.

3 MS. KRUGER: Okay. They weren't using --

4 they weren't pipetting it?

5 MS. ENRIGHT: No, they were not pipetting.

6 The only time when the consumers used pipettes were

7 when the consumers pipetted whole blood that was other

8 than their own.

9 MS. KRUGER: Okay.

10 MS. ENRIGHT: Or if they were doing

11 control studies, because there is no other good way to

12 do that.

13 MS. KRUGER: Okay. I didn't see anywhere

14 in the literature -- and I may have missed it -- or in

15 your presentation, answering questions of size of

16 drop. Can the consumer touch the strip? If the

17 consumer smears the blood, are there any error codes

18 if the patient does anything wrong, so they know that

19 there isn't enough blood? How long after they put the

20 blood on the strip do they have until they can put it

21 in? Is there anything on the strip that tells them

22 they haven't gotten enough blood? Can they add more

1 blood? And those are questions that I think are
2 really important in terms of the consumer being able
3 to use it.
4 The other thing is I think that Mr.
5 Connolly is making some assumptions about our
6 patients. One of the biggest problems we have is
7 technique, and that I see -- that's all I've done for
8 the last 18 years is work with people with diabetes.
9 And the biggest problem we have is their ability to
10 get all of these things accomplished.
11 Some of the newer meters, they can
12 accomplish that. But I'll tell you that the
13 techniques we see and the variabilities and the
14 accuracy in some of the older models of machines are
15 not good. And if you don't have the ability to do
16 some of these things, even though those patients have
17 diabetes and they are doing monitoring, it's not going
18 to help the accuracy.
19 Yes, in some of our newer machines that's
20 true, but if you don't have it built in, just because
21 they have diabetes, we're not going to see better
22 accuracy than what you are presenting today.

1 And then another comment. I would agree
2 as just supporting Dr. Clement and Dr. Rosenbloom in
3 terms of the ADA standards of care for measurements of
4 lipids. The frequently is certainly -- we need to
5 talk about how you label that in terms of your
6 frequency.
7 MS. ENRIGHT: May I address one of her
8 comments?
9 MS. KRUGER: Please.
10 MS. ENRIGHT: The one comment regarding
11 the consumers. One of the things that we did in
12 selecting, we were very careful that we selected
13 consumers and that we, in our demographic data that we
14 gathered on the consumers, we made sure that we had
15 relatively naive consumers; that is, that they had no
16 previous or almost no previous experience with finger
17 sticks.
18 The other piece of that is most of these
19 folks were not diabetics, which we asked. And you
20 make a good point that diabetics sometimes do have
21 great difficulty with a finger stick. But the
22 difference, even in a diabetic versus the consumers,

1 some of the places where we performed these studies
2 were at shopping malls, and we really had a -- we were
3 really in a worst-case scenario.
4 And I think the diabetic, whether or not
5 they have good technique in performing a finger stick,
6 they at least have the benefit of a diabetes educator
7 or the physician. They're allowed to be given some
8 sort of instruction. And we were instructed that
9 these folks were to be given absolutely no instruction
10 and no coaching.
11 MS. KRUGER: You're making assumptions
12 again. Eighty percent of our patients are never seen
13 by a provider as a diabetes educator or by a person
14 who is in diabetes. That's all I'm saying to you is
15 you need to be careful about the assumptions you're
16 making. You're making too many assumptions.
17 Okay. One other comment. You made a
18 comment also, Mr. Connolly, that if a patient is on
19 medication, and they can look at their triglycerides,
20 that potentially that will keep them on drug. That's
21 a two-edged sword as well because very often a patient
22 who is doing very well on blood pressure medication,

1 or very well on triglyceride medication, or lipid-
2 lowering medication, when they see good numbers,
3 that's when they stop the medication because, after
4 all, they're doing better. So it's also a two-edged
5 sword.
6 MR. CONNOLLY: Two things. One, with the
7 test strip, one of the things we started off with in
8 the very early days of the company were sample size.
9 There is a lot of people in the industry that believe
10 that sample sizes are much larger than they really
11 are. The definition of hanging drops all over the
12 place.
13 But if one were to consider 10-year old
14 standards at hanging drops are somewhere between 20
15 and 40 microliters, with the larger lancets and with
16 professional people doing it, maybe that's true. We
17 believe sample sizes are much, much smaller than that
18 in reality, for diabetics testing each day. And they
19 probably should be.
20 If you want them to test more often, you
21 can get them to use smaller lancets. There is less
22 pain involved. They don't mind testing more often.

1 We've gotten a lot of people who weren't testing
2 involved in testing by using some of the new devices
3 right now that require less sample.
4 We have made the materials in the sample
5 deposition area outside that to be very, very
6 hydrophobic. So it creates -- it loses some of the
7 problem of the sample going in other places.
8 In regards to the people using these
9 things, I've seen people walk -- well, I've seen one,
10 but it was enough to convince me there is no way.
11 There was an instrument that had just been run sitting
12 on the table, and it said -- there was a result
13 displayed, whatever it was. The patient pricked their
14 finger and deposited the drop of blood on the display.
15 Didn't get it result, but it was obvious that this is
16 a huge problem.
17 One of the things we do by dosing outside
18 the meter -- if you -- if a lot of these diabetics
19 we're talking about, or people in the general public
20 -- the over 40 crowd, the bifocal crowd, or, with me,
21 the trifocal crowd -- I mean, if you've ever tried to
22 look through a finger, or, worse yet, put a strip in

1 a meter and put your head down at the edge of the
2 table, and turn your head sideways, your
3 trifocal/bifocal thing turns into, where is this
4 thing?
5 And by using a strip that you could hold
6 up to eye level, deposit the blood on the strip, I
7 think we minimize the errors that a lot of folks have
8 in sample deposition on those things. And I think,
9 again, the smaller sample size is a big help.
10 And the other assumptions that if your
11 cholesterol is good, and you stop taking the statins
12 -- we've seen that with some of our employees, which
13 I thought was interesting, because we're all on the
14 compliance side. And then the same employee who
15 stopped taking the statin, who does a lot of roadshows
16 for us in demonstrating the product, his cholesterol
17 kept going up and up. And he started taking the drug
18 again.
19 So I guess it is a two-edged sworn. One,
20 will they stop? And, secondly, will they start again?
21 It would seem to me the only thing -- it's like a
22 bathroom scale, I guess. I mean, I've got one I look

1 at regularly, but I have a hard time impacting that
2 unless I take it seriously.
3 CHAIRMAN NIPPER: It sounds like the
4 elements for a clinical study somebody needs to do.
5 Dr. Lewis?
6 I'm sorry. Were you finished, Dr. Kruger?
7 MS. KRUGER: Yes, I am. Thank you.
8 CHAIRMAN NIPPER: Thanks.
9 Dr. Lewis?
10 DR. LEWIS: Yes. My question would go to
11 the labeling again. And I wonder if there's anything
12 that indicates the most suitable time for sampling, so
13 that the user has some well-understood idea if fasting
14 is required and what that means, which I know from
15 experience can mean anything, depending on, you know,
16 how the individual takes that.
17 MS. ENRIGHT: That's an excellent
18 question, because, as you know, triglycerides varies
19 significantly depending on the time of the day and
20 when the last meal was taken. Based on input from the
21 FDA, we used the -- in the labeling, the NCEP
22 recommendation that the sample come from a person

1 that's been fasting for 12 hours prior to the test.

2 DR. LEWIS: Is the term "fasting" spelled

3 out in any way?

4 MS. ENRIGHT: I'd have to take another

5 look at the labeling, but I think -- I think -- and

6 somebody can correct me if I'm wrong because I think

7 we have the labeling -- I think it says not having

8 eaten for the last 12 hours. I think that's how we

9 define it to the consumer.

10 DR. LEWIS: As far as drinking and what

11 liquids?

12 MS. ENRIGHT: For best results, you should

13 test after fasting, no food, only water, for 12

14 hours --

15 DR. LEWIS: Oh, okay.

16 MS. ENRIGHT: -- prior to testing.

17 DR. LEWIS: Thank you.

18 CHAIRMAN NIPPER: I'd like to know if your

19 copy of the labeling is different than ours, because

20 in the packet my copy of the labeling -- and I was --

21 and I'm Dr. Nipper -- was -- I saw the note for best

22 results test when you have not eaten for 12 hours, a

1 parenthetical comment under "Quick Guide."

2 Did I miss something somewhere? Oh, yes.

3 Here we go, another one under "Specimen Collection and

4 Preparation." That's where you were. I apologize.

5 MS. ENRIGHT: Okay.

6 CHAIRMAN NIPPER: So it's in two places,

7 Woody.

8 MS. ENRIGHT: Yes. And we may check

9 because there have been -- based on what I presented,

10 we have made several iterations. And I know what you

11 have in the packet you may have -- you'll want to look

12 at the very latest labeling that you have because we

13 did revise the labeling based on the letters from the

14 FDA.

15 CHAIRMAN NIPPER: Good.

16 MS. ENRIGHT: So there were a number of

17 requests, and I believe we -- I believe we -- to the

18 best of our ability, we honored all of those requests.

19 And if we didn't and misunderstood those, we will make

20 those changes.

21 CHAIRMAN NIPPER: Thank you very much.

22 Did your question get answered, Dr. Lewis?

1 DR. LEWIS: Yes, thank you.

2 CHAIRMAN NIPPER: Okay.

3 Dr. Deeg, we'll call on you in the
4 afternoon to give this, after we -- I'm sorry to be
5 time constrained, but I don't want to hold up -- we
6 need to take a break in a minute or two, and then I
7 don't want to step on the FDA's time.

8 Dr. Janosky?

9 DR. JANOSKY: Yes. I have a question
10 about the consumer clinical study, in particular, and
11 then available data in general, if there are
12 additional available data. It's my understanding of
13 the consumer clinical study -- I would call it
14 clinical, but I think you're referring to it as a
15 consumer study -- DNO380 approximately. Were there
16 any values obtained outside the 400 range?

17 And my comment is especially -- is a
18 follow up to some presentation that Dr. Deeg I guess
19 had given this morning about values outside the 400
20 range, what they might mean, etcetera. If I read that
21 consumer study, I don't see any values outside of that
22 range. And I see, in fact, very few values outside of

1 the 200 range.

2 Am I correct, or do more data exist that

3 we were not presented with?

4 MS. ENRIGHT: You are correct that more

5 data exist that you were not presented. There has

6 been -- I have in front of me all of the submissions

7 we have made to the FDA, and I know you were given --

8 you were provided some selected pieces that should

9 give you a flavor for this.

10 But one of the submissions is one that we

11 made June 4, 1999, and that was -- we refer to two

12 different studies in there, and there are -- there

13 were two different studies. One, I believe, was at

14 four sites, and a five-site study, and we summarized

15 those in the September 20th submission, which I

16 believe you have those. But the June 4th submission

17 does have the data of the previous study.

