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U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION
CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEETING OF THE
CLINICAL CHEMISTRY AND CLINICAL
TOXICOLOGY DEVICES PANEL
OF THE
MEDICAL DEVICES ADVISORY COMMITTEE

* * * *

Monday, October 29, 2001

8:08 a.m.

Gaithersburg Hilton
620 Perry Parkway
Gaithersburg, Maryland

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P R O C E E D I N G S

Call to Order

DR. KROLL: Good morning, everyone.

I would like to call to order this panel meeting. My name is Martin Kroll, and I am the panel chair.

To begin with, what I'd like to do is have Dr. Bernard Statland, who is Director of the Office of Device Evaluation, give us some opening remarks.

Opening Remarks

DR. STATLAND: Good morning.

This meeting was originally to take place a little more than a month ago, and because of the tragedy of the 11th of September, we decided, and I think appropriately so, to postpone it.

I think it is also very poignant that we did not cancel this meeting; we merely extended the date on which it should take place because of the importance of the topic that we are going to talk about today.

I first of all would like to thank all the people who have participated in putting this meeting together, to the panelists and experts who have come here to give of their time, their knowledge, and their expertise, and to everyone

1 here in this room.

2 I would like to start out by saying that
3 there are four things that I believe we all agree
4 to, and there are certain things we disagree on.

5 The first point that we agree on is that
6 diabetes and the management of diabetes is a
7 significant public health problem in our country
8 and throughout the world.

9 The second point that we all agree on is
10 that patient self-testing of blood glucose has
11 played a very important role in the management of
12 diabetes and more than likely in the prevention or
13 at least amelioration of tertiary consequences of
14 this disease.

15 The third point that I think we agree to
16 is that patient blood glucose values should be
17 accurate, should be accessible, and should be as
18 painless as possible.

19 Any problem meeting any one of these three
20 objectives will call into place the type of testing
21 that is being considered.

22 And the fourth point that it appears we
23 agree to is that alternative site testing has in
24 fact led to decreased pain on the part of the
25 patient.

1 There are some things that we do not have
2 a complete consensus on, and that point is whether
3 or not alternative site testing is as accurate as
4 it needs to be for patient evaluation of their
5 particular issue.

6 One thing I'd like to do, even though I
7 have a very short presentation, is I'd like to
8 compare two philosophers--Plato and Aristotle. I
9 like the Greeks, and I like the Greek philosophers.

10 There was a debate--probably apocryphal--
11 between these two philosophers on the number of
12 teeth that a horse has. Plato said based upon
13 logic, based upon perspective, the number must be
14 32.

15 Aristotle said I'm not sure if it's 32 or
16 28, but there is one thing for sure--the best thing
17 to do is open the horse's mouth and count the
18 teeth.

19 Well, today, we have a debate as to what
20 is the analytic performance and clinical
21 appropriateness of alternate site glucose, and
22 today, we are going to "count the teeth," or in
23 this situation, we are going to look at the data.

24 The last word that I would like to say is
25 that under Dr. Feigal's leadership, CDRH has been

1 very tuned into looking at the internal science of
2 what we are doing within our Center, and the basis
3 of this is that the facts and the information and
4 the science will prevail.

5 Today's meeting really begins to approach
6 this issue. We are going to look at the
7 information, we are going to look at the facts, we
8 are going to see if we can come to appropriate
9 conclusion.

10 Last but not least, I would like to end as
11 I began. It is a real tribute to what we are doing
12 in this country and certainly to what we are doing
13 in the FDA that we bring people together with
14 varying interests, with different types of
15 expertise, and different perspectives. We share
16 information in an open and deliberate manner, and
17 hopefully, by the end of the day, we'll find out
18 how many teeth reside in the horse's mouth.

19 Thank you very much.

20 **Conflict of Interest Statement**

21 MS. CALVIN: Good morning. I will read
22 the Conflict of Interest Statement.

23 "The following announcement addresses
24 conflict of interest issues associated with this
25 meeting and is made part of the record to preclude

1 even the appearance of an impropriety."

2 "To determine if any conflict existed, the
3 Agency reviewed the submitted agenda and all
4 financial interests reported by the Committee
5 participants. The conflict of interest statutes
6 prohibit Special Government Employees from
7 participating in matters that could affect their or
8 their employers' financial interests. However, the
9 Agency has determined that participation of certain
10 members and consultants, the need for whose
11 services outweighs the potential conflict of
12 interest involved, is in the best interest of the
13 Government."

14 "Therefore, a waiver has been granted for
15 Ms. Davida Kruger for her financial interests in a
16 firm at issue that could be potentially affected by
17 the Panel's recommendations. The waiver allows
18 this individual to participate in today's
19 discussion. A copy of this waiver may be obtained
20 from the Agency's Freedom of Information Office,
21 Room 12A-15 of the Parklawn Building."

22 "We would like to note for the record that
23 the Agency took into consideration other matters
24 regarding Drs. Martin Kroll and Arlan Rosenbloom.
25 These individuals reported past and/or current

1 interests in firms at issue, but in matters that
2 are not related to today's agenda."

3 "The Agency has determined, therefore,
4 that they may participate in the panel
5 deliberations."

6 "Dr. Jose Cara reported past interest in
7 firms at issue for matters related to today's
8 discussions. Since the agenda involves only
9 general matters, the Agency has determined that he
10 may participate in the discussion."

11 "The Agency would also like to not for the
12 record that Ms. Diane Lellock, who is the panel's
13 Patient Representative today, has acknowledged a
14 personal financial interest with a firm at issue."

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

21 "With respect to all other participants,
22 we ask in the interest of fairness that all persons
23 making statements ore presentations disclose any
24 current or previous financial involvement with any
25 firm whose products they may wish to comment upon."

1 I will also give a brief summary of the
2 last panel meeting.

3 On November 13, 2000, the panel discussed
4 guidance documents for prescription use drugs of
5 abuse 510(k)'s and OTC drugs of abuse 510(k)'s;
6 recommendations for the prescription use guidance
7 related to study designs and establishing cutoffs;
8 recommendations for the OTC guidance related to
9 confirmation testing, studies, labeling,
10 applicability to OTC alcohol testing, and cutoff
11 performance.

12 On November 14, the panel discussed a
13 510(k) for the Psychomedics Corporation's opiate
14 assay. The panel addressed the adequacy of the
15 method used to establish and characterize assay
16 performance, self-reporting issues, minimum dose
17 sensitivity, potential for bias from individual
18 differences, and environmental exposure effects on
19 drug retention.

20 Now I believe the panel will introduce
21 themselves, but I would like to first acknowledge a
22 few new faces.

23 Dr. Ahmann is one of our newer
24 consultants. This is his first meeting, so be nice
25 to him.

1 Dr. Cara is from one of our CDRH panels;
2 and Ms. Diane Lellock agreed to serve as the
3 patient rep, actually about two weeks before the
4 meeting, so we are happy to have her.

5 Dr. Rosenbloom, could you start?

6 **Introductions**

7 DR. ROSENBLOOM: Arlan Rosenbloom,
8 Professor Emeritus of pediatrics at the University
9 of Florida.

10 MS. KRUGER: Davida Kruger, Certified
11 Nurse Practitioner, Henry Ford Health System,
12 Detroit, Michigan.

13 DR. CLEMENT: Steve Clement, clinical
14 endocrinologist, Georgetown University.

15 DR. KROLL: Martin Kroll, Director of
16 Clinical Chemistry at the Dallas VA Medical Center
17 in Dallas.

18 DR. AHMANN: Andrew Ahmann, Associate
19 Professor of Medicine, Oregon Health Sciences
20 University, Portland, Oregon; clinical
21 endocrinologist.

22 DR. CARA: Jose Cara, Section Head,
23 Pediatrics, Endocrinology, and Diabetes, Henry Ford
24 Hospital.

25 DR. MANNO: Barbara Manno, Louisiana State

1 University Health Sciences Center in Shreveport,
2 Louisiana, professor, and I am a forensic
3 toxicologist.

4 DR. LANSKY: Fred Lansky, Ortho-Clinical
5 Diagnostics, the Johnson & Johnson Company. I am
6 the Industry Representative.

7 MS. LELLOCK: Diane Lellock, mother of two
8 diabetic children.

9 DR. GUTMAN: Steve Gutman. I am the
10 Director of the Division.

11 DR. HENDERSON: I am Cassandra Henderson.
12 I am a maternal-fetal medicine practitioner in New
13 York and Chief of Maternal-Fetal Medicine at Our
14 Lady of Mercy.

15 DR. KROLL: Good.

16 Now the FDA is going to make some
17 presentations for us.

18 **FDA Presentations**

19 DR. BERNHARDT: Good morning, ladies and
20 gentlemen and distinguished panel members.

21 My name is Patricia Bernhardt. I am a
22 reviewer of glucose devices in the Division of
23 Clinical Laboratory Devices.

24 We appreciate the interest and
25 participation of the panel, industry, health care

1 professionals, and the public in assisting FDA in
2 evaluating the role of alternative sample site
3 testing for self-monitoring blood glucose systems.

4 We are here today to discuss new
5 information about a potential public health concern
6 regarding the measurement of blood glucose in
7 samples obtained from sites other than the
8 fingertip.

9 I will identify our concern, explain our
10 expectations for this meeting, provide an overview
11 of our review of these devices, show several
12 different examples of data presentation formats,
13 and ask for your recommendations.

14 [Slide.]

15 This slide hypothetically illustrates the
16 concern. The solid line represents a fingertip
17 blood glucose pattern, and the dotted line
18 represents an alternate site pattern. The
19 horizontal arrows show a lag between fingertip and
20 alternate site measurements when glucose is rising
21 and falling rapidly, and the vertical arrows
22 demonstrate truncation in the alternate site
23 pattern as compared to the fingertip pattern.

24 You will hear the term "discordance" being
25 used this morning. Within the context of FDA's

1 presentations, "discordance" will refer to a lack
2 of agreement between fingertip and alternate site
3 glucose measurements. These sine curves illustrate
4 discordance that may be seen between sampling
5 sites.

6 [Slide.]