18 And it will take me a little bit of time

19 to pull this data out. I have all of the data on

20 disk, and I can tell you -- I can pull it up, and I

21 can tell you exactly how many we have. It is somewhat

22 difficult to get results. We did not screen our

1 consumers. We did not pre-screen the consumers, so
2 they were based on the general population.
3 And, of course, any result above 500 was
4 outside the linearity of the device. We did have
5 results above 500, but those were excluded from the
6 analysis because they read high on the BioScanner.
7 DR. JANOSKY: Right. I had seen that
8 earlier. I am not necessarily looking for exact point
9 estimates, but one of the issues that I did see by
10 examining your data is that there seems to be bias in
11 terms of underestimation, and actually quite severe in
12 certain cases.
13 So I'm trying to get a feel for what about
14 categorization, and what about these upper levels.
15 How bad is that bias in terms of this underestimation?
16 Because you are talking about making decisions
17 typically on these higher points, a point of 400, a
18 point of 120. And that's where the bias is quite
19 large.
20 MS. ENRIGHT: Yes. I think Dr. Pasqua
21 spoke to that and the total system error. Actually,
22 the total system error, as you noticed, percentage-

1 wise goes down at the higher levels right around 400.
2 It does go down. But the absolute result -- one other
3 thing we did take a look at, because in the analysis
4 we did find that there was somewhat of a negative
5 bias, and that's why Dr. Pasqua presented the
6 recommendation.
7 We did find that there was a bit of a
8 bias, not only between -- there was a bit of a bias
9 that came somewhat from our reference method, and our
10 reference method is not the CRMLN method. Even though
11 it correlates well to the CRMLN method, there was a
12 bias on the reference method.
13 And our suggestion was that perhaps we
14 need to revisit and use -- even though the method
15 correlates well to the CRMLN -- because of the bias
16 what we need to perhaps do, and we're willing to do,
17 is revisit and in our own laboratory for setting the
18 calibration curve on the device, perhaps use the CRMLN
19 method in our own laboratory.
20 DR. JANOSKY: Okay.
21 MS. ENRIGHT: To eliminate that bias.
22 DR. JANOSKY: Yes. I'd probably like to

1 talk more about the issue, but perhaps after the FDA
2 presents.
3 CHAIRMAN NIPPER: Okay. Thank you.
4 Dr. Doumas?
5 DR. DOUMAS: About when to run this test?
6 CHAIRMAN NIPPER: Basil, pull that
7 microphone over a little nearer to you.
8 DR. DOUMAS: I'm sorry.
9 CHAIRMAN NIPPER: Thank you.
10 DR. DOUMAS: About the frequency of
11 running the test, the recommendation is attributed to
12 Dr. Naito. Do you know if Dr. Naito sees or treats
13 patients?
14 MR. CONNOLLY: Yes, he does. He sees
15 them; he doesn't treat them. He's not a physician.
16 DR. DOUMAS: Exactly. So why in the world
17 a recommendation was based on somebody who is not a
18 physician, not a clinician or even a physician? I
19 mean, this is really surprising to me.
20 MR. CONNOLLY: That's a question for the
21 FDA.
22 DR. DOUMAS: The FDA recommended Dr. Naito

1 to you?

2 MR. CONNOLLY: They recommended that we

3 follow the NCEP guidelines, which were I think in much

4 authored by Dr. Naito, is that not so?

5 DR. DOUMAS: I don't think so. I don't

6 think the guidelines -- the NCEP guidelines really

7 agree with the statement that you have when to do the

8 test.

9 The next question that I have is:

10 expected values -- a physician or health care

11 professional will discuss target values specifically

12 appropriate for each patient. It reads, "If the

13 manufacturer has available a physician who will

14 discuss the values with the patient," is this -- my

15 assumption is that -- is my assumption correct?

16 MS. ENRIGHT: That the manufacturer has a

17 health care professional?

18 DR. DOUMAS: Says a physician or health

19 care will discuss. I mean, I read it two or three

20 times, and my impression is that you have a physician

21 available that will discuss with the patient the

22 values.

1 MS. ENRIGHT: No, that was not the intent
2 of that.
3 DR. DOUMAS: Then, I think this needs to
4 be changed, that the patient should consult with a
5 physician.
6 MS. ENRIGHT: Okay. That was the previous
7 verbiage. That was used in a previous insert and very
8 similar to some that other manufacturers used. But we
9 will change that based on that and based on your
10 recommendations. We'd be happy to make those changes.
11 DR. DOUMAS: Thank you.
12 MS. ENRIGHT: Thank you.
13 DR. DOUMAS: Dr. Manno?
14 DR. MANNO: I'm going to, first of all,
15 say the product insert -- correct me if I'm wrong, but
16 you're going to include two sets of directions, both
17 the OTC set of directions and the professional set for
18 -- because the strips are basically the same.
19 MS. ENRIGHT: That's correct.
20 DR. MANNO: Okay. Well, in that case,
21 then, you have a definition of fasting in the
22 professional kit as nine hours, and you have 12 hours

1 in the OTC kit. If people have a choice, they're
2 going to take the path of least resistance. That's
3 one point.
4 MS. ENRIGHT: Yes, a very good point. Let
5 me address that and lay that to rest. You have --
6 that is a draft of an older insert. This is only the
7 OTC. The professional was included for informational
8 purposes only. They will be consistent, but these
9 have been on different paths. Our professional
10 triglycerides also has been submitted for FDA
11 clearance, and that insert needs to be, once again,
12 updated to be consistent.
13 DR. MANNO: If you have -- I'm just
14 curious why you just didn't make one insert specific
15 for the OTC, so that people don't get confused in one
16 through the professional.
17 MS. ENRIGHT: Well, actually, we do have
18 one for the OTC and one for the professional. Because
19 the package includes both inserts, because it's the
20 same package that's sold to both markets, we do make,
21 for instance, the references. We don't feel like the
22 consumer is necessarily going to be interested in the

1 references that are included in the professional
2 insert.
3 And if they are interested, they can look
4 at the professional insert because it's included in
5 the package. But --
6 DR. MANNO: Okay.
7 MS. ENRIGHT: -- if you have other
8 suggestions -- this was a difficulty for our glucose,
9 which is both over the counter as well as
10 professional. We used one insert. That was my
11 preference, to use one insert, but there were so many
12 issues surrounding an OTC product that we needed to go
13 to a second insert. We also did that for our
14 cholesterol product for that reason.
15 DR. MANNO: Okay. Again, on instructions
16 to the user on this, there is just kind of a general
17 statement, number 5, is, "Wait. Read results." Most
18 of those things -- most of the hand-held units that I
19 have had experience with make a general statement to
20 the user that this is the time when the reaction is
21 good. Don't put it on there and wait two days to read
22 it.

1 It would seem to me that there should be
2 a reiteration of a time window that that reaction is
3 good -- to give a good result. And in that same vein,
4 when you get down to the end -- again, it's step 5 in
5 the thing -- they say to wait, read the results.
6 In the fine print it tells them to check
7 the strip after they have done the test to be sure
8 that they've gotten the correct drop size on, but yet
9 it's not in the five-step narration here with the
10 pictures of what to do.
11 I think that it's a lot to ask of the
12 consumer to remember from the beginning what they
13 should be doing at the end in order to assure that the
14 right drop of blood is there, etcetera, and that they
15 have a good test, in spite of the slide that you have
16 flashing up there.
17 MS. ENRIGHT: So you feel that's better
18 placed at the beginning?
19 DR. MANNO: I think it should just be a
20 short statement and in the last steps here. Add a
21 step. In any laboratory procedure, any place, you've
22 got QA issues. And one of the things you look at is

1 -- at the very end of anything is how -- is everything
2 correct?
3 MS. ENRIGHT: I'll just ask the FDA,
4 perhaps at the end when we have recommendations, I
5 think the FDA will probably summarize -- have the FDA
6 summarize this and come up with -- comes up with a
7 consensus on recommendations for changes in the
8 labeling. And we will gladly make appropriate
9 changes, based on the FDA's input.
10 DR. MANNO: Okay. I would like to ask a
11 question about the statement of compliance. Seventy-
12 five percent of the people nine months later are not
13 on there anti-lipid drugs. And was this a study that
14 was cited, or was this anecdotal from the company reps
15 for the meds? And did they give you any reasons that
16 they thought this may -- why people were non-
17 compliant? Did they bring up things like side
18 effects?
19 MR. CONNOLLY: No. I've not seen any
20 studies. I got this from two sources. One from two
21 of the manufacturers, one of the earlier statin
22 providers and one of the current ones. And also from

1 -- apparently -- I'm not aware of the mechanism, but
2 apparently there is a way that the pharmaceutical
3 people monitor prescription refillment and usage
4 through the pharmacies and the sales things with
5 patients.
6 DR. MANNO: Well, that is -- yes, that is
7 biased, too, to the extent that people who are not on
8 the drug may be changed to another drug. But I'm
9 concerned, as a pharmacologist/toxicologist, that
10 there may be reasons why people are not taking it.
11 Again, as Ms. Kruger said, you have to be
12 kind of careful with that compliance claim.
13 DR. DEEG: Dr. Manno, just a quick
14 comment. There is actually literature supporting the
15 compliance rates on various lipidemic agents.
16 DR. MANNO: Okay.
17 DR. DEEG: So those numbers are recent.
18 DR. MANNO: And one --
19 CHAIRMAN NIPPER: Dr. Manno, I'm sorry to
20 interrupt. Pull to microphone a little closer to you.
21 DR. MANNO: Oh, I'm sorry.
22 CHAIRMAN NIPPER: There are some people

1 out in the hall that are watching you on a monitor and
2 they can't hear you.
3 DR. MANNO: Oh, okay. Didn't realize
4 that. Thank you.
5 I'd like to ask you if you've
6 characterized the reaction curve. As I understand it,
7 this is a multi-enzyme type coupled reactions. And
8 you have problems with total air. Have you really
9 characterized that so that you're in the right range,
10 especially when you've got such large errors, so that
11 you know you are in the right range on your measures?
12 Did you just do that zero to 400 or 500?
13 DR. PASQUA: We calibrate our curve with
14 -- against our reference method. We take blood
15 samples against our reference method in venous blood,
16 and then pipetted the strips to capture our raw data,
17 which is percent R. It's an end point, percent R.
18 And then from that, we fitted -- basically
19 fit a curve to a hyperbolic function, and then create
20 a table of percent R versus mils per deciliter, a 12-
21 point table, which the meter, once it gets a percent
22 R reading, will interpolate -- it will linear

1 interpolate between the 12 points.

2 So we --

3 DR. MANNO: So you've never actually seen

4 how far you go with this reaction, and get the shape

5 of the curve where the cutoffs -- where you're

6 beginning to curve and drop off.

7 DR. PASQUA: We have difficulty obtaining

8 high samples. But we do have -- we have gotten

9 samples above 400, so we know that at least it's 400

10 for sure.

11 DR. MANNO: Okay. You've answered my

12 question. Thank you.

13 And I want you to just clarify one point

14 for me, and I don't know if it will be you or one of

15 the other people, but you state that it's a whole

16 blood procedure, or test. And, of course, you've

17 checked it against a serum method.

18 Also, it's stated in here that there's a

19 difference in the method of red blood cell separation,

20 and I'm wondering that -- the statement is that you

21 centrifuge the blood through the predicate method to

22 get serum. Then you say that the test strip separates

1 the red blood cells, allowing developed color to read
2 on the reactionary of the membrane.
3 So are you really reading a whole blood
4 sample reaction, or are you reading a serum?
5 MR. CONNOLLY: John said I could give my
6 version.
7 DR. MANNO: Which is the right version?
8 (Laughter.)
9 MR. CONNOLLY: I think it's difficult to
10 tell. It's mostly serum, predominantly serum, that's
11 down there, yes. Obviously, red blood cells don't
12 contain the things that we're measuring here, except
13 in some of our other tests. But for things like
14 glucose, cholesterol, ketones, triglycerides, it's
15 mostly serum. And by "mostly serum," if I had to
16 guess, I would guess it's 95 percent serum.
17 There is probably some lysis that occurs,
18 and there are probably -- red blood cells can do
19 wonderful things in tiny holes, so I'm sure there are
20 some red blood cells getting to --
21 DR. MANNO: Do you know the pore size of
22 the strip?

1 MR. CONNOLLY: Yes.

2 DR. MANNO: Are you at liberty just to

3 make a --

4 MR. CONNOLLY: I think they are -- it's

5 .45 micron.

6 DR. MANNO: Okay. Thank you.

7 CHAIRMAN NIPPER: Thank you, Dr. Manno.

8 Dr. Everett?

9 DR. EVERETT: My questions deal largely

10 with whether or not tests, again, measure what you say

11 it does. And I'd like to start by clarifying again,

12 what is the working range of the test strips? Any

13 representative can answer.

14 DR. PASQUA: Right now, 30 to 500 mils per

15 deciliter.

16 DR. EVERETT: Do you know if the precision

17 and accuracy changes over that range? Or is it

18 constant?

19 DR. PASQUA: Well, I'd say from the low

20 end to about 200 mils per deciliter we see a

21 proportional error in the random error -- in the

22 precision. And then about from 200 to 400, it seems

1 to stay relatively constant -- the precision.

2 CHAIRMAN NIPPER: Speak into the

3 microphone. There you go.

4 DR. PASQUA: Okay. Do you want me to

5 repeat everything or --

6 CHAIRMAN NIPPER: No.

7 DR. PASQUA: Okay.

8 CHAIRMAN NIPPER: Just keep going.

9 DR. PASQUA: So, in other words, if you

10 look at the -- that's why the precision at the high

11 end at 400 is pretty good. It's less than five

12 percent, and it seems that the SD stayed relatively

13 constant at 200 to 400.

14 The bias -- if you use the linear

15 regression versus reference -- the predicate method,

16 it seems to be -- it gets much, much worse as you go

17 higher. It gets much more negative. But if you take

18 the actual points -- the bias -- around like 400 and

19 200 that I did and average that bias, it's not as bad.

20 I think what's happening is if I -- we need to have

21 more points at the high end to really get a better

22 idea what the curve is.

1 I think that high end isn't being weighted
2 property, and we're underestimating. I mean, we're --
3 and that's why we might have the low bias, if I were
4 to take a guess.
5 DR. EVERETT: Okay. And the other thing
6 is: are there any contraindications to the use of the
7 instrument?
8 MR. CONNOLLY: I wouldn't swallow it. Not
9 that I know of.
10 DR. EVERETT: Okay. And I guess my last
11 question is -- this was one of the ones that some of
12 the members have already asked. And that is, in a
13 sense, where does the use of this instrument fit into
14 looking at triglyceride levels in patients as opposed
15 to ordering the traditional wet bench lab test?
16 If we still have the same recommendation
17 of nine- to 12-hour fasting before we do it -- I'm
18 still not sure, where does it fit into managing
19 patients?
20 MR. CONNOLLY: I'd like to answer the
21 first part of that, and Dr. Deeg the second part of
22 that. I have to remember the first part now that I

1 got that statement out.

2 (Laughter.)

3 Diabetes as a disease, compared to other

4 diseases, I think is probably -- categorically, you

5 could say it's the only disease that's truly managed

6 and treated at home. Other diseases -- cardiovascular

7 disease, cancer, whatever -- where you're in some kind

8 of a clinic or hospital for therapies, or radiation,

9 or chemo, or whatever, but diabetes is something that

10 is truly managed at home. Number one.

11 And I think most of this information that

12 can be used at home by the patient -- be it

13 triglycerides, cholesterol, any of the lipids -- that

14 he can work with himself, and his professional is key.

15 Hang on while I get the rest of this now.

16 How long do I have to answer this, Dr. Nipper?

17 CHAIRMAN NIPPER: Be as brief and concise

18 as possible, sir.

19 MR. CONNOLLY: You can follow up on the

20 compliance and --

21 DR. DEEG: I think from my perspective, in

22 terms of treating these patients, one, for me, it

1 provides additional data points that -- to see how
2 they're doing over the interim between when I'm seeing
3 them in the office sort of thing, and then the issues
4 that have been raised before in terms of their
5 providing feedback, positive or negative, to the
6 patient in terms of how they're doing in complying.
7 MR. CONNOLLY: Once the patient has gone
8 on a blood draw -- I mean, if the patient comes in,
9 sees the doc, they draw a blood sample, send it to the
10 whatever reference lab, which is common, and the
11 results are back in two or three days, or whatever it
12 is. You know, the patient is gone, and the
13 opportunity of the doctor with the patient is gone.
14 And I think that's a real missed opportunity in
15 working with a patient for the physician.
16 DR. EVERETT: Well, in a real sense,
17 that's not quite accurate either. Many times we've
18 planned to do the test before the patient arrives.
19 The patient comes in a day or two early, got the test
20 done, so when the patient comes in for the office
21 visit the lab results are there as well.
22 MR. CONNOLLY: Right.

1 DR. EVERETT: And that's my concern about
2 how you describe how this test is going to fit into
3 the other things that doctors do and how we counsel
4 the patients and how we deal with them. This has just
5 gone awry with these misinterpretations, or bold
6 gestures of what we do. And that's not quite
7 accurate.
8 But, again, that's a subject for a
9 different time. My other question is this test and
10 its performance -- has it been measured against many
11 of the drugs, looking for things that might interfere
12 with the test as it relates to drugs and medications
13 that many of the hyperlipidemic patients are on?
14 MR. CONNOLLY: Yes. But back to your
15 other question here, to ask the patient to come in the
16 office twice for a visit so it's convenient for the
17 doctor, that's not convenient for the patient. And
18 the patient may not wish to do either one of those or
19 find another physician that goes the other route where
20 he only has to make one visit.
21 Someone else will have to answer
22 interference issues.

1 Are you asking for more information that
2 what's given in the table by Dr. Anaokar for the
3 interferences we look at?
4 DR. EVERETT: Yes.
5 MR. CONNOLLY: No, that's -- we showed you
6 everything we have.
7 DR. EVERETT: But, so if there are various
8 drugs that will interfere with the ability of the
9 instrument to measure triglyceride levels, that has
10 not been done, is that correct?
11 MR. CONNOLLY: I don't know which drugs
12 you're referring to. Can you help me here?
13 DR. EVERETT: Assume the patients, as you
14 already mentioned, are on many of the anti-lipid-
15 lowering medications. Some are on hypertension
16 medications. Diabetics tend to be on lots of drugs.
17 They are to lower their lipid levels, their
18 triglyceride levels, their glucose levels.
19 Have we looked at whether or not any of
20 those will interfere with the test?
21 DR. PASQUA: No. No, we haven't, but I
22 don't think you can -- we to do that, but I thought

1 you meant something like presumed that it will.

2 DR. EVERETT: I don't know. That's why

3 I'm asking.

4 DR. PASQUA: No, I don't --

5 DR. EVERETT: Because these patients are

6 typically on many medications.

7 MS. ENRIGHT: Maybe I can address that.

8 One thing that we did not do with our data, that we

9 did not show you, is for each and every patient, the

10 382, we have data that shows what medications they're

11 on. And if you'd like, we can sort that data, and we

12 find those patients that are on lipid-lowering drugs.

13 And we can do those calculations. We do -- we have --

14 we do have that data available.

15 DR. EVERETT: Okay.

16 MS. ENRIGHT: So we can calculate that for

17 you.

18 DR. EVERETT: Well, that's up to Dr. --

19 MR. CONNOLLY: Dr. Everett, I think this

20 reaction principle that we use is pretty standard.

21 It's been around since probably the late '70s, GPO

22 triglycerides, so I think anything that interferes

1 with anyone else using this reaction system we'd have
2 the same thing. I wouldn't expect any difference,
3 since it's the same reaction principle.
4 DR. EVERETT: Sounds reasonable. But if
5 you never look, how would you know?
6 MR. CONNOLLY: Well, if that's a question,
7 I think we need to go back and look at the predicate
8 devices and see if those people looked at the same
9 interferences. I mean, we'd be happy to do the study
10 to see if there's interference there, if the panel
11 feels that it warrants it. But I'm not sure as to --
12 is anyone here aware of the predicate device we used,
13 that interferences were done in that -- on those
14 products?
15 DR. DOUMAS: May I answer this?
16 CHAIRMAN NIPPER: Dr. Doumas? And then
17 Dr. Rosenbloom had a follow up.
18 DR. DOUMAS: I don't think you can compare
19 systems where the sample serum is diluted 40 or 50
20 times with the system that you have undiluted serum.
21 I mean, there is another instrument on the market, a
22 major instrument which sometimes that interference is

1 there because there is no dilution of the sample
2 whatsoever.
3 But in most systems, when the sample is
4 diluted 10, 20, 30, 40 times, before the reaction has
5 been run, then you get a different interference. You
6 may have no interference when the sample is diluted,
7 and interference when you have no dilution of the
8 sample.
9 I'm not saying that those things will
10 interfere, because I have no idea if they will. But
11 there is a difference how you do interference studies.
12 In tests that you have, the sample, as such, is being
13 analyzed without dilution, without the serum, and when
14 the sample is diluted quite a bit when the reaction is
15 being performed.
16 MR. CONNOLLY: I'm pretty certain that the
17 amount of sample to substrate ratios in the chemical
18 reaction would be the same in this product. I can't
19 say this categorically, but I'll bet it's within very
20 close to the same thing you see in large analyzers.
21 So there is no dilution effect of sample to substrate.
22 It's just in a dry phase by which there is less water.

1 But as to actual reactants, they would be the same.

2 DR. EVERETT: My last question deals with

3 the target audience for use in your instrument. Is it

4 confined to just diabetics, or any patient that we

5 would like to know what their triglyceride levels are?

6 MR. CONNOLLY: We'd like it to be for all

7 patients. We are focused on diabetics, but there are

8 a lot of patients we think this would be of use to.

9 CHAIRMAN NIPPER: You had a followup

10 question, Dr. Rosenbloom.

11 DR. ROSENBLOOM: Yes, it was a follow up.

12 I share Dr. Everett's concern about the lack of actual

13 testing in patients who are ingesting the materials

14 that might interfere. But also, the package insert,

15 in its list of limitations, does not indicate that

16 certain drugs or vitamins will be -- would interfere,

17 although in other correspondence the sponsors say that

18 it does. And I wondered why this was left out of the

19 package insert, or if this is just an error.

20 DR. MANNO: It's in the -- excuse me --

21 CHAIRMAN NIPPER: Dr. Manno?

22 DR. MANNO: It's in the -- listed on the

1 professional insert that will also be included.

2 DR. ROSENBLOOM: But it's not in the --

3 DR. MANNO: It's not in the --

4 DR. ROSEBLOOM: -- not in the patient

5 insert?

6 DR. MANNO: -- in the OTC insert.

7 MS. ENRIGHT: Yes, that's correct, because

8 that was deemed more important for the professional.

9 It wasn't included in the OTC. And, again, if that's

10 a recommendation, we include it in the OTC.

11 One of the requirements for the OTC

12 package insert is that it be written at a seventh

13 grade level, and some of that information, you know,

14 based on the guidelines that we were given does exceed

15 what was recommended for the OTC insert.

16 But, you know, again, based on the

17 consensus and what the FDA recommends, we'll make

18 whatever changes you find appropriate.