7 When discordance occurs, the differences
8 are seen during times when the glucose levels are
9 rapidly changing--that is, in a non-steady state.
10 In some cases, these differences are so marked that
11 the fingertip result may be in the hypo- or
12 hyperglycemic range, but the alternate sample site
13 results are in the normal range.

14 Although the devices appear to be
15 analytically sound, the discordance during times of
16 rapidly changing glucose is random and
17 unpredictable. It is not clear if the phenomenon
18 is site-specific or device-specific. You will hear
19 more about this from others during the course of
20 the morning.

21 Now that FDA is aware of the potential
22 discordance between glucose results obtained from
23 the fingertip and from sites other than the
24 fingertip, our intent is that diabetics will be
25 able to use these devices in an appropriate manner.

1 [Slide.]

2 We understand the benefit of obtaining
3 samples for glucose measurement from alternate
4 sites. There is less pain associated with sampling
5 from alternate sites, and consequently, users will
6 be more likely to test themselves more frequently.

7 We want to ensure that these devices will
8 provide users with the appropriate information
9 necessary to manage their diabetes.

10 [Slide.]

11 Our expectations for this meeting are to
12 learn what studies have already been done; to learn
13 whether the discordance is a physiological
14 phenomenon that will occur with all devices or is
15 device-specific; to learn the types of study
16 designs that should be used to identify conditions,
17 situations, and/or devices in which potential
18 discordant results may occur, and to learn about
19 the experiences of patients and health care
20 practitioners with alternate sample site glucose
21 testing.

22 [Slide.]

23 Historically, FDA's review of these
24 devices has not differentiated between the
25 evaluation of blood glucose measurements from the

1 fingertip and from alternate sites. Since 1999,
2 when the first alternate sample site glucose
3 testing devices 510(k) was cleared for marketing,
4 alternate sample site blood glucose testing has
5 been demonstrated to be substantially equivalent to
6 fingertip testing under the conditions of use
7 chosen by the device manufacturers.

8 Consequently, while our current review
9 process evaluates testing under conditions of hypo-
10 and hyperglycemia, it does not evaluate testing
11 during rapid glucose changes. If it is determined
12 that additional studies are needed, we seek your
13 advice on the design of studies, the conditions to
14 be studied, and the formats of data presentation to
15 best help us identify situations and devices that
16 are likely to produce discordant results.

17 FDA does not know if harm has occurred as
18 a result of glucose testing with samples obtained
19 from alternate sites. Our premarket clearance
20 process and postmarket reporting program have not
21 identified situations or devices where discordance
22 may be seen.

23 Although FDA has received MDR reports on
24 devices that have been cleared for alternate sample
25 site testing, these reports do not differentiate

1 between sampling sites. FDA became aware of this
2 problem when manufacturers who market or plan to
3 market these devices provided us with information
4 on discordance when they submitted different and
5 individual approaches and possible solutions to
6 address the issues.

7 [Slide.]

8 Some companies indicate that sampling from
9 the palm, or rubbing the site before sampling, or
10 using a suction-type collection device eliminates
11 or lessens the differences between fingertip and
12 alternate site measurements. Other companies have
13 proposed addressing the issue of potential
14 discordance with labeling warnings that advice
15 using alternate sample site testing at times when
16 the results are most likely to be equivalent to
17 fingertip testing results--in other words, during
18 time when a user is expected to be in steady state.

19 If studies to address concerns with
20 alternate sample site glucose testing are
21 recommended, we plan to use your advice as the
22 basis for guidance for industry and review. We
23 have chosen the following examples of data
24 presentation formats to foster a discussion about
25 what type of study design is most appropriate for

1 identifying whether a device or a site is likely to
2 show discordance as well as under what conditions
3 discordance is likely to be seen.

4 [Slide.]

5 This slide shows data presented in a
6 Clarke Error Grid. It depicts an accumulation of
7 individual data points obtained from patients
8 demonstrating changes in glucose. Results from the
9 fingertip and from another site are plotted against
10 each other. The error grid divides the data points
11 into regions of varying clinical significance by
12 the type and extent of treatment that may be
13 initiated by the result,

14 [Slide.]

15 This next data presentation shows a time-
16 elapsed plot of an individual's glucose
17 measurements over a given time period where
18 fingertip and arm samples were obtained
19 concurrently in the same patient under home use
20 conditions. This type of presentation shows the
21 discordance between different sampling sites when
22 glucose is changing and identifies incidences where
23 a fingertip result may be hypo- or hyperglycemic,
24 yet the alternate site result is normal.

25 [Slide.]

1 This slide shows a bias plot, also known
2 as a Bland-Altman plot, produced with data from
3 many individuals. This type of plot shows the
4 range of discordance between the two sampling
5 sites.

6 [Slide.]

7 This last format is a linear regression
8 graph comprised of data points from many
9 individuals with unidentified glucose patterns. By
10 plotting the glucose results from one site versus
11 another, the variance from perfect agreement is
12 seen for each data point.

13 Greater detail about the use of these
14 different formats of data presentation will be
15 provided by our statistician shortly.

16 When looking across applications, we
17 identified several points that we think should be
18 recognized when developing guidance to standardize
19 our review of alternate sample site testing
20 510(k)s. We would like your input in determining
21 if an appropriate study design should include an
22 evaluation of these points..

23 [Slide.]

24 Blood glucose testing before meals,
25 regardless of the device used, demonstrated

1 comparable blood glucose results between samples
2 obtained from the fingertip and those obtained from
3 alternate sites.

4 When discordance occurred, the differences
5 were observed after meals. However, some patients,
6 regardless of the device used, demonstrated
7 comparable blood glucose levels between sampling
8 sites some of the time, even when blood glucose was
9 in a non-steady state.

10 Testing was not performed at night, and
11 the effects of exercise and concurrent illness were
12 tested in a limited way.

13 [Slide.]

14 We would like recommendations from the
15 panel on the following questions.

16 Question 1: Historically, FDA has not
17 requested sponsors to provide data collected during
18 non-steady state conditions in 510(k) submissions
19 for self-monitoring blood glucose devices. Should
20 FDA's review of these devices include dynamic as
21 well as steady state data, or are there more
22 appropriate and less burdensome ways to address
23 this public health issue?

24 If additional data are necessary to
25 characterize device performance, what is an

1 appropriate study design that will capture
2 potential discordance during episodes of rapidly
3 rising and falling glucose levels?

4 What is the minimum dataset to be studied?

5 What are the appropriate analytical or
6 statistical tools to be applied to the data--for
7 example, standard regression analysis, Clarke Error
8 Grid analysis, time-elapsd plots.

9 [Slide.]

10 Question 2: Should FDA require
11 manufactures to include strong cautionary labeling
12 about this problem unless they provide data
13 demonstrating that the discordance is unlikely to
14 occur with their particular device?

15 [Slide.]

16 Question 3: Should FDA rescind the
17 clearance for labeling for alternative site testing
18 if the 510(k)s do not address this new scientific
19 issue; make these products prescription home use;
20 or require additional data and labeling changes?

21 [Slide.]

22 Question 4: Are there other activities or
23 issues that FDA should consider with regard to this
24 important public health issue, such as a public
25 health alert; targeted postmarket surveillance;

1 educational outreach activities to stakeholders and
2 other Government and non-Government entities to
3 promote additional research in this area?

4 Thank you for your attention.

5 Dr. Marina Kondratovich will now present a
6 statistical overview of various types of data
7 presentations FDA has seen in 510(k) submissions
8 for alternate sample site glucose testing devices.

9 DR. KONDRATOVICH: Good morning. My name
10 is Marina Kondratovich. I am a statistician from
11 the Division of Biostatistics.

12 We will hear today a lot of information in
13 detail about specific studies on today's topic. We
14 will see a big variety of study designs.

15 In my brief presentation, I would like to
16 touch on some very basic characteristics, such as
17 glucose level states, types of measurements, and
18 basic characteristics of patients.

19 The data from these studies can be
20 analyzed by different types of statistical
21 analysis. You already saw several examples of data
22 analysis. I would like to make a few comments on
23 regression analysis, different plots, error grid
24 analysis, and agreement tables.

25 [Slide.]

1 Glucose level states can be approximately
2 classified in three groups: steady state--the
3 glucose level of such state can be obtained, for
4 example, during fasting testing; dynamic state--
5 when glucose level is changing rapidly. The rate
6 of change in the glucose level is a very important
7 characteristic. You will see studies which have
8 measurement in dynamic states, but the observed
9 rates of change in the glucose level are different;
10 perhaps this is a reason why the different
11 conclusions are drawn from these studies.

12 For example, in some studies, the
13 intravenous injection of rapid insulin was used,
14 which gave the average drop of about 200 mg/dL in
15 one hour, while exercise of some specific type gave
16 an average drop of about 50 mg/dL in one hour.

17 Stabilizing state--an example of such
18 glucose level can be obtained during 2 hours post-
19 meal testing when the average drop is about 35
20 mg/dL in one hour.

21 [Slide.]

22 Types of measurement of all study designs
23 can be divided into two types--single-point
24 measurements and time series measurements.

25 Consider the single point measurement.

1 The typical scheme is the following. One hundred
2 subjects were tested once--for example, finger and
3 arm--during a normally scheduled clinic visit.
4 Such study design provides a mixture of
5 measurements of blood glucose levels in different
6 states--steady, stabilizing, dynamic.

7 For dynamic state, some subjects can have
8 an increase in blood glucose, and arm measurement
9 tends to be lower than finger measurement. Some
10 subjects can have a decrease in blood glucose, and
11 arm measurements tend to be higher than finger
12 measurements.

13 A very important characteristic of such
14 study design is the distribution of time after a
15 meal. For example, in the study with the
16 [inaudible] distribution of time after a meal, 58
17 percent of blood glucose measurements were in
18 dynamic state.

19 The statistical analyses stratified by
20 time after meal are very useful. In some studies,
21 patient information about state of glucose level is
22 absent, so such stratified analysis is impossible.

23 [Slide.]

24 The time series measurement can be divided
25 into two groups--measurements at special time

1 points and monitoring.

2 [Slide.]