19 CHAIRMAN NIPPER: Can you make it brief?

20 DR. MANNO: Yes. The three that you chose

21 to list on the professional as not interfering are

22 acetaminophen, ibuprofen, and solicolites. And many

1 of the people -- your target population will be on
2 those drugs. So that would be a natural question for
3 a consumer who is on that drug, one of those drugs, to
4 ask.
5 I think it would be nice if they had that
6 information easily available to them.
7 MS. ENRIGHT: I think that's a reasonable
8 suggestion, and we'll look to the FDA reviewer if they
9 feel that's appropriate in OTC. But we have no issues
10 with including that.
11 CHAIRMAN NIPPER: Thank you.
12 Dr. Everett, did you have other questions?
13 DR. EVERETT: No, I'm done.
14 CHAIRMAN NIPPER: Dr. Rej?
15 DR. REJ: Thank you. I feel a little bit
16 like my favorite Dilbert cartoon, where the hapless
17 engineer who is last around the table --
18 (Laughter.)
19 -- says, "All of the good comments have
20 been taken already."
21 (Laughter.)
22 But I think I have a few questions I think

1 will be useful in keeping in mind before we hear the
2 FDA presentation. It has to do with comparison of the
3 BioScanner results with the reference method. I don't
4 know who is best to answer that question.
5 But in the design of the study, you
6 mention that consumers measured their own
7 triglyceride. There was a professional measurement of
8 triglyceride by the proposed device. And then a
9 venous sample was taken and assayed by the reference
10 method.
11 MS. ENRIGHT: That's correct.
12 DR. REJ: Okay. And the data that's in
13 the package that we received from the FDA, which
14 results from your device are shown?
15 MS. ENRIGHT: Absolutely the consumer.
16 This was a consumer over-the-counter submission.
17 DR. REJ: Okay.
18 MS. ENRIGHT: The professional is included
19 in a separate submission, and we were asked to submit
20 that separately. So it will be addressed as a
21 separate issue.
22 DR. REJ: Do you have data showing the

1 comparison of your device in the hands of the consumer
2 and a professional that you can share with us today?
3 MS. ENRIGHT: I'll have to see if I can
4 pull that out for you. I brought a large amount of --
5 a large amount of data, and I have some data. I'll
6 have to see what I can pull out for you today.
7 DR. REJ: Okay.
8 MS. ENRIGHT: We were asked specifically
9 to leave that out of the OTC so -- for your package,
10 and we do have --
11 DR. REJ: Okay. So this is the consumer
12 versus the --
13 MS. ENRIGHT: That is the consumer --
14 DR. REJ: -- the -- and looking at the
15 graph that you showed of the chemistry used, I assume
16 that your device measures glycerol as well as
17 triglyceride?
18 MS. ENRIGHT: Yes, it's not glycerol
19 blanked.
20 DR. REJ: Okay.
21 MS. ENRIGHT: That's correct.
22 DR. REJ: And your comparative method

1 within your lab, does that include glycerol
2 measurement?
3 MS. ENRIGHT: Yes, it does.
4 DR. REJ: Okay. And so everybody is
5 reading from the same book, does the reference method
6 measure glycerol?
7 MS. ENRIGHT: The CRMLN is a glycerol
8 blanked method, the CRMLN method is.
9 DR. REJ: Okay. So that the bias -- okay.
10 The bias, then, is -- seems to be, then, even greater
11 if you had compared it to a non-glycerol blanked
12 reference method or comparative method, correct?
13 MR. CONNOLLY: I think it's the other way.
14 But no.
15 CHAIRMAN NIPPER: Can we let Dr. Kimberly
16 jump in, if she needs to, here?
17 DR. KIMBERLY: I was looking at the data
18 the other day, and PBRF reported by total and net.
19 And what they used in their consumer study was versus
20 the total and not -- so theirs is a total net -- total
21 triglycerides.
22 DR. REJ: Okay. So the true triglyceride

1 was not used as a comparative?

2 DR. KIMBERLY: Right.

3 DR. REJ: The bias would be even greater

4 had those data been used.

5 DR. KIMBERLY: Yes.

6 CHAIRMAN NIPPER: Thank you.

7 DR. REJ: And one -- I know that you made

8 reference in your presentation that you sought

9 guidance from the FDA regarding comments on the OTC

10 package insert. But I'd like to know -- and you asked

11 the FDA how they would like it calculated, but I'd

12 like to know how you calculated the statement that the

13 consumer layperson, in their own home, with accurate

14 results 95 percent of the time --

15 MS. ENRIGHT: Yes.

16 DR. REJ: -- was calculated.

17 MS. ENRIGHT: Yes, I believe that was

18 based on a 95 percent confidence interval. I'd have

19 to get those --

20 DR. REJ: No, that says 95 percent of the

21 time.

22 MS. ENRIGHT: Yes. I think I'll have to

1 consult with Dr. Pasqua. And if I can get you that
2 answer later, and let me make sure how we did that
3 calculation, I'll get you that information.
4 CHAIRMAN NIPPER: Thank you, Dr. Rej.
5 In the interest of time, I'd like the
6 panel to take a -- can we take a 10-minute break? And
7 then we'll hear from the FDA when we have less
8 biological urgency.
9 Thank you everyone for bearing with us
10 while we got through this.
11 (Whereupon, the proceedings in the
12 foregoing matter went off the record at
13 12:06 p.m. and went back on the record at
14 12:22 p.m.)
15 CHAIRPERSON NIPPER: I would like to
16 introduce a person who needs no introduction, Arleen
17 Pinkos.
18 MS. PINKOS: I don't know about that.
19 CHAIRPERSON NIPPER: You've already been
20 here this morning, remember?
21 MS. PINKOS: As Dr. Nipper so humbly
22 introduced me, I'm Arleen Pinkos. I am one of the

1 reviewers in the Chemistry and Toxicology Branch and
2 the primary reviewer for this product. During the
3 next hour, we are going to have a number of speakers
4 for you. Unfortunately, because we don't share all
5 the slides back and forth before the presentation,
6 there is a little bit of overlap. We'll try not to
7 bore you too much.
8 Before I get into what we are going to be
9 talking about, I was asked to make a clarification on
10 the cholesterol product that was brought up earlier.
11 We did do a little bit of research. Back in 1995, we
12 did have a cholesterol product that came through for
13 review for over-the-counter. At that time, NCEP did
14 not outline goals for total error. They did, however,
15 outline goals for bias. That device did meet it, but
16 apparently since then, the total error that NCEP has
17 identified is beyond what that product was for. It
18 was okay when it prossed, passed by us, is all I can
19 say at this point.
20 In the first 10 minutes, I am going to
21 cover two main topics, a summary of the special
22 considerations given to over-the-counter products,

1 followed by an overview of some of the performance
2 studies. Next, Carol Benson, also a reviewer in the
3 Chemistry Branch, will present a summary of total
4 error calculations. Total error, as you all know, is
5 identified by NCEP as an important measure of device
6 performance.
7 Then, Dr. Irony, our statistician, will
8 summarize some observations from her review. She will
9 be followed by Dr. Ginsberg, who is a lipid expert.
10 He will be giving us a little bit of perspective about
11 over-the-counter triglyceride products and what's
12 going on there.
13 Then finally, I'll return back to the
14 podium to review some of the questions that we would
15 like you to cover during your deliberations.
16 I would also just like to mention that Dr.
17 Kimberly here has very nicely agreed that if we would
18 like her to, once we move into open discussion, if we
19 would like her to give her overview of CDC's lipid
20 standardization program, she is willing to do that.
21 Okay. When reviewing products, the
22 division considers whether the device will be used

1 professionally or whether it will be used by lay
2 users. The minimum performance thresholds for
3 granting marketing clearance are different for these
4 two devices because the people running the tests are
5 different, and the environments where they will be
6 used are different.
7 I will first describe the process by which
8 we clear a professional product, then go over some of
9 the special considerations given to over-the-counter
10 products. During the review of a 510 case submission,
11 FDA determines whether or not the device is
12 substantially equivalent to the predicate device. The
13 term "substantially equivalent" is not defined by law,
14 and the Division frequently grapples with determining
15 the appropriate standards by which to judge
16 equivalence. This question is particularly
17 problematic when there is no gold standard by which to
18 evaluate the device.
19 In general, the Division makes its
20 determination through analysis of the fundamental
21 performance parameters of the device, such as accuracy
22 and precision. The device is determined to be

1 equivalent if the performance characteristics are
2 roughly the same as those of the predicate device.
3 When deciding whether close is close enough, the
4 Division frequently allows more error in a device when
5 it's going to be used by professionals.
6 We do this because professionals are
7 trained to perform instrument procedures, including
8 maintenance and QC. They know how to interpret the
9 results. But perhaps more importantly, because they
10 understand the limitations of the test result and
11 because limitations can be adequately conveyed in
12 professional labeling.
13 Another important consideration is that
14 the test result is interpreted by a clinician, along
15 with other laboratory tests and the patient's clinical
16 signs and symptoms.
17 When the Division reviews an OTC product,
18 performance characteristics are still the primary
19 focus of equivalence of the equivalence determination.
20 However, because a device will be used by lay users,
21 additional considerations must be part of that
22 decision.

1 There are three primary areas of
2 consideration. First, the device should produce
3 clinically meaningful results when operated by the lay
4 user. Second, the results should be interpretable by
5 a lay user, consumers should be able to understand
6 what the results mean, and what to do with them.
7 Third, the potential benefit should outweigh the
8 possible risks.
9 I would like to spend a few minutes on
10 each of these three points. The lay user must be able
11 to generate clinically meaningful results using the
12 device. Those results should be comparable to those
13 obtained by professionals. Results must be reliable
14 enough to provide clinical benefit. As with
15 professional use devices, we are again faced with the
16 question of what is the appropriate minimum
17 performance threshold. How accurate must a test be?
18 In the case of this particular product, we
19 are lucky enough to have a reference point. NCEP has
20 identified performance goals for us, and we'll be
21 talking about those in more detail in a few minutes.
22 To assess whether results are clinically meaningful,

1 FDA suggests that accuracy and precision studies be
2 performed by lay users.
3 Lay users should be representative of the
4 population likely to purchase the device, and have a
5 wide variety of socio-economic and educational
6 backgrounds. FDA prefers that accuracy be measured
7 against an established reference methodology if one is
8 available.
9 These studies should be designed so as to
10 mimic the setting in which the device will be used.
11 For example, the consumer should only have access to
12 the package insert for instructions. The sample
13 collection procedure should be the same as what will
14 be done by the consumer. A finger sample should be
15 evaluated in the study if that is the sample type that
16 will be used by the consumer. This is important
17 because the Agency has observed that whole blood
18 samples generally don't perform as well as serum or
19 control materials.
20 Why is it so important to have the proper
21 studies performed? In short, because consumers play
22 a significant role in the quality of results that are

1 generated. Those results can vary significantly from
2 the results generated by professionals. There are
3 many factors that influence that end result.
4 Consumers receive no training and have no
5 oversight. They are not as experienced in performing
6 and interpreting tests. They generally do not
7 understand the importance of QC practices, using
8 proper technique or the need to follow directions
9 exactly. In most cases, consumers do not understand
10 the importance of proper reagent storage or performing
11 maintenance.
12 Evaluation of labeling is very important
13 in a consumer study. The consumer must be able to
14 read the package insert and know exactly what
15 functions to perform in order to maintain the system
16 and run the test. Labeling should clearly tell the
17 consumer what to do when they get certain results. A
18 good consumer study will evaluate the effects of all
19 these factors.
20 Test results must be easy for a lay user
21 to interpret. The reliability of an over-the-counter
22 product is very important. Consumers are making a

1 medical decision to act or not act based on a single
2 test result. Unlike their professional counterparts,
3 lay users do not have the benefit of other tests or
4 medical history upon which to base their decision.
5 Interpretation of results can also be complicated by
6 the fact that a test may have limitations that are
7 difficult for a lay user to understand, such as bias
8 or imprecision, or as we discussed earlier,
9 interfering substances.
10 The importance of labeling can not be
11 over-emphasized. The package insert is the only
12 source of information for the consumer concerning how
13 to perform the test, run and evaluate QC, properly
14 maintain the instrument, and understand what to do
15 with the test result. The Agency recommends a seventh
16 grade reading level for over-the-counter products.
17 Finally, our third consideration is
18 whether the benefits of the device outweigh the risks.
19 This question is a subjective one, but there are a few
20 key elements that are worth reviewing. What are the
21 benefits of having this test at home? Does the device
22 generate clinically-acceptable results? It may not be

1 necessary for a device to be perfect in order to
2 provide benefit to the user.
3 How likely is it for the consumer to get
4 an incorrect result? Are the test procedures simple,
5 without little likelihood of error? Finally, if a
6 consumer does get a wrong result, what will happen?
7 Will they not go to their physician or might they
8 adjust their medication on their own?
9 In conclusion, there are three
10 considerations that must be given to over-the-counter
11 products. Can a lay user reliably and consistently
12 generate a clinically-meaningful result? Did the
13 consumer accuracy and precision studies mimic actual
14 use? Is the result interpretable? Does the labeling
15 capture the meaning of the result, and what to do when
16 certain results are obtained. Finally, do the
17 benefits outweigh the risks?
18 Now I would like to move on to the second
19 half of my presentation, which is a brief overview of
20 the key performance studies that have been done.
21 That's not to say that there aren't other studies in
22 here. I think there were linearity studies that we

1 have already discussed.

2 One of the questions that you asked this

3 morning from the nurse's perspective is one that I

4 might just take a minute on, because there was some

5 discussion about it. That was the short sample

6 problem and the size of the drop. That was certainly

7 something that we're always concerned with, with whole

8 blood assays.

9 The sponsor's address to that is to

10 visually put a drop size or the circle size that's

11 adequate. You can certainly provide some input on

12 that. But they also did a short sample study where

13 they evaluated a sample and titered it down by adding

14 smaller and smaller and smaller drops, to see if the

15 short sample detection system was adequate.

16 What was found was that the short sample

17 mechanism was not as accurate as you would like it to

18 be. It was actually possible to get a result that was

19 half of what the true value was before the detection

20 system kicked in. That was one of the reasons why we

21 had them add as a final step to turn a strip over and

22 visually look at it to see if it looked like there was

1 a short sample. So whether that's an adequate
2 mechanism for over-the-counter products, you can
3 certainly weigh in on that.
4 Before I move into the performance
5 studies, I just wanted to present the performance
6 goals set by NCEP for triglycerides. Much of our
7 interactions with the sponsor have focused on
8 gathering information to characterize BioScanner's
9 performance in this area. I would like to mention
10 that NCEP recommends that accuracy of triglycerides be
11 characterized against CDC's reference method.
12 Although a direct method comparison to that method is
13 not possible, CDC does have a list of reference
14 laboratories that are standardized against the
15 reference method.
16 Okay. I would like to now present a brief
17 overview of the sponsor's three accuracy studies,
18 along with the resulting regression data. The first
19 study compares BioScanner's results from lay users to
20 results from serum samples run by the predicate
21 device. The predicate device, as we have discussed
22 earlier, was the Sigma reagent system run on an

1 autoanalyzer using serum samples. This study involved
2 381 samples.
3 The second study compares results from 47
4 serum samples analyzed by the Sigma method to results
5 from a laboratory standardized against the CDC
6 reference method, Pacific Biometrics.
7 Then the third study involved results from
8 fingerstick samples analyzed by lay users on the
9 Bioscanner compared to results from venus samples
10 analyzed by the same CDC standardized lab. That study
11 involved 220.
12 I know we have been talking about a lot of
13 different accuracy studies going back and forth, so
14 hopefully that will put a little bit of perspective on
15 that for you.
16 There have been three different types of
17 precision studies performed. The sponsor's precision
18 claim is a C.V. of five percent, or within 20
19 milligrams per deci-liter, whichever is greater.
20 NCEP's recommendation, you recall, was a precision of
21 less than or equal to five percent.
22 I am not going to dwell on any of the

1 charts that I am going to show you because they are in
2 your packets. Again, I only want to provide them as
3 a reference point for you.
4 The first study involves the only study
5 evaluating whole blood. The analysis was performed by
6 three lay users on two levels of EDTA collected
7 samples. This study was of particular interest
8 because the whole blood sample typically demonstrates
9 poorer precision than serum-based materials. The
10 within run data is here before you, separated into
11 three tables, with each table representing one
12 consumer. The only thing that I wanted to point out
13 to you on this table was that the C.V.s range from 1.7
14 to 8.8 percent.
15 The second study involves the analysis of
16 serum-based control materials by 20 consumers at three
17 sites. The three levels of control were run on the
18 same day. The only thing I want to bring out to your
19 attention is that the single point estimates for C.V.
20 range from 4.2 to 10 percent.
21 The third precision study involved
22 analysis of control materials by consumers. I have to

1 apologize because there was a little bit of
2 miscommunication about who ran this study. I think
3 the packets that were sent out to you indicated that
4 this study was run by professionals, as my slide does.
5 So can make those corrections. But it is indeed
6 control materials run by consumers.
7 This study is the only study where we had
8 total imprecision results generated. Again, the only
9 thing I wanted to point out were the single points of
10 estimates for C.V.s ranged from 3.2 to 10.6 percent.
11 The third and final area that I wanted to
12 touch on were the interference studies. The sponsor
13 identified two critical substances that interfere with
14 triglyceride measurements, ascorbic acid and elevated
15 hematocrit levels. The sponsor has also taken a
16 rather unique approach to characterizing the
17 interference from cholesterol. We would like you to
18 address that during your deliberations.
19 Any questions? Okay, then we'll have
20 Carol Benson come up.
21 CHAIRPERSON NIPPER: We'll hold questions
22 for Arleen and Carol and the other presenters until

1 the end. We may lay over until after lunch with a
2 little bit. After we assuage Dr. Rej's feelings of
3 being the last one, we'll start with him.
4 MS. BENSON: I'm Carol Benson. I will be
5 presenting the estimate for total analytical error for
6 the BioScanner triglyceride device. At this time, the
7 cholesterol reference method laboratory network,
8 otherwise known as the CRMLN, has no formal program in
9 place to provide a certification of traceability for
10 manufacturers of triglyceride devices like there is in
11 place for total, HDL, and LDL cholesterol. Therefore,
12 it is necessary to calculate the estimate of total
13 analytical error based upon the information supplied
14 by the manufacturer. The total analytical error takes
15 into account the inaccuracy and the imprecision of the
16 device.
17 The steps used to estimate the total
18 analytical error are as follows. Calculate the
19 percent bias at the NCEP cutpoints using the percent.
20 The equation percent bias equals the test value minus
21 the reference value divided by the reference times
22 100.

1 Use the coefficient of variation from the
2 precision study. Calculate the total error using the
3 equation, total error equals 1.96 times the total CV
4 plus the percent bias.
5 First, we calculate the bias at the NCEP
6 cutpoints using the regression equation from the
7 comparison study of the 220 samples. The results are
8 as follow. At 100 milligrams per deciliter, the bias
9 is minus eight percent. At 200 milligrams per
10 deciliter, the bias is -11.5 percent. At 400
11 milligrams per deciliter, the bias is -13 percent.
12 Next, we calculate the estimate of total
13 error using the C.V. from the different precision
14 studies that were submitted by the manufacturer. The
15 results are presented in different scenarios as
16 follows. Scenario number one is an estimate of total
17 error by using the C.V. from the precision study using
18 the control materials. As Arleen pointed out, that's
19 incorrect about the professionals. It was actually
20 performed by the consumers.
21 The results are as follows: at 100
22 milligrams per deciliter, the total error is about

1 28.8 percent. At 200 milligrams per deciliter, the
2 total error is 26.8 percent. At 400 milligrams per
3 deciliter, the total error is 22.1 percent.
4 The next two scenarios as estimates of the
5 total error using the within run C.V. from the
6 precision study in which the consumers tested the
7 whole blood at two concentrations of triglyceride, 189
8 milligrams per deciliter and 423 milligrams per
9 deciliter. These values are near the NCEP cutpoints.
10 The results are presented for the two
11 consumers who obtained the lowest within run CV and
12 the highest within run CV. Scenario number two is the
13 estimate for the total error for the consumer with the
14 lowest within run CV. At approximately 200 milligrams
15 per deciliter, the total error would be estimated to
16 be 14.8 percent. At approximately 400 milligrams per
17 deciliter, the total error would be estimated to be
18 24.6 percent.
19 Scenario number three is an estimate of
20 the total error for the consumer number one, with the
21 highest within run CV. At approximately 200
22 milligrams per deciliter, the total error is estimated

1 to be 26.8 percent. At 400 milligrams per deciliter,
2 the total error is estimated to be 30.5 percent.
3 In summary, we can say that the total
4 analytical error estimates using the total CV from the
5 precision study using control materials ranged from
6 22.1 percent to 28.8 percent. The total error
7 estimates using the lowest and the highest within run
8 CV using whole blood performed by the consumers ranged
9 from 14.8 percent to 24.6 percent for consumer number
10 three, and from 26.8 percent to 30.5 percent for
11 consumer number one.
12 CHAIRPERSON NIPPER: Thank you.
13 DR. IRONY: Hello. Can you hear me? I
14 need to use the computer, so I will speak from here,
15 if it's okay with everybody.
16 I am a statistician that's in charge of
17 reviewing this device. I will illustrate a little bit
18 what was talked up to here so we can have a deeper
19 understanding of what was going on.
20 For the precision studies, especially in
21 the consumer study, we had only three consumers. Each
22 consumer used two levels of whole blood. So these

1 were basically the results. As we can see here, there
2 is a huge variation because we are using only three
3 consumers. If we were using 10 consumers, we would
4 also encounter variation, but we'll be representing
5 better the population that will use this device.
6 For instance, if you look at the consumer
7 two and consumer three, they are measuring
8 approximately the same level, level 204 and 189. We
9 can say okay, these levels are close to 200 milligrams
10 per deciliter. But for one of the consumers, the
11 standard deviation was three, for the other one was
12 13.
13 What this tells us is that there is a high
14 variability and the point estimates are very crude.
15 We shouldn't use point estimates. The best way to do
16 it is to consider interval estimates.
17 So what we have here is the computation of
18 the interval estimates here. This tells us we have
19 more chance to get the right values when you use an
20 interval rather than using a point estimate. But
21 still, if you look at consumer two and consumer three
22 for the levels of triglycerides that are close enough,

1 we have two confidence intervals that don't even
2 overlap. So again, this reflects the high variability
3 on these measurements on only three consumers.
4 What will be the interpretation of this
5 random error? The interpretation is to follow. If we
6 really knew the standard deviation, if we had true
7 deviation there, 95 percent of measurements for the
8 consumer will be within 1.96 standard deviations from
9 the mean. That will be true only if we knew the
10 standard deviation. As I told you before, there is a
11 lot of uncertainty about the estimated standard
12 deviations from these particular studies.
13 So let's see what will happen if we will
14 get the upper levels of this confidence intervals.
15 Let's say consumer number two, for instance, mean
16 triglyceride measured was 204. The upper level of the
17 standard deviation was 38. What that means is we will
18 expect that 95 percent of the measurements taken by
19 consumer two will be below 240 milligrams per
20 deciliter, when in fact, it's mean was 204. This is
21 for only one consumer. This may vary a lot because
22 the population of consumers will vary.