3 The typical scheme of the measurements at
4 special time points is the following. One hundred
5 ninety patients test their glucose level for a
6 total of 10 days, finger and arm at following time
7 intervals: pre-breakfast, one hour post-breakfast,
8 two hours post-breakfast, pre-lunch, one hour post-
9 lunch, and so on; bedtime.

10 [Slide.]

11 The typical scheme for monitoring is the
12 following. Six subjects were brought into a clinic
13 in the morning and tested, finger and arm, for
14 blood glucose level every 15 minutes for 6 hours.

15 The important characteristic is how the up
16 and down movement of the glucose level was
17 initiated. Different procedures produced different
18 rates of change in the glucose level. For example,
19 the consumption of a usual meal and the procedure
20 giving an oral glucose load after reaching a
21 maximum intravenous injection of insulin give
22 different rates of change in the glucose level.

23 For time series measurements, measurements
24 at special points and monitoring time profiles for
25 every subject is a very useful way to present and

1 analyze data.

2 For example, set time profiles for every
3 patient allow to estimate the rate of change in the
4 glucose level, find time points with maximum
5 difference between finger and arm measurements,
6 specify the patient with different pattern of
7 observed difference, and many other things.

8 [Slide.]

9 The results of the particular study should
10 be generalized to whole population of patients who
11 use or will use this device, so the subject in
12 these studies must be a representative sample from
13 intended use population.

14 To be sure about that, the study should
15 have information about study participants such as
16 type of diabetes, insulin user or non-insulin user,
17 also the subject demographic characteristics as
18 age, gender, body mass index, diabetes mellitus
19 duration, and others are very important.

20 [Slide.]

21 The statistical analysis stratified, for
22 example, by the type of diabetes can be useful.

23 [Slide.]

24 The data from these studies are usually
25 analyzed by the following statistical tools:

1 regression analysis, error grid analysis, and
2 tables of agreement.

3 I would like to emphasize that the
4 statistics don't directly tell us whether the
5 measurement of glucose levels from alternative
6 sites are acceptable; rather, they provide
7 estimates of error which allow us to judge the
8 acceptability.

9 Design of study and quality of data,
10 measurement of the right subject under the right
11 conditions, are very important.

12 [Slide.]

13 Regression analysis. Both finger and arm
14 results are subject of measurement error.
15 Therefore, Deming or orthogonal regression is more
16 appropriate.

17 Consider the hypothetical example with
18 single point measurement. There are three subjects
19 with increasing glucose levels, so the arm
20 measurements underestimate finger measurements.

21 There are another three subjects with
22 decrease in glucose level, and the arm measurement
23 overestimates finger measurements.

24 The regression line for all six
25 measurements can be a diagonal because the linear

1 regression determines the slope and intercept of
2 the best-fitting line in average.

3 There is a well-known joke among
4 statisticians. One statistician put his head in a
5 hot oven and put his feet in a cold refrigerator.
6 When he was asked "How are you?" he replied: "I am
7 fine on average."

8 When biases of different direction are
9 expected in different subsets of the data, the
10 regression analysis stratified, for example, by the
11 time after meals are very useful.

12 [Slide.]

13 Difference plots--another name, Bland-
14 Altman plots--allow one to display the difference
15 between finger measurement, Variable X, and arm
16 measurement, Variable Y, for every [inaudible]
17 measurement. We will see plots of difference Y
18 minus X against X, and the example of that plot is
19 presented in this figure.

20 Also, you will see the plots of relative
21 differences, Y minus X divided by X in percent.

22 The very important characteristic is the
23 limits of agreement--these two numbers--limits of
24 agreement--95 percent of differences lie between
25 these two limits.

1 In this example, limits of agreement equal
2 minus 49, plus 51.

3 [Slide.]

4 The error grid analysis divides the plot
5 of arm measurement versus reference method in the
6 regions of clinical interpretation. Regions A and
7 B represent values that are clinically relevant.
8 In Clarke Error Grid Analysis, Zone A is defined
9 as clinically accurate measurement within plus or
10 minus 20 percent of the reference; Zone B is
11 defined as error greater than plus or minus 20
12 percent, which may or may not cause the patient to
13 initiate treatment; Zones C, D, and E are defined
14 as measurements deviating from reference values by
15 either over- or underestimation, and these errors
16 could adversely affect the patients.

17 [Slide.]

18 Probably you will see other types of error
19 grid analysis. For example, it was suggested an
20 error grid as intensive insulin therapy error grid.
21 The basic idea is the following. Individual
22 glucose readings are used to adjust insulin doses
23 according to the following algorithm: Adjustment
24 factor equals blood glucose minus target glucose
25 divided by 40.

1 So if a glucose monitor reads within 40
2 mg/dL of true glucose level, then adjustment factor
3 is correct. Zone A, for example, in Clarke Error
4 Grid and in intensive insulin therapy grid are
5 different. For some range of reference values,
6 Zone A of Clarke Error Grid is larger than Zone A
7 of intensive insulin therapy grid, and for some
8 reference values, it is opposite. So the direct
9 comparison of the different error grid results is
10 not easy.

11 In error grid analysis, a big number of
12 measurements in some particular reference range,
13 for example, normal values of glucose levels, can
14 affect drastically the percent of points in another
15 range, for example, hypoglycemic values. So error
16 grid analysis stratified on hypoglycemia,
17 normoglycemia and hyperglycemia is very useful.

18 [Slide.]

19 The same idea is used in agreement table 3
20 by 3. This table is presented for illustrative
21 purposes. In the hypoglycemic state, there are
22 about 600 measurements. In normal range, there are
23 about 6,000 measurements. And in hyperglycemic
24 range, there are about 1,000 measurements.

25 The presentation of data in said tables is

1 useful because big numbers of measurements in
2 normal range and in hyperglycemic state do not
3 affect the percent of incorrect values in
4 hypoglycemic range.

5 The total sum of percent in every column
6 equals 100.

7 [Slide.]

8 The 3-by-3 table can be reduced to the
9 table 2-by-2 if we are interested in evaluation,
10 for example, hypoglycemic detection. Then,
11 agreement of alternative site with finger-stick
12 positive and finger-stick negative can be
13 calculated. Agreement of alternative site with
14 finger-stick positive equals the ratio of this
15 number to the total number of events.

16 Also, the whole receiver operating curve
17 can be constructed, and areas under this curve can
18 be estimated. I would like to stress that the
19 finger-stick is not a perfect standard, so all
20 these estimates are measures of agreement.

21 [Slide.]

22 So when you consider the results of
23 studies, the following basic aspects of study
24 design should attract your attention, such as type
25 of measurement in this study--single point

1 measurement, measurements at special time points,
2 or monitoring; state of glucose level--steady,
3 stabilizing, dynamic; the rate of change in the
4 glucose level observed in this study; and the basic
5 characteristics of patients in this study.

6 Also, we would like your input in
7 determining the basic features of the study design
8 which is most appropriate for this problem.

9 Thank you for your attention.

10 DR. KROLL: I'd like to thank the FDA
11 presenters, Patricia Bernhardt and Dr. Marina
12 Kondratovich.

13 I would now like to have the sponsors give
14 their presentations, and each sponsor will have 20
15 minutes total time to present.

16 First, we'll hear from Dr. Nina Peled.

17 Let me just remind each sponsor to tell us
18 what their affiliation is.

19 **Sponsor Presentations**

20 DR. PELED: Good morning, ladies and
21 gentlemen, colleagues, friends, distinguished
22 panel, FDA members.

23 I am here speaking for Amira Medical. My
24 name is Nina Peled, and I am the Vice President of
25 Scientific Affairs and have a strong interest in

1 the topic at hand.

2 Amira Medical has a device for alternate
3 site testing, and I am here to present to you maybe
4 a little different angle than other presenters that
5 you will hear today. Where a lot of the data that
6 you are going to see relates to arm testing, I am
7 going to hopefully present a solution in data that
8 I am going to show you.

9 I am hoping that you are going to use your
10 judgment in looking at the data and evaluating it
11 for its scientific merit.

12 [Slide.]

13 I'm going to give you a little background.
14 First of all, being in the business of diabetes for
15 a long time, one of the big issues that patients
16 always mention is the pain associated with finger-
17 sticks. Off-finger testing sites or alternate
18 testing sites were actually looked for to avoid
19 that pain. So companies were looking for body
20 sites that are not as painful as the finger, and
21 Amira Medical, the company I am representing,
22 introduced a blood glucose monitor called the
23 AtLast. We introduced it 2 years ago, and it has
24 been on the market ever since.

25 [Slide.]

1 A little history. It was assumed all
2 along that glucose in any capillary sample will be
3 the same from any body site. Arm samples from
4 subjects repeatedly showed good accuracy, and this
5 was the data we presented to FDA when we obtained
6 clearance, and this is the data we continuously
7 produce as we make every lot of test strips. We
8 always do a clinical study, and in all of our
9 clinical studies, the accuracy is maintained.

10 However, studies were usually conducted in
11 patients who are at a minimum of 2 hours
12 postprandial, and the reason for that is we usually
13 do a battery of tests, we look at several lots, we
14 look at several meters; so the whole testing
15 program is quite long, and we don't want the
16 patient to be moving physiologically on us between
17 the time we take the reference and the time we do
18 the AtLast testing.

19 So we asked--and it was a common practice
20 in the industry--patients to come in at a minimum
21 of 2 hours postprandial. This way, we were assured
22 there would be no strong shifts in the testing
23 protocol.

24 [Slide.]

25 However, new information came about as we

1 at Amira were looking for future products and were
2 trying to look at continuous monitors, for example,
3 and we started to look at patients over time--
4 before a meal, after a meal. And lo and behold, we
5 had seen a lag in arm data, and we immediately
6 rushed to present this data to the FDA and had
7 actually composed new labeling that we had
8 disseminated to our customers to indicate that.

9 It had been postulated that the lag is due
10 to a lower perfusion rate in the arm compared to
11 the finger.

12 [Slide.]

13 So what to do now? With this
14 understanding of low perfusion rate, we started to
15 look for other body sites. Again, we intended to
16 lower pain, so we were trying to look for sites
17 that would provide two attributes--one, they would
18 be low in nerve ending, therefore, no pain; and
19 two, they would be as well-perfused as the finger.
20 And we identified the palm to be a site that will
21 justify and maintain those two attributes.