1 So we have, as I said, a small sample.
2 This was a random error taken in a short period of
3 time. We had no data to estimate a day-to-day or a
4 long-run variation. That's it for the precision
5 studies.
6 Now I would like to talk a little bit
7 about the comparison of method study. We had 220
8 patients. We compared the measurements taken by the
9 BioScanner versus the CRMLN lab reference.
10 So it was performed a regression analysis,
11 and again, I like confidence intervals rather than
12 point estimates. So the point estimate for the slope
13 was .85, but at 95 percent confidence interval, was
14 between .81 and .90.
15 The intercept, the point estimate for it
16 was in this particular study, 7.2, but the confidence
17 interval was between -2.7 and 17.1. In this case, the
18 confidence interval for the intercept does encompass
19 zero. The slope does not encompass one. Just to
20 remind you, a perfect or ideal linear fit will be when
21 the slope was one and when the intercept was zero.
22 That will be the ideal. It never happens this way.

1 So the linear regression equation is given
2 by the this equation that I am writing on the bottom,
3 but that's again, this is the point estimate. So for
4 us to take a look and see how the regression was
5 behaving in this particular case, we can look at this.
6 This is the regression line, and this, the red line is
7 the regression line, and the points are actually the
8 measurements that were performed.
9 As we can see, there were like a few
10 points that will deserve further investigation. They
11 are far from the line. What we performed is also an
12 analysis of residuals. I will explain what a residual
13 is.
14 A residual in this case is the difference
15 between the actual measurement from the BioScanner
16 device, and the predicted measurement by the
17 regression line. So an ideal residual will be zero.
18 In other words, what you are estimating is actually
19 the right -- what you are measuring. This is zero.
20 So ideally, the residuals will be distributed evenly
21 around this line. As we can see, we have more
22 residuals that are negative, but the positive

1 residuals are larger. You have like three points, the
2 observation number 140 and 77 and 120 there,
3 particularly far from this line. The only thing we
4 can say is that image deserved for the investigation.
5 That is the distribution of the residuals.
6 The median residual was -5. That means 50
7 percent of the residuals were below -5. The maximum
8 residual was that one that's shown, the observational
9 number 140, and was 108. That means for that
10 particular case, the measurement given by the device
11 over estimated the regression line by 108.
12 Now as I told you, I like confidence
13 intervals. I don't like point estimates. So what we
14 did, we estimated the average systematic error or also
15 called bias, for the three decision levels, which are
16 100 milligrams per deciliter, 200 milligrams per
17 deciliter, and 400 milligrams per deciliter. In all
18 cases, what's happening is an under-estimation of the
19 values. For instance, for the case 400 milligrams per
20 deciliter, what was measured by the bias was actually
21 349, but the confidence interval would be between 339
22 and 359. That means that the estimated bias in this

1 particular case will be -51. If we build confidence
2 interval for the bias, it's going to be between -51
3 and -41. That's of particular point of interest
4 because it's a decision point. It's a point when
5 decisions are made.
6 Now it is very important to mention that
7 the regression method assumes no error in the
8 reference method. In other words, we are assuming
9 that the CRMLN lab is a measurement without error. In
10 case there is error in that measurement, the slope
11 could be attenuated, in other words, will be maybe
12 slightly smaller than what should be, using the
13 regression method.
14 As I mentioned before, an ideal linear fit
15 will be intercept zero and slope one. In this case,
16 the residuals are not evenly distributed, about zero,
17 we have more negative residuals than positive ones.
18 Our three positive residuals that deserve further
19 investigation.
20 As was mentioned before in this meeting,
21 we have lack of observations about the level 400
22 milligrams per deciliter, which is a very important

1 level because it's a decision level.

2 Now I used another method to estimate the
3 bias, which is called the Bland Altman method. What
4 is done, what it does is the following. We plot the
5 differences between the measurements done by the
6 BioScanner and by the reference, which is the CRMLN
7 lab. We plot these differences against the mean, the
8 mean between the BioScanner and CRMLN Lab, because in
9 fact, we don't know what is the actual level of
10 triglyceride. So we use the mean between both.

11 The redlines here, the red bars, they
12 indicate intervals within 15 percent of the mean. So
13 you can see the points here. Again, you can see from
14 this graph that we would need more points around the
15 level 400 milligrams per deciliter to evaluate the
16 device in a better way.

17 Now from these comparison of methods, we
18 can get the mean difference between the reference
19 method and the BioScanner. The mean is -21 milligrams
20 per deciliter. The standard deviation is 33
21 milligrams per deciliter. The median difference is
22 also negative, it's -25. The maximum positive

1 difference is +95. The maximum negative difference is
2 -92 milligrams per deciliter.
3 The distribution of the differences. This
4 is a histogram. You can tell from the histogram then
5 you have more negative differences than positive
6 differences. In fact, we have 75 percent of the
7 differences are negative, and 25 percent are positive.
8 That concludes my presentation.
9 CHAIRPERSON NIPPER: By that last
10 statement, you don't mean that there's 75 percent of
11 the observations, there's no difference? You mean 75
12 percent of the differences show a negative bias.
13 Right?
14 DR. IRONY: Right. That's what I meant.
15 CHAIRPERSON NIPPER: Thank you.
16 Holding questions, leaving some time for
17 our next speaker, we are delighted to have Dr. Henry
18 Ginsberg. We appreciate his coming to talk to us.
19 The floor is yours Dr. Ginsberg.
20 DR. GINSBERG: Thank you. I was asked in
21 my view, to give an overview of triglycerides, a
22 little bit about metabolism, and their role as a risk

1 factor. You have heard much of my talk already. Dr.
2 D. gave a very nice presentation. The slides are very
3 similar, so I'll move through my presentation focusing
4 on issues that I think, I believe are relevant to the
5 presentations today. Maybe we'll get more out of the
6 question and answer period than the presentation
7 itself.
8 I thought I would start off, and I didn't
9 know the range of expertise of the panelists, to make
10 a quick point about the fact that we are always
11 interested in cholesterol and triglyceride, and we
12 talk about them together all the time. They are
13 totally different molecules, other than the fact they
14 are both lipid or organic soluble.
15 This is important for the discussion today
16 in the sense that cholesterol, being a component of
17 all the cell membranes of the body and being used to
18 make hormones and bile, is a very stable measurement
19 in plasma. Total blood cholesterol or serum
20 cholesterol, I think, under ideal conditions of
21 constant diet and activity, the day-to-day variability
22 is about five percent of that measurement, so it's

1 probably somewhat higher than that in real life.
2 Again, the body regulates synthesis versus intake.
3 These membranes are turning over very slowly.
4 In contrast, triglyceride is energy. That
5 is all we use it for. We burn it. We burn the fatty
6 acids to C02 and water, or we store the fatty acids on
7 a glycerol backbone as triglyceride in our fat cells.
8 For that reason, what we move through the blood stream
9 on a day-to-day basis varies much more. Day-to-day
10 variability under fairly controlled situations is
11 about 25 percent. In fact, in studies where you are
12 using a drug or a diet or any other intervention and
13 you are looking at changes in triglyceride, you need
14 a minimum of three measurements over some period of
15 time before or after the pertibation to minimize
16 biologic variability in order to gain the statistical
17 power.
18 The reason that we talk about triglyceride
19 and cholesterol together is because they are both
20 insoluble in plasma, and nature therefore gave us
21 lipoproteins. So we have the triglyceride and the
22 major form of cholesterol, cholesterol esta with a

1 fatty acid attached, in the core of the lipoprotein
2 particle. Those two would not be able to move through
3 the plasma as naked molecules. So they are wrapped up
4 on a phospholipid coating with one or more proteins.
5 The protein is called apoproteins, are key to the
6 function and the sites of delivery of the
7 lipoproteins. They also determine really whether they
8 are atherogenic or anti-atherogenic.
9 The two lipoproteins that we are
10 interested in talking about today are the triglyceride
11 rich lipoproteins, the first being the chylomicron,
12 described as really a fat drop. I call it an oil
13 droplet. The reason that the chylomicron is an oil
14 droplet is that it carries what we have eaten in terms
15 of cholesterol and triglyceride.
16 In an average day, someone eating an
17 average American diet is eating about 40 to 70 grams
18 of fat. They are only eating possibly 300 to 500
19 milligrams of cholesterol. Even when you add in the
20 cholesterol secreted in the bile, we still -- orders
21 of magnitude, many orders of magnitude differences in
22 amount of triglyceride is being absorbed from the gut

1 versus cholesterol.

2 So we have a lipoprotein that is 95
3 percent or so triglyceride by weight. Tens of
4 thousands of triglyceride molecules, in fact, and
5 maybe hundreds of cholesterol esta molecules, and then
6 the coating that is phospholipid in protein.

7 So we have the gut making the
8 chylomicrons. They are secreted into the lymph. They
9 enter the bloodstream. They really have two
10 functions. They are to deliver the energy we have
11 eaten to fat cells and to muscle cells. Fat cells for
12 storage, and muscle cells for utilization. They do so
13 by traversing the circulation in the capillary beds of
14 fat and muscle. They meet up with an enzyme,
15 lipoprotein lipase, which can get into the core and
16 lipolyse, hydrolyze the triglyceride. The fatty acids
17 can be released and they are taken up by the
18 appropriate cells, the atopocytes or the misocytes in
19 the muscle, and utilized.