22 What I want to present to you today is the
23 performance of the palm in numerous studies that we
24 have conducted in both dynamic and nondynamic
25 states.

1 [Slide.]

2 Our first study is--and I put it in
3 quotes--"steady-state," because as you very well
4 know, a person with diabetes is not "steady," but
5 this is the best "steady" you can get on a person
6 with diabetes.

7 So this is the typical protocol of
8 bringing a subject in at a minimum of 2 hours
9 postprandial and comparing their single point
10 values to the YSI plasma values off of a finger
11 sample.

12 And by the way, in all the studies that I
13 am going to show today, the reference is always the
14 YSI plasma values of finger samples, so that is the
15 reference used all across.

16 [Slide.]

17 Here is the regression of about 275 data
18 points on the palm, across the measuring range or
19 almost across the entire measuring range. As you
20 can see, the correlation is very tight; the results
21 are very close to each other.

22 [Slide.]

23 On the next slide, you see the regression
24 statistics where we are looking at slopes very
25 close to 1.0. There are three lots involved in the

1 study, and I am presenting the data per lot and for
2 all lots. So slopes close to 1.0, negligible
3 intercepts, and very high correlation coefficients,
4 indicating very good accuracy of palm samples in
5 steady-state.

6 [Slide.]

7 Our arm data, by the way, is very similar
8 to what you see on the palm when we are talking
9 about 2 hours fasting.

10 [Slide.]

11 Our next study escalates the situation,
12 and now we are looking at random glycemic states.
13 We accomplished that by asking participants to come
14 to our clinic at any time of the day. In our
15 handouts, you will see a distribution of what
16 fasting state they were at. In this particular
17 study, there were people at 8 hours fasting, 4-6
18 hours fasting, 2-4 hours fasting, and even 28
19 participants in zero to 2 hours post-mealtime.

20 [Slide.]

21 Again, the correlation is shown on the
22 board now. Excellent accuracy is demonstrated in
23 what I call random glycemia, and the regression
24 statistics are following.

25 [Slide.]

1 Again, a close to unit, an intercept which
2 is negligible, and high correlation coefficient.

3 I did not present the data on Clarke Error
4 Grids, but we can easily do that, and you will see
5 a very high percentage of the data points in the A
6 Zone. There are a few data points in the B Zone
7 very close to the A.

8 [Slide.]

9 Again, with escalation, now we are going
10 to what I call the high glucose load. The intent
11 of this study, just so there is no controversy and
12 arguments afterwards--we were not going to mimic
13 reality or a real diet or real therapy in this
14 study. What we want to do is really give it the
15 full challenge possible, although it is not what a
16 patient goes through in his normal life. So we are
17 accentuating and trying to magnify a possible lag
18 in our data, and we did that by giving the patient
19 75 grams of glucose, which is the load one would
20 get in a glucose tolerance test. However, at the
21 same time, we have them self-medicate to counteract
22 that glucose load so it is not completely a glucose
23 tolerance test.

24 And again, we are looking at a large
25 number of data points of palm samples compared to

1 the YSI plasma measurement of finger samples.

2 [Slide.]

3 The first thing I want to show you is time
4 course data. From the patients we looked at, I
5 picked two who had exhibited a high rate of glucose
6 change. Just to give you an idea, this patient you
7 are looking at now had on the rise a change of 1.22
8 mg/dL per minute, and on the way down, minus 1.35
9 mg/dL per minute.

10 As you can see, the two graphs are kind of
11 hugging each other. The palm and the finger are
12 very close to each other.

13 [Slide.]

14 This is our second patient, and this one
15 is climbing up and down even steeper. On the
16 glucose rise, he is going 2.22 mg/dL per minute; on
17 the way down, the rate of decline is minus 2.62
18 mg/dL per minute, so quite steep. And again, the
19 two lines are very close to each other. The palm
20 and the finger are almost alike. Hopefully, that
21 was impressive.

22 [Slide.]

23 The next graph takes all the data from
24 this high glucose load study and puts it on a
25 regression. Correlation is excellent. I believe

1 96 percent of the data points--and I'll have to
2 confirm the exact number--are in the A Zone in this
3 particular study. There is nothing to do with the
4 C, D, or E of the Clarke Error Grid, if people are
5 interested in that sort of analysis. But it is a
6 very close correlation.

7 [Slide.]

8 The regression statistics are now on the
9 board. We are looking at a slope of 1.0, an
10 intercept of 2.4, and a very high correlation
11 coefficient of 0.98. This is a very extreme study
12 that a patient with diabetes will never have to go
13 through, because we are talking about a 70-gram
14 load of glucose. And even under those very extreme
15 conditions, the palm and the finger are the same.

16 [Slide.]

17 Just to give you a little contrast here, I
18 was not going to talk about the arm per se, but I
19 wanted to show you what would be the situation on
20 the arm. And in this particular study, the high
21 glucose study, we did both the arm and the palm in
22 comparison to the finger. So you are going to see
23 similar data that you have just seen on the palm on
24 the arm.

25 [Slide.]

1 This is Patient Number 1 that you have
2 seen before, and this is what his arm data looks
3 like. As you can see, going up, we are not going
4 to the same peaks on the arm as the finger does;
5 and when coming down, there is a lag in the arm
6 glucose compared to the finger.

7 [Slide.]

8 Patient Number 2, the one who was even
9 more extreme, again, on the up, there is a lag; the
10 arm is a little lower than the finger. Coming
11 down, the arm is a little higher than the finger.
12 And just for a point of reference, if you ever look
13 at venous blood in samples that the hospitals use,
14 on the way up in glucose, you will see a very
15 similar correlation between venous blood and the
16 finger. The finger is always higher than venous.

17 [Slide.]

18 Here is the data for the arm for all data
19 points included in that study. All patients across
20 the measuring range--and you can see quite some
21 noise in that data--just to contrast it, I am going
22 to bring back the palm data to show--it is exactly
23 the same patients, exactly the same time--how tight
24 the palm data is compared to the arm.

25 [Slide.]

1 So the palm samples under all glycemc
2 conditions compare well with those found in finger
3 samples. The data supports lag-free performance
4 for palm samples. And when lag is detected in arm
5 samples, it is not present in palm samples, and
6 therefore, we don't think you need to have 10,000
7 data points to prove the case here.

8 [Slide.]

9 Just to complete the story--and you have
10 seen our two patients before going down in glucose;
11 we did not bring them completely down to
12 hypoglycemia, although on the way down, you could
13 see that the two lines are superimposing on each
14 other--we on purpose focused just on hypoglycemia
15 and brought in patients, some with insulin and some
16 with exercise, and we brought them down into the
17 hypoglycemic range. This was done under the
18 supervision of the health care providers, and that
19 person had been instructed on the amount of insulin
20 and the timing of the insulin.

21 So this is another patient now going into
22 hypoglycemia. The red dots are the finger samples;
23 the blue diamonds are the palm. And again, there
24 is no difference between the palm and the finger
25 other than the typical noise between two

1 measurements.

2 [Slide.]

3 Patient Number 2 going into hypoglycemia,
4 again, no difference between the palm and the
5 finger.

6 [Slide.]

7 Looking at the data in totality for just
8 the hypoglycemia study, I have put it on a Clarke
9 Error Grid because the data is very clustered, and
10 regression statistics will not do it justice. But
11 this is just to show you the distribution of the
12 data points in this case.

13 Most of the data is in the A Zone. We do
14 have one D Zone point in this case that the data
15 represents a 16-mg difference between the finger
16 and the palm, where the palm was 0.86--let me read
17 the exact numbers for you--the palm was 0.83 and
18 the finger was 0.67, and that brought it into the D
19 Zone, but it is really a negligible difference.

20 In that plot, 92 percent of the data
21 points were in the A Zone.

22 [Slide.]

23 So as we look at detection of
24 hypoglycemia, I think that as we look at the palm,
25 we are seeing timely detection of hypoglycemia--and

1 I on purpose call it "timely" because as you know,
2 Mr. Koschinsky has a paper out there, and it is
3 titled "Risky Detection of Hypoglycemia," so this
4 one is "Timely Detection of Hypoglycemia in Palm
5 Samples." And the performance of palm samples is
6 identical to what is found in finger samples.

7 [Slide.]

8 To give you an idea of the range of
9 glucose change that we found in all of our patients
10 throughout the studies that we looked at, we are
11 seeing a rate of change between 0.88 and 2.31 mg/dL
12 per minute when glucose levels were on the rise,
13 and a change of minus 0.32 to 2.62 mg/dL per minute
14 when glucose levels were falling; so quite a wide
15 range.

16 [Slide.]

17 As far as comfort, which is the issue that
18 led us to alternate site testing, we had been on
19 the market with arm testing for a while, so when we
20 looked at the palm, we didn't even bother to
21 compare it to the finger because we knew that was
22 very painful; we just compared palm and arm testing
23 and asked patients their preference as far as pain
24 and comfort between the palm and the forearm.
25 Then, we also asked subjects to rate their pain

1 experience on a scale of 0 to 5 and tell us how
2 they would rate it.

3 [Slide.]

4 Seventy-six percent of our participants
5 chose the palm versus the arm for testing. One
6 hundred percent of the subjects rated AtLeast blood
7 sampling from the palm as "no pain" or as "very low
8 discomfort," so it was between 0 and 1, the rating
9 that we received on a scale of 0 to 5.

10 [Slide.]

11 In conclusion, the palm is well-perfused,
12 and you can find that in physiology textbooks. The
13 palm provides glucose results that compare well
14 under all conditions with finger results. Palm
15 testing affords detection of hypoglycemia at the
16 same time as indicated by finger samples. And the
17 palm of the hand was identified as a comfortable
18 testing site.

19 And, as I count it, the number of teeth in
20 this horse's mouth is 32.

21 [Slide.]

22 Then, key messages--and I may be repeating
23 myself, but I really want to get to the last point
24 which is important--the palm is a body site free of
25 lag compared to the finger; data supports lag-free

1 correlation; it is easy and virtually painless to
2 test from; and pain and discomfort resulting from
3 finger-sticks is a big hurdle to compliance with
4 prescribed testing regimes.

5 [Slide.]

6 And finally, data supports immediate
7 clearance of the palm without labeling
8 restrictions. And this is to the panel members who
9 may not know the situation. Amira Medical had
10 presented the palm in a 510(k) submission 7 months
11 ago. This submission is on hold because of issues
12 found in arm samples and because of FDA's concern
13 for those issues.

14 I think that we are presenting here a very
15 clear case that the palm does not have any lag, and
16 I would like to request this esteemed panel to make
17 a recommendation to the FDA to immediately clear
18 the palm.

19 Thank you so much for your attention.

20 DR. KROLL: Thank you.

21 Now we'll have Dr. Ronald Ng from Abbott
22 Laboratories present.

23 DR. NG: Good morning. I am Ron Ng, and I
24 am Director of Medical and Clinical Affairs at
25 Abbott Laboratories, MediSense Products.

1 As we all agree, the accuracy of alternate
2 site testing is a very important issue, and this
3 morning I will present to you the data on our Sof-
4 Tact System.

5 [Slide.]

6 The Sof-Tact System demonstrates
7 clinically acceptable results on both the arm and
8 the finger under conditions of changing glucose
9 levels or dynamic conditions.

10 This was shown in our initial studies and
11 has been confirmed by subsequent studies.

12 [Slide.]

13 This is the Sof-Tact System in my hand.
14 It is a fully-automated and integrated device for
15 alternate site testing. It increases perfusion at
16 the sampling site.

17 When we went into the design of this
18 system, we knew that it was important to increase
19 perfusion at the site. So when I explain to you
20 how it works, it will become clear.

21 When you want to do a test, all you have
22 to do is place the device on the arm and press the
23 button. There is a vacuum pump inside this device
24 which will produce a vacuum on your skin, and this
25 vacuum will pull the skin up into this special area

1 that is designed via geometry specifically for
2 stretching the skin before lancing.

3 So this device will vacuum your skin for a
4 predefined time to increase perfusion. Then, the
5 lancet is released automatically, and it passes
6 through a hole in the test strip and lances the
7 skin. The vacuum continues to pull on the skin,
8 and it draws blood to the surface.

9 As you can see in all these pictures, the
10 skin is stretched into the meter. Blood is then
11 automatically transferred to the test strip, and
12 the glucose test is initiated.

13 [Slide.]

14 Here is some data showing that stretching
15 the skin indeed increases blood perfusion at the
16 sampling site. On this graph, the Y axis is the
17 perfusion expressed as percent of baseline value.
18 On the X axis is the skin height; that means how
19 high is the skin stretched inside the meter.

20 Now, of course, in this study which was
21 using the Laser Doppler blood flow measurement, we
22 analyzed different skin heights to show a
23 coloration between skin height and the vacuum and
24 increase in perfusion.

25 The current Sof-Tact device is set to

1 stretch the skin up to a height of about 3.5 mm,
2 and that corresponds to an increase of perfusion of
3 threefold. And this is just the increase of
4 perfusion before lancing.

5 The Sof-Tact, as I said, is designed
6 specifically for alternate site testing, and there
7 are substantial differences between how it collects
8 a blood sample compared to other devices.

9 After you select a site to perform
10 testing, the Sof-Tact automatically applies a
11 vacuum to increase blood perfusion at the site and
12 positions the skin for testing. You compare that
13 with other alternate site testing devices, and
14 there is no automatic preparation of the site by
15 the device.

16 After lancing, the Sof-Tact maintains the
17 vacuum for a predetermined time, and then it moves
18 the strip to obtain the blood sample. The Sof-Tact
19 uses 2.7 microliters of blood.

20 In the design of the Sof-Tact, since we
21 know we have to increase perfusion, we also
22 designed it to achieve that sample volume, and if
23 insufficient blood is pulled out by the vacuum, the
24 device is designed not to start the test; so you
25 will not get an erroneous result.

1 The whole time the vacuum is maintained
2 during sampling, when the Sof-Tact detects enough
3 sample has been collected on the test strip, it
4 will release the vacuum at that point, and the
5 glucose test is initiated.

6 This is in contrast to other devices which
7 the user would manually collect a sample typically
8 in the range of 0.3 to 1.5 microliters.

9 So we have designed the Sof-Tact really
10 specifically for alternate site testing and have
11 all kinds of checking mechanisms to make sure that
12 the test is performed successfully; otherwise, the
13 user will not get a result, and the Sof-Tact
14 automatically prepares the site to increase
15 perfusion before lancing and additionally after
16 lancing, because the vacuum is continued.

17 [Slide.]

18 The first study I want to share with you
19 is the Lay User Study which involved 5 trial
20 centers and more than 300 individuals with very
21 diverse demographics.

22 [Slide.]

23 Here, I present the data using the Clarke
24 Error Grid, because we feel that at the end of the
25 day, the question we have to answer is is the

1 accuracy clinically acceptable. So we go right to
2 that question and use the Clarke Error Grid to
3 analyze our results.

4 Here, we show the Sof-Tact on the right-
5 hand side finger results compared to the finger
6 reference, laboratory reference. And on the left-
7 hand side is the Sof-Tact arm results compared to
8 the finger reference.

9 As you can see, they both provide accurate
10 results, and the results are clinically acceptable
11 according to the Clarke Error Grid analysis.

12 [Slide.]

13 We also analyzed our data again looking at
14 the subset of patients who are in the dynamic
15 state, right in steady-state, because in our study,
16 we have already asked each subject how long has it
17 been since they last ate or had a sugary drink; and
18 of those 300-some patients that you have seen data
19 for on the previous slides, 260 of them had caloric
20 intake within 3 hours prior to testing. So we
21 looked at those data carefully, and as you have
22 already seen, all the results were clinically
23 acceptable.

24 [Slide.]

25 But in the next slide, we also provide you

1 a time course. What you see here on the X axis is
2 time after the subject had eaten is all the way
3 from zero to 3 hours postprandial. On the Y axis
4 is the percent bias or the percent difference
5 between the arm results versus the finger
6 reference.

7 And here, you can see the line of plus or
8 minus 20 percent. What you see here is that the
9 majority or 93 percent of the arm results are
10 forward in that 20 percent line.

11 We also plot the mean value for the
12 selected times here, and a regression line is done
13 through them. What you see here is that the
14 maximum difference is at 60 minutes after eating,
15 but it was only about 4 percent, the arm lower than
16 the finger on average, and the results are still
17 clinically acceptable.

18 So if I summarize this, you see a slight
19 difference at 60 minutes, but that difference is
20 clinically acceptable.

21 [Slide.]

22 We have done additional studies to re-look
23 at the dynamic states. The three that I am going
24 to present this morning are the meal tolerance
25 test, the oral glucose tolerance test, and

1 hypoglycemia study.

2 [Slide.]

3 In those studies, we also tried to include
4 independent control, independent method, to measure
5 the arm glucose. We know we cannot use the YSI
6 laboratory instrument because it requires too much
7 blood for a test; we cannot do that on the arm.

8 We picked the HemoCue because it is
9 accurate and precise, is 510(k) cleared for
10 diagnosis of diabetes, and it requires only 5
11 microliters of blood for a test.

12 So we set up the Sof-Tact vacuum mechanism
13 to collect sufficient blood from the arm for each
14 HemoCue test. The objective was to demonstrate
15 that the Sof-Tact sample collection mechanism is
16 key to producing clinically acceptable results from
17 the arm.

18 [Slide.]

19 Let's look first at the meal tolerance
20 test. I'm going to present this study, which had
21 50 patients with diabetes enrolled. We monitored
22 their glucose levels after intake of a liquid meal,
23 Ensure, and their glucose was measured on arm and
24 finger at defined time intervals.

25 We found that 6 of the 50 patients had

1 rapid glucose drop faster than 1.7 mg/dL per
2 minute, or faster than 100 mg/dL per hour. These
3 data have been submitted for publication.

4 [Slide.]

5 The 6 patients with the most rapid decline
6 of blood glucose are shown here. This column shows
7 the peak rate of glucose drop, and you see that
8 half of them were faster than 2 mg/dL per minute.
9 In this patient, Patient Number 2, the glucose even
10 dropped to hypoglycemic region, 50 mg/dL.

11 If we look at the accuracy of all these
12 results, we find that 100 percent of the results
13 are clinically acceptable.

14 [Slide.]

15 Patient Number 2, I will show you the
16 detail here. You see rapid rise and then rapid
17 drop of glucose, and it dropped to 50 ml/dL
18 according to finger reference. And when we
19 compared the arm result versus the finger value,
20 all results were clinically acceptable.

21 [Slide.]

22 Here, I show all 50 patients, 860 pairs of
23 arm/finger values, using the Clarke Error Grid
24 analysis, and 100 percent of the arm results from
25 the Sof-Tact were clinically acceptable.

1 [Slide.]

2 This is the independent control using the
3 HemoCue to do the test, but we used the Sof-Tact
4 sample collection mechanism on the arm to collect
5 the blood. With this set-up, 100 percent of the
6 HemoCue arm results were clinically acceptable.

7 On the right panel, just to give you a
8 time course, this is the time course average bias
9 of the HemoCue arm results versus the finger
10 reference, and the maximum difference at 60 minutes
11 is about 4 percent, but the difference is
12 clinically acceptable, and as you see, all the
13 individual results are clinically acceptable. And
14 this is very consistent with what we have shown you
15 earlier with the postprandial data.

16 [Slide.]

17 So in terms of the meal tolerance test,
18 with the Sof-Tact sample collection mechanism, both
19 Sof-Tact and HemoCue provide clinically acceptable
20 results from the arm at various postprandial times.
21 Therefore, there is no basis to limit the use of
22 Sof-Tact after eating.

23 [Slide.]

24 Next, I will present data on the oral
25 glucose tolerance test. This study involved 12

1 patients with diabetes. We monitored their glucose
2 level after drinking 100 grams of glucose and then
3 measured the arm and finger glucose at defined time
4 intervals. These data have also been submitted for
5 publication.

6 [Slide.]

7 Here are the rates of glucose change for
8 all 12 patients in the study. In this column is
9 the peak rate of glucose increase, and you can see
10 that these are very, very rapid rates of glucose
11 changes. Most of the rates exceed 2.0 mg/dL per
12 minute to a high of almost 6.0. In this column are
13 the rates of glucose decrease, and again, rapid
14 rates are seen to a high of 6.0 mg/dL per minute.