20 What's left is what we call a chylomicron
21 remnant. It still has the cholesterol it started out
22 with, but has lost, if you're efficient at this

1 lipolysis step, lost about 80 percent of the
2 triglyceride. This particle really heads to the
3 liver. Most of these remnants are taken up by the
4 liver, where they really I think tell the liver what
5 dietary cholesterol intake has been, so the liver then
6 can regulate its own synthesis of cholesterol. That's
7 what happens.
8 Now this process is one in which because
9 there's only milligrams of cholesterol being eaten,
10 there's really very little change in total cholesterol
11 throughout the day. So not only on a day-to-day
12 basis, but even over a 24-hour basis, total
13 cholesterol doesn't really change significantly.
14 On the other hand, triglycerides can go up
15 by folds in different people, depending on how much
16 fat they have eaten, because they are taking in many,
17 many grams of triglyceride in a meal. The level, the
18 rise in triglyceride and the duration of that rise
19 depends on a number of factors. It depends on
20 obviously how much fat you have eaten. Then it
21 depends on the efficiency of the lipoprotein lipase
22 step. In diabetics and in many, many people with

1 hyper triglyceridemia, there are partial defects, sub-
2 optimal levels of protein or activity of the protein,
3 lipoprotein lipase. There are other factors that play
4 into the efficiency of this first step.
5 In general, if someone has a fasting
6 triglyceride of 50 to 100, and they eat a meal with
7 let's say 20 grams of fat, their triglyceride might go
8 up to 100 or 150 milligrams per deciliter at the peak.
9 They would be back down to baseline within three to
10 four hours. If someone starts at 250 to 300, and they
11 eat that 20 grams of fat, they may go up to 600, 800,
12 even 1,000. They may not come back down to baseline
13 for 10 to 12 or even 14 hours.
14 So you do have this tremendous variability
15 in the postprandial state. In fact, before coming
16 here today, and not really having much of the
17 information about the product, I thought off hand that
18 this utility of this product would be to have people
19 see what happens to themselves after they eat a meal,
20 and that it might have some influence on compliance
21 with a low-fat diet, because those changes would be
22 much more dramatic than what people might see after a

1 few days on a diet and looking at their fasting
2 levels. I can get back to that.
3 I was a little disappointed with the fact
4 that the method seems to be calibrated in linear up to
5 about 500. But clearly, people could see if they were
6 up over that limit, they could see differences. Since
7 we would be dealing with big differences in the
8 patient population of interests, that might be a
9 utility of looking, having people -- and I'm not
10 thinking of people doing this every day, but at least
11 during a diet change and diet instruction period.
12 There is a specific disorder that has two
13 genetic bases. It's called Type 1,
14 hyperlipoproteinemia. Either people are missing the
15 lipoprotein lipase, and so they never break down the
16 triglyceride and make the remnant, or they are missing
17 a protein called apo C2, which is a necessary
18 activator of lipase.
19 In either case, after these people eat a
20 meal, whatever fat they have taken in sits around for
21 very, very long periods of time. Clinically, these
22 people have platosplenomegoly, because the way they

1 get rid of the chylomicrons is actually to phagatacize
2 them into macrophages in the spleen and the
3 macrophages in the liver, the cutfer cells.
4 They get these eruptors anthromas because
5 they actually get triglyceride levels in the many
6 thousands. Some of them run 10,000 triglycerides.
7 They actually get collections of chylomicrons that
8 block capillaries in the skin and burst those
9 capillaries. You get achnea form eruptions. You can
10 actually see, if you look in their retina, you see
11 tomato soup or yellow looking blood vessels. If you
12 draw their blood, it looks like cream of tomato soup
13 within minutes, very frequently.
14 So these people have this complex of
15 signs, but it's clinically relevant because they get
16 pancreatitis. We don't know exactly why they get
17 pancreatitis because all these lipoproteins are much
18 smaller than red cells. But they probably when they
19 have triglycerides in the thousands and they are
20 mostly lipoprotiens, they act -- chylomicrons is
21 probably an aggregation or a fusion of the
22 chylomicrons. Then they can be large enough to cause

1 capillary occlusions. You get some microinfarks, and
2 you get pancreatitis.
3 So another potential utility I thought of
4 this over-the-counter home-use triglyceride would be
5 in this very small population of people, maybe one in
6 100,000, who run triglycerides over 1,000, and who
7 might be able to know when they are getting close,
8 that is about the point where the pancreatitis risk
9 goes up, certainly over 2,000. But again, that would
10 be -- that's clearly limited by the methodology. I
11 don't know then if even if this small population would
12 be helped if they knew they were over 500 or not
13 because they are almost always, even on the strictest
14 lowfat diet, they tend to run triglycerides of 500 to
15 1,000.
16 Now the chylomicrons themselves are not
17 thought to be atherogenic, but the chylomicron
18 remnants are. Chylomicron remnants accumulate in many
19 people for a number of reasons, in part probably
20 because there's less then optimal lipoprotein lipase.
21 Even though I classify the remnant as coming after the
22 lipolysis step, there is a lot of overlap between

1 those two classes.

2 There are also other defects at the site

3 of the liver in terms of remnant removal, that can

4 lead to the accumulation of these remnants. In

5 diabetics and in anyone with hyper triglyceridemia, at

6 baseline and a low HDL, you will get prolonged post

7 perandial lipemia and a lot of those particles will be

8 chylomicrons, but a lot will be the remnants.

9 This is a study done in rabbits, but it

10 has been proven in humans now to be relevant, that if

11 you take rabbits and feed them a high cholesterol

12 diet, they get cholesterols in the thousands. A lot

13 of these particles are the remnants. These remnants

14 get into the vessel wall. This is rabbit aorta

15 stained for lipids, showing atherosclerosis. Then

16 some of these rabbits, blood was taken. The remnants

17 were isolated and radio-ionated, injected into other

18 rabbits. They were sacrificed. The aortas were taken

19 out and stained, but they were also slapped on an x-

20 ray film. An autoradiograph showed that the ionated

21 remnant was getting right into the vessel wall.

22 Now from human studies, we have been able

1 to isolate very low density lipoproteins, which I'll
2 address in a moment, and chylomicron remnant-like
3 particles from the coronary arteries of individuals
4 undergoing bypass surgery. So it's not just LDL that
5 gets into the vessel wall. It clearly is remnants of
6 chylomicrons, remnants of VLDL, and probably even
7 VLDL. So these triglyceride rich lipoproteins are
8 atherogenic.
9 This is a study showing one of many
10 studies showing that post perandial lipemia, the rise
11 of triglycerides after a meal is higher in people with
12 coronary disease. This was a case control study of
13 men undergoing angiograms, and divided into those with
14 more or less than 50 percent stenosis in one vessel.
15 Those designated as cases had higher triglyceride
16 levels, whether or not they were uncorrected or
17 corrected for starting levels. So again, knowing post
18 parandial triglycerides might be helpful, in other
19 words.
20 Having said that, I would point out that
21 the correlation between the fasting triglyceride and
22 the post parandial peak is about .7 in all the large

1 studies that have been done. You can guess to a fair
2 degree, about a 50 percent accuracy I guess, of who
3 will have a high post parandial triglyceride. But
4 there are people who have low HDL and who maintain a
5 low fasting triglyceride by being active and being
6 thin, but who are unmasked when they eat a fat meal,
7 and have much higher triglycerides. They probably
8 have lipoprotein lipase problems.
9 So in terms of a screening of the
10 population, just as we like to screen for cholesterol
11 and for fasting triglycerides and HDL, doing a post
12 parandial triglyceride or a non-fasting triglyceride,
13 you will pick up some people who will probably be at
14 risk for coronary disease. Therefore, it should have
15 further screenings on them. Most of them will have,
16 or certainly almost all of them will have a low HDL as
17 well.
18 Now the very low density lipoprotein is
19 sort of the mirror image of the chylomicron except
20 it's not related to the intestine or to dietary energy
21 intake. It is related to endogenous energy balance.
22 So the VLDL is about 70 percent triglyceride, and

1 about 20 percent -- 15 percent cholesterol with the
2 coating phyospholipidem protein.
3 It's coming from the liver, but it has
4 again, a very parallel pathway of metabolism. The
5 first role of the VLDL is the liver energy in the form
6 of triglyceride, the fat and muscle. That energy now
7 is coming from the liver. It does so by interacting
8 with lipoprotein lipase in those same capillary beds.
9 The importance here is that very low density
10 lipoproteins and chylomicrons are competing for the
11 same lipoprotein lipase pathway. So if you start out
12 with excess fasting triglycerides and you eat fat, you
13 are just going to make it more difficult for your
14 lipase to handle the chylomicron triglyceride load.
15 After this step, you end up with a VLDL
16 remnant. I have already told you that that certainly
17 is an atherogenic particle. A lot of this VLDL
18 remnant goes back to the liver, just like the chylo
19 remnant did, but in addition and unlike the
20 chylomicron remnant, the VLDL remnant can be further
21 modified to become low density lipoprotein.
22 The vast majority of insulin-resistant

1 diabetic patients and the vast majority of people who
2 are just hyper triglyceridemia, hyper triglyceridemic,
3 make too many VLDL in their livers, put out too many
4 VLDL, overcome the capacity of lipase, have higher
5 triglycerides. Then you could also see they are going
6 to make more remnants sooner or later, and they are
7 liable to make more low density lipoproteins as well.
8 The common causes of hypertriglyceridemia
9 Type 2 diabetes, probably the most common cause, plus
10 insulin resistance, and I'll show you a slide a little
11 later to point that out, the mechanisms, very badly
12 controlled Type 1 diabetics can have
13 hypertriglyceridemia. They will both over produce.
14 Lipoprotein lipase is an insulin-sensitive or insulin
15 regulated enzyme. So both the Type 2s and the Type 1s
16 who are not well controlled will have somewhat
17 decreased lipoprotein lipase.
18 Excess energy. Any time we are in excess
19 energy balance, we'll make triglycerides out of
20 anything that's around. We'll do that in our liver,
21 and we'll send out the triglycerides for storage on
22 VLDL. So those are the major. Obviously everything

1 is genetic. The genetics confound the energy excess
2 of obesity, and the various non-insulin resistance
3 genes will confound the effect of insulin resistance.
4 You already saw that hypertriglyceridemia
5 is associated with other risk factors. I have
6 mentioned chylomicron remnants and VLDL remnants.
7 There's also low HDL cholesterol levels, and these
8 "atherogenic" small dense LDL.
9 I would just put this into a quick scheme
10 for you. In the insulin-resistant or diabetic
11 patient, there are increased levels of free fatty
12 acids in the bloodstream because instead of storing
13 energy efficiently in fat, the fat cells are
14 constantly breaking down their own triglyceride and
15 releasing fatty acids. They get to the liver where
16 they liver doesn't need them for energy, puts them
17 back into a triglyceride molecule, which stimulates
18 the assembly and secretion of the VLDL, so you have
19 hypertriglyceridemia. How high, well that's dependent
20 on a number of other genes, but let's say anywhere
21 from 150 to 500 in the average insulin resistant
22 and/or Type 2 diabetic patient.

1 Once you have high triglycerides, you will
2 have a low HDL cholesterol because cholesterol from
3 HDL will move into the VLDL and exchange for
4 triglyceride. There is a protein called cholesterol
5 that's the transfer protein, that mediates that step.
6 You will also have a small dense LDL
7 because cholesterol from LDL can move back into its
8 precursor VLDL in exchange for triglyceride. That
9 triglyceride can be acted upon by lipase's shrinking
10 the LDL. So these three -- and they are all probably
11 atherogenic states. These are atherogenic particles.
12 These are at least, if not more atherogenic than
13 normal LDL, and a low HDL is probably an important --
14 a loss of anti-atherogenic potential of HDL in terms
15 of either anti-oxidant activity in the vessel wall or
16 clearing cholesterol out of the extra cellular space
17 in the vessel wall and bringing it back to the liver.
18 What's the evidence? You have seen, as
19 I'll move real quickly, certainly in epidemiologic
20 studies like the Paris perspective study, this is a
21 German study in Munster called the pro-cam study.
22 Triglycerides are important, particularly when LDL

1 cholesterol is high or HDL is low.

2 You saw the Copenhagen study. Important
3 data that in a multivariate analysis, there was still
4 at least in a tertile calculation evaluation, there
5 was still a doubling of risks which was significant
6 between the lowest and highest tertiles.

7 This is a biograph showing the results of
8 a multivariate analysis done in many, many studies,
9 with 46,000 men and 10,000 women. This is a
10 univariate analysis showing that a rise in
11 triglyceride of 90 milligrams per deciliter increased
12 risk in men by 30 percent, and in women by 75 percent.

13 When they did a multivariate analysis
14 here, and a lot of us think they are not that useful
15 because triglycerides in HDL and triglycerides in LDL
16 are linked in a variety of complicated ways, this
17 dropped to 15 percent, but was still significant.
18 This was significant at 35 percent. So triglyceride,
19 even in this complex mathematical analysis, with
20 enough power stands out as adding prediction for risk.