15 But if we look at all the results, again,
16 we see clinically acceptable results. Actually,
17 all except one single data point that I will show
18 you in the corner, B Zone adjacent to the A area.
19 So we really see clinically acceptable performance
20 even during rapid changing glucose level in the
21 oral glucose tolerance test.

22 [Slide.]

23 Here are all the data points from this
24 study--211 pairs of data from the 12 patients--and
25 the only point that was outside the A and B zone is

1 right here in the corner, very close to the A zone
2 is that point.

3 So really find clinically acceptable
4 performance accuracy with the Sof-Tact arm testing.

5 [Slide.]

6 Here are the data for the HemoCue with all
7 the patients, 204 pair of points. And again, all
8 the data points were clinically acceptable.

9 [Slide.]

10 So for OGTT, with the Sof-Tact sample
11 collection mechanism, both Sof-Tact and HemoCue
12 provide clinically acceptable results from the arm
13 in conditions of rapidly changing glucose
14 concentrations.

15 Therefore, there is no basis to limit the
16 use of Sof-Tact to conditions of rapidly changing
17 glucose concentrations.

18 [Slide.]

19 Let's go to the hypoglycemia study. We
20 enrolled 5 patients with diabetes into this study.
21 We allowed the subjects' glucose to drop below 75
22 mg/dL, and we kept the subjects in hypoglycemic
23 state for about 15 minutes and then had them drink
24 orange juice. Glucose was then measured on arm and
25 finger at 15 minutes before and after drinking the

1 orange juice.

2 [Slide.]

3 Here are all the data in the study. The
4 left panel is Sof-Tact arm versus finger; the right
5 panel is HemoCue arm versus finger. And as you can
6 see here, 100 percent of the Sof-Tact and HemoCue
7 data were clinically acceptable.

8 [Slide.]

9 Now, on the next slide, we will use some
10 more stringent criteria to really look at the
11 hypoglycemia accuracy of the Sof-Tact.

12 What you see here on the left panel is the
13 Sof-Tact finger results versus the reference finger
14 value. On the right panel are the Sof-Tact arm
15 results versus the finger reference value.

16 We used the Draft ISO criterion, which is
17 plus or minus 15 mg/dL when glucose values are
18 below 75 mg/dL. So with this stringent criterion,
19 we see all the results are very tightly inside this
20 criterion, indicating that Sof-Tact provides good
21 accuracy in the hypoglycemic patients.

22 [Slide.]

23 And we went back and looked at the other
24 studies to see if there was any other hypoglycemic
25 data we should also look at, and we saw some in the

1 meal tolerance test, so we combined both studies,
2 and there was a total of 26 Sof-Tact arm results in
3 the hypoglycemic range, which means below 70 here,
4 and 25 out of 26 Sof-Tact arm results, which means
5 96 percent, were within 15 mg/dL of the YSI finger
6 reference values.

7 The other results differed only by 15.6
8 mg/dL. So it really showed the accuracy of the
9 Sof-Tact in detecting hypoglycemia.

10 Therefore, there is no basis to limit the
11 use of Sof-Tact in hypoglycemia.

12 [Slide.]

13 So I have shown you this morning four
14 studies involving more than 400 patients, close to
15 2,000 pairs of arm/finger results, and you saw that
16 all the data points except one were in Zones A and
17 B. So we see clinically acceptable accuracy of the
18 Sof-Tact.

19 [Slide.]

20 In conclusion, our study data supports use
21 of Sof-Tact in both static or steady-state as well
22 as dynamic glucose conditions.

23 Each manufacturer should characterize its
24 device in both static and dynamic conditions with
25 labeling appropriate to performance. The Sof-Tact

1 performance is consistent with current labeling
2 claim, and no new limitations are required.

3 Thank you very much.

4 DR. KROLL: Thank you, Dr. Ng.

5 Now we will hear a presentation by Dr.
6 David Horwitz and Sara Weaver from LifeScan. I'd
7 just remind everybody that you have 20 minutes.

8 DR. HORWITZ: Good morning, members of the
9 panel, FDA, guests. My name is David Horwitz, and
10 I am Vice President, Medical and Regulatory Affairs
11 at LifeScan; also a Board-certified endocrinologist
12 with 18 years clinical practice previously.

13 I will be assisted in my presentation
14 later by Sara Weaver, who is Marketing Manager and
15 formerly a diabetes educator.

16 [Slide.]

17 LifeScan currently markets two meters that
18 are presently labeled for alternate site testing
19 They are the One Touch Fast-Take Meter and the One
20 Touch Ultra Meter.

21 What I would like to do is present two
22 studies today. The first one is one that we
23 previously presented at this year's meeting of the
24 American Diabetes Association in June. The study
25 design there consisted of 42 patients with

1 diabetes. Each subject was tested at six time
2 points--before meals, 60, 90, 120, 150, and 180
3 minutes post-meal; at the finger, the forearm, and
4 the thigh with the One Touch Ultra System; and also
5 fingertip YSI glucose measurements were used for
6 comparison in this study.

7 [Slide.]

8 What I am showing here are similarities of
9 readings. I am using the word "similarity" rather
10 than "accuracy" because I want to stress that we
11 believe the accuracy is the same at each anatomic
12 site, and what we're talking about now is the
13 similarity between the various anatomic sites.

14 In each case, I have talked about readings
15 within 20 percent of tolerance. The current
16 standard for blood glucose meters is that 95
17 percent of values should be within 20 percent of
18 the YSI values for glucose over 100 and within 20
19 mg below 100. I have simplified this to just call
20 it 20 percent here.

21 As you can see, the fingertip values
22 consistently meet the 95 comparison to the
23 fingertip YSI values. However, when we look at
24 both forearm and thigh values, we see good
25 comparison in the pre-meal values, but at 60 and 90

1 minutes following the meal, we see that the
2 similarity between the values tends to fall; but by
3 120 minutes and then at 150 and 180 minutes
4 following the meal, again we see good similarities
5 between values, so the arm values and the fingertip
6 values are certainly equivalent there.

7 [Slide.]

8 The conclusions from this study were that
9 alternate site testing before meals gives accurate
10 results in nearly all patients. However,
11 postprandial testing may not give consistent
12 results between the sites.

13 [Slide.]

14 We did a second study where we took these
15 same subjects and brought them back again. We took
16 38 of those 42 subjects to retest them, basically
17 using the same protocol to look for subject-to-
18 subject consistency.

19 What we found here were results generally
20 consistent with the first study that also showed
21 that within a subject, there was a good deal of
22 variability.

23 [Slide.]

24 I am just going to show two very quick
25 examples of patients here, on the first day and the

1 second day. The first day in this particular
2 patient, you see the lag that we have come to
3 expect between our alternate site and fingertip
4 values. However, on the second day, you can see
5 generally good agreement; and the difference you
6 will notice between those two days is in the rate
7 of change of blood glucose. We all know that
8 diabetic patients can be in good glycemc control
9 one day and, with little visible change in diet,
10 insulin or anything, somewhat less good control.
11 And the lag depends not here on the particular
12 patient--the same patient, the same meal--but
13 basically just day-to-day variability in the
14 patient.

15 [Slide.]

16 The second patient again the same thing--
17 we can see differences in agreement between the
18 sites based on the rate of change in high glucose
19 on days when there is a high glucose rate of
20 change.

21 [Slide.]

22 I think this is probably the most
23 important take-home lesson that I can give you
24 today. Here I have plotted the rate of change of
25 glucose against the difference between the arm and

1 the finger here. There are a couple of
2 conclusions.

3 One, the greater the rate of change in
4 glucose, either up or down, the greater the
5 difference between arm and finger values.

6 The second finding is just looking at a
7 meal test itself, we see a wide range of rates of
8 change of glucose, from more than minus 2.0 to more
9 than plus 2.0 in terms of mg/dL per minute here.

10 We have looked at other correlations. We
11 have looked at patients with Type I and Type II
12 diabetes, body mass index, age of the patient,
13 duration of diabetes. None of those was
14 significant. The only thing that seemed to be
15 related here was the rate of change of blood
16 glucose in these particular studies.

17 [Slide.]

18 In terms of subject preference, blood
19 glucose testing frequency is obviously an important
20 part of maintaining good control, and we asked
21 subjects if they are likely to test more frequently
22 with alternate site testing, and after the second
23 round of testing in these patients, 79 percent of
24 patients said they were likely or very likely to
25 test more often.

1 Interestingly, the first time we studied
2 this group of patients, only 55 percent said that,
3 and the difference between 55 and 79 is
4 statistically significant here. I don't think it
5 is random variation. I think the difference is
6 these were now patients who had been exposed
7 several months previously to alternate site
8 testing, had an opportunity to use it, and I think
9 are answering the question more on the basis of
10 experience than actual frequency, although in this
11 particular study, we do not actually log frequency
12 of testing in the studies.

13 [Slide.]

14 I'd like to turn now to a second study, a
15 study that was done in Europe with 222 subjects in
16 10 countries, 2,400 total comparisons. This was
17 basically at-home comparison of finger and arm
18 testing. No reference method was used. Testing
19 was done at the subjects' usual testing times, with
20 no control over relationship to meals, et cetera.

21 There is a disclaimer that initially we
22 intended this to be a marketing study planned
23 before we were aware of this relationship between
24 rate of change of glucose and arm/finger
25 differences. So although we believe the data are

1 accurate and well-documented, it would not be the
2 type of study we would ordinarily submit to the FDA
3 in terms of documentation.

4 [Slide.]

5 In terms of the qualitative data, 80
6 percent of the subjects here had less pain or no
7 pain, I think confirming what other people have
8 previously shown about this.

9 [Slide.]

10 However, another thing which hasn't come
11 out in previous presentations is that a very
12 important perceived benefit of alternate site
13 testing in this group of patients was protecting
14 the fingertips. People whose fingertips were
15 necessary to their occupations or their hobbies, be
16 it keyboard use, be it playing a musical
17 instrument, being a surgeon or whatever, protecting
18 the fingertips was as important or more important
19 than pain protection. That is a very important
20 benefit to patients in this.

21 [Slide.]

22 We analyzed this data by an error grid
23 analysis, and I'll point out that for proper use of
24 an error grid, it should be a reference method
25 against a meter method. What we actually have here

1 is two different meter methods, so remember this
2 takes the variability of both measures into
3 account.

4 You can see that with the testing done in
5 this study, random testing which was not done in
6 relation to meals or anything, but just when
7 subjects usually test, we actually got 96 percent
8 of all points in the A Zone or the B Zone,
9 regardless of when samples are drawn. Remember A
10 and B Zones are zones that are felt to be
11 clinically meaningful.

12 There is, if you look, though, down at the
13 hypoglycemic range, a little spillover into the D
14 Zone, which is one of the concerns that has been
15 raised about alternate site testing.

16 [Slide.]

17 If we look at the data in the study that
18 were obtained in the morning fasting studies, you
19 can see that if we look at fasting samples, 99
20 percent of all points are in the A and B Zones; and
21 again, if we look at the hypoglycemic samples here,
22 we generally see good agreement with only minor
23 spillover into the very corner of the D Zone in a
24 very small number of patients there.

25 [Slide.]

1 The MDR or Medical Device Reporting data
2 of adverse events we think is an important
3 indicator of whether or not there are actually any
4 safety issues with alternate site testing.

5 What I have done here is taken data from
6 our Fast-Take meter that was done in the 12 months
7 before alternate site labeling was cleared for the
8 Fast-Take meter there. So before alternate site
9 labeling, we see an MDR rate of 0.01 MDRs filed per
10 million strips shipped per 12 months or per year.

11 With the Ultra meter, we see the number of
12 MDRs is approximately the same, 0.02--there is some
13 rounding in here--and there is no reference to AST.
14 And with reference to AST, there is actually 0.01,
15 the same as pre-AST labeling. That 0.01 actually
16 corresponds to exactly three MDRs that were filed,
17 none of which relates to injuries due to
18 inaccuracy. One was forearm pain, one was hives
19 and was believed to be a reaction from the lancer
20 cap, and one from bruising; but as I said, none
21 related to accuracy or mistreatment of diabetes
22 related to alternate site testing.

23 [Slide.]

24 The purpose of the panel, as you all know,
25 is to provide advice and recommendations to the FDA

1 on the types of data and/or labeling needed to
2 address problems associated with using blood
3 samples from alternate sites. So I would like to
4 give LifeScan's recommendations here.

5 [Slide.]

6 We believe the data should address normal
7 perturbations in glucose, most specifically, meals,
8 medication, and exercise; and we have shown meal
9 data, and as you have seen, meal data seems to
10 cover the range of glucose excursions typical of
11 most patients' everyday life and also seems to
12 include that which is due to exercise. And because
13 our patients were taking their normal medications,
14 be it oral agents or insulin, during the study, we
15 believe that that was also covered in this.

16 We also think that the recommendations on
17 labeling should be site-specific and relate
18 specifically to arm, thigh--and we didn't do palm,
19 but palm obviously would be another site--and not
20 lump all alternate site testing together.

21 We believe labeling should address the
22 expected variations that are appropriate, or at
23 least appropriate times, for alternate site
24 testing, and I'll give you more specifics about
25 that, and then give precautions about hypoglycemia

1 when necessary.

2 [Slide.]

3 So in summary, our proposed labeling
4 should point out to patients that under certain
5 conditions, samples obtained from the arm may
6 differ from the fingertip; conditions where these
7 differences are most likely to occur are when blood
8 glucose is changing rapidly; when it is changing
9 rapidly, we believe that fingertip values will show
10 changes more rapidly than the arm.

11 Our recommendation to patients is that
12 when blood glucose is falling, testing with a
13 fingertip sample may identify hypoglycemia sooner
14 than a test with an arm value; and that arm values
15 we believe should be used only for testing prior to
16 or more than 2 hours after a meal, an insulin dose,
17 or physical exercise.

18 [Slide.]

19 Furthermore, testing performed within 2
20 hours after a meal, within 2 hours of an insulin
21 dose or physical exercise, or if the patient feels
22 that the glucose level may be changing rapidly,
23 should be done from the fingertip.

24 Fingertip testing should be done if there
25 is a particular concern about hypoglycemia, such as

1 driving a car, particularly if a person is known to
2 suffer from hypoglycemia unawareness.

3 And we believe that routine testing before
4 meals can be done either at the fingertip or the
5 arm.

6 [Slide.]

7 We actually tested this labeling to be
8 sure that patients really would understand these
9 limitations if they were in the labeling. We did a
10 36-subject labeling comprehension study. We
11 assessed reading abilities based on the SORT-R test
12 and demonstrated that comprehension was at least 81
13 percent.

14 [Slide.]

15 This basically shows the range of reading
16 levels in our study population. The majority had
17 at least a high school graduate education, but we
18 did have patients in the study with reading levels
19 from the fourth grade up.

20 [Slide.]

21 Labeling comprehension, as you can see,
22 shows that 89 percent of subjects recognize that
23 exercise can influence it; 89 percent recognize
24 that following a meal, they may be different.
25 Probably the most important, 97 percent were able

1 to understand that when the blood glucose was
2 changing rapidly, fingertips would detect the
3 changes more rapidly.

4 [Slide.]

5 One hundred percent understood that a
6 meal, insulin dose, or exercise could cause the
7 blood glucose to change rapidly; 97 percent
8 understood the concept of testing by the fingertip
9 if there is concern about hypoglycemia.

10 The last question, 81 percent got it
11 right; that was when routine testing should be
12 done. With hindsight, we have worded the question
13 more properly, and subjects were interpreting it as
14 when should they routinely test rather than how
15 they should routinely test; we think that
16 rephrasing the question would get a better answer.

17 [Slide.]

18 In conclusion, we believe that many
19 patients desire the ability to test alternate
20 sites. The available data provide a good
21 indication of that uses and limitations of
22 alternate site testing. Under proper
23 circumstances, alternate site or arm testing
24 specifically is a useful predictor of fingertip
25 glucose levels, and appropriate labeling is

1 understood by patients.

2 What I would like to do now is turn the
3 podium over to Sara Weaver who is going to talk
4 very briefly about some of our health professional
5 education programs that we are using to try to
6 communicate this to the health professionals.

7 MS. WEAVER: Hi. My name is Sara Weaver,
8 and I am the Marketing Manager at LifeScan. Prior
9 to working in the business world, I was a diabetes
10 educator in both inpatient and outpatient settings
11 for 5 years.

12 One of my responsibilities at LifeScan is
13 to develop materials and programs to talk about our
14 products and services. For the last 5 months,
15 alternate site testing has been our number one
16 priority.

17 We started in June at the American
18 Diabetes Association and had a live product panel.
19 And in lieu of talking about a new product, we
20 talked about alternate site testing.

21 Dr. Horwitz presented the data that he
22 just talked about; as well, Dr. Koschinsky, whose
23 data will be presented this afternoon, talked to
24 health care professionals about his clinical
25 findings on alternate site testing.

1 We also had a poster session about
2 alternate site testing at the American Diabetes
3 Association meeting, and as well, we have material
4 that says "One-Touch Ultra: Promote Patient
5 Success with New Alternate Site Testing
6 Guidelines."

7 Then, in order to reach health care
8 professionals who were not in attendance at the
9 American Diabetes Association meeting or the
10 American Association of Diabetes Educators meeting,
11 we mailed a direct mail piece that reached over
12 90,000 health care professionals. The direct mail
13 piece had both the clinical findings that Dr.
14 Horwitz just presented as well as the FDA labeling
15 that was approved for alternate site testing,
16 talking about the appropriate times for patients to
17 use alternate site testing.

18 We also have a sales force that calls on
19 20,000 health care professionals, and for the last
20 5 months in the marketplace, their number one
21 product position has been alternate site testing.
22 What this means is that when they walk into a
23 health care professional's office, the first thing
24 they talk about is alternate site testing and the
25 appropriate use of it in practice.

1 They have an alternate site testing kit
2 which has a lot of information for both the health
3 care professional and the patients.

4 We have a brochure in the kit, "Frequently
5 Asked Questions about Alternate Site Testing," and
6 these were compiled from questions that came in
7 from health care professionals on our customer
8 service line. As well, there is a patient brochure
9 which is available at retail where our products are
10 sold and in physician offices, and it is "One-Touch
11 Ultra: What You Should Know About Alternate Site
12 Testing." It goes over the labeling and the
13 appropriate times for use of alternate site
14 testing.

15 In addition in the alternate site testing
16 kit is this piece that promotes success with
17 alternate site testing amongst your patients.

18 So I just wanted to share with you that at
19 LifeScan, we have taken the responsibility and
20 taken it very seriously to educate both our patient
21 customers as well as our health care professional
22 customers on alternate site testing and the
23 appropriate use of it.

24 Thank you.

25 DR. KROLL: Thank you.

1 We now have a few minutes if any panel
2 members have any questions for any of the sponsor
3 presenters.

4 Dr. Cara?

5 DR. CARA: In any of the studies that were
6 reported this morning, were there any individuals
7 less than, in one case, 14 years of age and in the
8 other, less than 18 years of age? In other words,
9 has alternate site testing been evaluated
10 thoroughly in the pediatric age group?

11 DR. PELED: We have done it throughout our
12 life in the marketplace and not particularly toward
13 the submission on the palm, but on arm samples, we
14 have done it down to very young children, and it
15 has been in use by very young children.

16 DR. CARA: And what have you observed?

17 DR. PELED: At the time, we weren't
18 looking for lags, but the accuracy was acceptable
19 as we were doing it normally 2 hours postprandial.

20 DR. CARA: But the issue of lag wasn't
21 addressed?

22 DR. PELED: No.

23 DR. KROLL: I would just remind everyone
24 to please state their name when they speak.

25 DR. HORWITZ: David Horwitz from LifeScan.

1 Not in the study we have shown today but
2 in the study we presented initially to the FDA with
3 our 510(k), one of the investigators was a
4 pediatric endocrinologist, Dr. Stewart Brink in
5 Massachusetts, who included children, some as young
6 as 8, in that particular study.