21 Again, what about intervention trials? Is
22 it important to know your triglyceride and lower it?

1 Well, in the Helsinki heart study, as you heard, the
2 majority of the benefit came from lowering
3 triglyceride in the group that hyper triglyceridemia
4 above 200 and a bad LDL to HDL ratio. This is the
5 placebo group, and this is the treatment group.
6 Treatment in the rest of the groups was
7 not significant in this study. That doesn't mean it's
8 not important, that this people didn't have lipid
9 disorders. All the power was here because this was
10 the worst group in the placebo group.
11 Finally, just two or three quick slides on
12 a study that was published in July in the New England
13 Journal. Again, you saw one slide, the VA Hit study,
14 which comes as close as we have to a study where not
15 changing LDL and starting with an LDL that was normal
16 to begin with was associated with benefits.
17 So this was a study focused on secondary
18 prevention, men who had had events, who would have low
19 HDL, normal LDLs, and moderate triglyceride levels.
20 They actually had HDLs of 32, triglycerides of 161,
21 which would not usually be considered high. An LDL of
22 111, which probably wouldn't be treated in most

1 offices, even if a man or woman had an MI already,
2 that's close enough to the goal in most instances that
3 people wouldn't treat that.
4 Yet when they would treat it with
5 gemfibrosel or placebo for five years, HDL went up
6 seven percent. Triglyceride dropped 25 percent. No
7 change in LDL, and a 22 percent reduction in events,
8 MI, and non-fatal and fatal CHD events, at 27 percent
9 reduction in stroke.
10 If you look at these data, getting into
11 the epidemiology, you cannot explain all the benefit
12 from the rise in HDL, not based on the epidemiologic
13 data that's been looked at. Therefore, you would have
14 to assume, I think, that triglycerides falling had
15 some independent effect and/or this change in size in
16 LDL that probably occurred would have some independent
17 effect. There are also data being presented at the
18 Heart Association next month indicating that the level
19 of remnants in these patients was predictive, and it
20 dropped during treatment with gemfibrosel.
21 So those are my slides. I would think
22 that -- I talked a little bit about the utility of an

1 over-the-counter device for post-parandial. For the
2 rare patient with several hypertriglyceridemia, I
3 think it falls a little short in the latter. I think
4 certainly to increase people's self knowledge and self
5 empowerment is always good. I think that allowing
6 people to screen themselves with an over-the-counter
7 device if they haven't been to their doctor and get a
8 triglyceride, particularly a non-fasting one, might
9 send more people to their physicians for appropriate
10 follow-up and fasting screening, et cetera.
11 I think the day-to-day biological
12 variability is a big problem here. If you add that to
13 test variabilities, I think there is the conundrum to
14 me, because most interventions for triglyceride, diet,
15 weight loss, exercise, even drugs that we use, lower
16 triglyceride in the range of 15 to maybe 40 percent.
17 I'm not sure what people -- will happen if somebody
18 goes on a diet for a couple of weeks, and because of
19 biologic variability and test variability, they look
20 worse or no different.
21 We have had that problem with cholesterol
22 tests with modest interventions. Before the Statons

1 were there, huge ability to lower LDL cholesterol,
2 physicians and the public were not convinced that many
3 of the things we could do for cholesterol were really
4 happening because measurement variability and
5 biological variability clouded that issue.
6 So I think I'll stop. I will be happy to
7 take questions with everyone else.
8 CHAIRPERSON NIPPER: Dr. Ginsberg, we
9 appreciate your presentation. We hope that -- will
10 you be able to stay after lunch to take questions?
11 DR. GINSBERG: For a while.
12 CHAIRPERSON NIPPER: Okay. Because we are
13 about half an hour beyond the schedule for lunch. I'm
14 sure it's sitting there. I'm sure that we'll all need
15 to replenish our triglycerides, particularly from the
16 potato chips.
17 If there is a member of the panel who has
18 a pressing question for Dr. Ginsberg before he leaves
19 the podium, now may be the time to ask it.
20 Dr. Doumas?
21 DR. DOUMAS: I have two quick questions,
22 Dr. Ginsberg. In view of the very high intra-

1 individual coefficient of variation, which is about 22
2 to 23 percent, do you feel that accuracy is more
3 important than precision in the measurement of
4 triglyceride?
5 DR. GINSBERG: Gee, that's a -- I mean if
6 I was -- no. I would think -- I think obviously they
7 are very separate issues. I am trying to quickly put
8 them into their appropriate places.
9 If I was testing my triglyceride at home,
10 and I wanted to know if what I was doing was helping,
11 then I would want precision. Right? So that I would
12 know that if I went up or down. Whereas if I wanted
13 to know what I was, certainly the first time, then I
14 would want accuracy.
15 So I think they are obviously both -- if
16 I had, for instance, if I have a triglyceride that's
17 truly 200, but it can either be 150 or 250, that
18 doesn't help me. If I do something and I go from 300
19 to 200, I also need precision there. So I am not sure
20 I can give you an answer which I would pick.
21 DR. DOUMAS: I'll follow up with the
22 second question, the same vein. In view again of the

1 very high coefficient, intra-individual coefficient of
2 variation, if you increase the random error, first of
3 all if you decrease the random error to zero percent,
4 or you from five percent to ten percent, the total
5 variability is hardly affected because we see the
6 total square is equal to the square of the analytical
7 plus the biological CV square.
8 When you have 23 square and five percent
9 square, that five percent doesn't alter the total
10 square root. I mean it alters very little.
11 I have something from a paper published by
12 Cooper, Jerry Cooper. It was published in Clinical
13 Chemistry, showing what the effect is really of the
14 random error on the total variability of triglyceride
15 measurement.
16 This is the reason I asked the first
17 question, is accuracy more important than precision,
18 than decreasing the analytical error.
19 DR. GINSBERG: I think in general, yes.
20 Again, it's difficult. If we do studies and we have
21 something that we expect to change, we do a multi-
22 center study and we have each of the centers doing the

1 TG at their own place, we want precision. Right? If
2 we're looking for delta, people have a little bias
3 with statistics. But in real life, when a patient is
4 looking at the number, I guess you would want
5 accuracy.
6 CHAIRPERSON NIPPER: Thank you very much.
7 We'll reassemble in about an hour. We appreciate the
8 FDA's presentation and the sponsor's presentation. We
9 will go chew on it a little bit.
10 (Whereupon, the foregoing matter went off
11 the record for lunch at 1:24 p.m. and
12 went back on the record at 2:26 p.m.)
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1 A-F-T-E-R-N-O-O-N P-R-O-C-E-E-D-I-N-G-S

2 (2:26 p.m.)

3 CHAIRPERSON NIPPER: We know that Dr.

4 Ginsberg has a plane to catch. We appreciate him

5 staying over the lunch hour to catch some questions.

6 So when we start with Dr. Rej and we go around the

7 panel, if we could concentrate our laser beams on Dr.

8 Ginsberg and let him get out of here, I think it would

9 be very helpful to him.

10 MS. PINKOS: Do you want to do that before

11 the questions?

12 CHAIRPERSON NIPPER: That's what we are

13 doing about questions. We have already heard from Dr.

14 Ginsberg's lecture, but we needed to do questions. So

15 I am sure that the panel has some questions for him.

16 Dr. Rej?

17 DR. REJ: It's always so hard to go first.

18 (Laughter.)

19 DR. REJ: Thank you, Dr. Ginsberg, for

20 your presentation. In your presentation, you, if I

21 quote you correctly, you said that it doesn't help you

22 very much -- you can't tell the difference between 150

1 and 250. Is that correct? Because 200 plus or minus
2 50 milligrams per deciliter?
3 DR. GINSBERG: When I was asked the
4 question about accuracy versus precision.
5 DR. REJ: Well, in terms that that 150
6 could equal 250, would not be helpful to you.
7 DR. GINSBERG: I think that there are two
8 issues. One, if you are working with methods that
9 even if you are working with precise methods, but the
10 intervention is modest, then biologic variability can
11 really be a detriment. We have all had, those of us
12 in the field have had patients who we have put on
13 diets. They can drop their cholesterol 10 percent on
14 a diet. They come back two months later, they have
15 been working really hard, and their cholesterol may be
16 a few points higher than it was previously, because
17 the lab happened to be on the high side and their
18 biologic variability was on that high side that day.
19 That is not helpful.
20 So on the other hand, triglycerides are.
21 Usually you can get bigger changes with things like
22 diet and exercise. So you have a wider window. But

1 obviously you need accuracy still. If someone was 200
2 and I had sent them home and I told them to really
3 work hard on diet, and they came in and they had lost
4 five pounds and they were truly biologically 150, but
5 because of a bunch of errors in biologic variability,
6 they were still 200, then I have to deal with that as
7 a physician.
8 DR. REJ: Right. Okay, well that goes to
9 the point of the question. That if you follow the
10 NCEP guidelines, then that basically for that same 200
11 milligram deciliter triglyceride, basically 170 equals
12 230. If you allow a total error of 30 percent, which
13 was one of the models that we saw today, then 140
14 equals 260. You gave the example of 150 equals 250,
15 if you have plus or minus 50 milligrams per deciliter
16 total error. I was wondering if you could comment on
17 the NCEP recommendations, which is something this
18 panel is going to have to get to, and how does that
19 fit into a total error budget for triglyceride
20 measurements. Is that one, realistic, and two, is it
21 clinically useful?
22 DR. GINSBERG: I'm not sure how to answer.

1 I mean I think the NCEP guidelines are outdated for
2 triglycerides. I would agree with what Dr. Deeg said
3 on that. I think that the ATP-3 is meeting, or will
4 meet soon. I think they will be changing those.
5 I think to say that 200 to 400 is
6 borderline is not appropriate any more.
7 DR. REJ: Okay. I am sorry. I was
8 referring particularly to the NCEP guidelines for the
9 measurement of triglycerides, not so much the cut-
10 point recommendations, but the total error of 15
11 percent and the bias, a bias factor of less than five
12 percent.
13 DR. GINSBERG: I think that you have to be
14 close to that, for any method to be valuable for
15 feedback. Because of the biologic variability. I
16 think you have to be close to that. Wet laboratories
17 have one percent, two percent TG coefficients or
18 variations. We need that because of the biologic
19 variability. So I think NCEP guidelines are
20 appropriate.
21 DR. REJ: Thank you.
22 I have some other questions, but they are

1 not for Dr. Ginsberg.

2 CHAIRPERSON NIPPER: Let's just hold those

3 until we let him catch his shuttle.

4 Dr. Everett, why don't we just proceed on

5 around the room for questions for Dr. Ginsberg, if you

6 don't mind.

7 DR. EVERETT: My questions deal with

8 again, whether this test works. But if you get beyond

9 that, how do you perceive that this test could be used

10 so that physicians will get maximum benefit? That is

11 the part I struggle with at the moment.

12 DR. GINSBERG: Well, I mean I don't see it

13 as a glucose home monitoring in a Type 1, obviously,

14 where people are changing their treatment every day,

15 if we are really going for optimal control. If you

16 look at glucose monitoring in Type 2s, they don't

17 really change their treatment most of the time on a

18 day-to-day or even few day, but they gather data that

19 lets them know where they are. It would fall closer,

20 certainly on that side of the range of utility.

21 But I would think that as I said, it might

22 have utility if I put a patient on a diet and they