7 DR. CARA: And what was observed?

8 DR. HORWITZ: And actually, Dr. Brink's
9 study, which was done before we began to do
10 informal meal testing, just random time of day
11 testing, he showed equivalency between arm testing
12 and finger testing at the times that subjects
13 usually did their testing, but it wasn't a stressed
14 testing with the meal or anything.

15 DR. ROSENBLOOM: I think Jose raises a
16 very interesting question, because there may be
17 quite different profusion issues in the children we
18 are concerned with as pediatricians. I think
19 that's something we need to address later in our
20 discussions.

21 DR. MANNO: I don't remember hearing age
22 distribution on the other end of the scale from the
23 pediatric group; how old were the patients.

24 The other thing I would ask is in using
25 the palm sites, was there any difference or

1 distinction between people whose palms were highly
2 calloused versus persons who weren't--the white
3 collar worker versus the blue collar worker is one
4 way of putting it. I just wonder if you saw any
5 differences there, or did you note that.

6 DR. PELED: Nina Peled with Amira Medical.

7 Yes, we had people with calloused palms.
8 Actually, where we are, which is in Scotts Valley,
9 California, it is quite a farmers community, so a
10 lot of our patients are coming from farms and have
11 calloused hands.

12 On the high side of the age groups, I
13 believe we went up to 64. It is listed per study
14 what the age ranges were.

15 DR. HENDERSON: I have a couple questions.
16 Were any of these devices--

17 DR. KROLL: Excuse me, Dr. Henderson. Dr.
18 Ng wanted to comment.

19 DR. NG: Ron Ng, Abbott Laboratories.

20 In our study, we looked at subjects over
21 70 years of age.

22 DR. HENDERSON: Dr. Ng, before you sit
23 down, how much does your device weigh?

24 DR. NG: Could you repeat that question,
25 please?

1 DR. HENDERSON: How much does your device
2 weigh?

3 DR. NG: Oh. I don't have the actual
4 specification.

5 DR. HENDERSON: It just looks awfully
6 bulky.

7 DR. NG: Yes, if you are thinking about
8 the size--the weight is pretty light because the
9 case is made of plastic. You might have seen it
10 when I put it in the case, and when it is in the
11 case, it is comparable to the size of a typical
12 glucose meter carrying case with a lancing device,
13 lancet, test strip. With our device, you could put
14 everything inside the Sof-Tact and carry it. So
15 the size of the carrying case is comparable to
16 meters designed for finger-stick testing, because
17 everything is already inside the meter.

18 DR. HENDERSON: Okay. In any of your
19 studies, did you address the issue of capillary
20 fragility as you are sucking with the suction
21 device? In particularly older patients or patients
22 who have capillary fragility, do you have any
23 increase in rupture with patients having bruises
24 and certainly skin necrosis?

25 DR. NG: We have not seen any problem.

1 When we look at, for example, the MDR report, we
2 have only two MDR reports so far of complaints on
3 the device, and one of the two was bruising. But
4 in our study, it is not a problem with bruising.

5 DR. HENDERSON: How many do you have in
6 use in the public now, currently?

7 DR. NG: Oh, there are thousands and
8 thousands in use both in the U.S. and outside the
9 U.S.

10 DR. HENDERSON: And you talked about the
11 younger age and the older age. Is there any data
12 on use in pregnancy?

13 DR. NG: We have not conducted studies
14 focusing on collecting data on pregnant subjects,
15 but it is conceivable that there are pregnant users
16 using our device--

17 DR. HENDERSON: In Europe, probably?

18 DR. NG: --but we have not done a study on
19 it.

20 DR. HENDERSON: Thank you.

21 DR. ROSENBLOOM: Rosenbloom.

22 I don't know if I missed it, but one of
23 the considerations would be duration of diabetes,
24 because with increased duration of diabetes, there
25 is decreased circulation and loss of skin

1 appendages, thickening of the skin, particularly of
2 the dorsum of the forearm that we described years
3 ago; I think there is less of that nowadays, but
4 even in relatively young patients--and duration
5 would be a good proxy for that problem.

6 Do we have data indicating whether
7 duration of diabetes might explain some of the
8 individual variability in the differences between
9 forearm, which is an "alternative" not an
10 "alternate" site. An alternate site would be one
11 you do every other time--it's an alternative site.

12 DR. HORWITZ: David Horwitz, LifeScan.

13 We actually addressed that question. In
14 fact, one of the initial hypotheses in our study
15 was that that would be important. A question came
16 up, actually, with one of our LifeScan employees
17 who had been using it who has had diabetes for
18 probably about 30 years, who said, "Gee, it doesn't
19 seem to give the same results on my arm as some of
20 my younger colleagues here."

21 We were just unable to demonstrate that.
22 We looked at it initially--actually, we repeated
23 subjects twice. The first time, there was a hint
24 that that might be the case; also, that it might be
25 related to body mass index because obesity might be

1 a factor in capillary profusion. But when we
2 brought subjects back, that part of the correlation
3 fell apart, and the only relationship we could
4 find--again, a fairly small study of 42 patients--
5 was that rate of change of glucose was the only
6 variable that correlated with differences.

7 DR. ROSENBLOOM: I would also think that
8 the suction device might have quite different
9 functional characteristics in those people who have
10 stiff forearm skin, and this can approach 40, 50
11 percent in Type II diabetes, I know.

12 DR. NG: So far, we have not seen any
13 correlation between the success rate in terms of
14 arm testing with our Sof-Tact device or accuracy
15 with the duration of diabetes.

16 DR. ROSENBLOOM: Thank you.

17 DR. AHMANN: Ahmann.

18 I have one question for Amira. You had
19 talked about palm testing, and you stated that it
20 was preferred over the arm. There are lots of
21 reasons why that might occur, including convenience
22 with long sleeves and other issues. You mentioned
23 a pain scale, and you gave favorable comment, but
24 you didn't actually give a relative means in terms
25 of the pain scale between the arm and the palm. Do

1 you have that data?

2 DR. PELED: Nina Peled, Amira Medical.

3 I don't have that data with me here, but
4 we do have that data, and the only data I was
5 presenting was when patients were asked to rate
6 their palm pain between 0 and 5, and most of them
7 were at 0 and 1.

8 Similarly, when we did arm studies, we had
9 obtained similar ratings on the arm.

10 DR. AHMANN: Okay.

11 I have one other question that is a
12 general question. Has anybody done anything that
13 looks at concomitant medications--aspirin, beta-
14 blockers, anything that might have any effect on
15 this?

16 DR. PELED: We have not.

17 DR. CARA: Cara.

18 Perhaps Dr. Horwitz or Ms. Weaver can
19 answer this question. You looked at the percent of
20 patients who were actually understanding of your
21 proposed guidelines or labeling. Did you look by
22 any chance to try to evaluate in some way what
23 percent of patients actually read the label?

24 [Laughter.]

25 DR. HORWITZ: Horwitz, LifeScan.

1 No, we actually haven't done that. We are
2 all interested in that. I think different read
3 different parts of the labeling, but I can't give
4 you a good number for that.

5 MS. LELLOCK: Diane Lellock.

6 One question I had that I read in the
7 material that was sent to me was it talked about
8 the lag time and rubbing "vigorously." Well,
9 sitting here earlier, I watched this little fellow
10 test his blood sugar, and I watched him rub. To
11 me, it was a quick rub, not a vigorous rub, and
12 that is a question I have. What is "vigorous"?
13 What does that mean--because for the average person
14 out there testing his blood sugar, we all have a
15 different thought of what that is, whether you are
16 4 or 80. Good question.

17 Can anybody address that?

18 DR. CONNER: Mr. Chairman, we have not yet
19 made our presentation, but if I could address that
20 question, please.

21 DR. KROLL: Yes, briefly. State your name
22 first.

23 DR. CONNER: I am Eve Conner from
24 TheraSense.

25 Our labeling instructions do include the

1 rubbing of the test side, and the way the
2 instructions are written, it is "Rub the test site
3 vigorously for a few seconds until you feel it
4 getting warm."

5 MS. LELLOCK: Okay.

6 DR. NG: Ron Ng, Abbott Laboratories.

7 In the design of the Sof-Tact device by
8 our company, we recognized the importance of
9 perfusion, and we know that rubbing increases
10 temperature, increases perfusion. That is why we
11 designed our device not to involve rubbing; it uses
12 the unique suction mechanism to stretch the skin.

13 Thank you.

14 DR. CLEMENT: I have a question for Dr.
15 Horwitz. I would like to see in your labeling
16 proposal--I think a lot of thought went into that--
17 one of the problems we see in Type I diabetic
18 patients is that even between meals, they can
19 become hypoglycemic right before their next meal if
20 their insulin is peaking for whatever reason, and
21 also exercise can cause--as we saw in some of the
22 data--fairly dramatic drops in blood glucose levels
23 as much as 50 points per hour or even more.

24 Have you thought about any of those issues
25 in your proposed labeling?

1 DR. HORWITZ: I think those are the
2 conditions we have tried to get at when we talk
3 about conditions where your blood glucose may be
4 changing rapidly. And patients can easily tell if
5 it is changing rapidly. You say how do you know,
6 but if one test is 200 and the next test is 80, you
7 know you are changing rapidly, and if your second
8 test was at the arm, the recommendation would be to
9 go back and recheck that at the fingertip to make
10 sure it is not actually below 80.

11 So I think that is built into the
12 recommendations and needs to be part of the
13 educational process.

14 DR. ROSENBLOOM: I think that was some of
15 what I have wanted to ask.

16 I was concerned when I first started
17 reviewing the labeling. We see patients who are
18 rapidly changing when they don't expect to be
19 rapidly changing, and instructions to not use the
20 alternative site at a time of rapid change is
21 confounded by that variability that even
22 experienced patients can't always tell when they
23 are in a time of rapid change. That is one of the
24 things that bothers me and that is, quite frankly,
25 the reason why my colleagues aren't using

1 alternative site testing, because you just don't
2 know when that rapid change is going to occur.

3 Certainly it is predictable that bedtime
4 and fasting morning and most pre-meals are stable,
5 but in between meals, as you have indicated, and
6 other times--5 hours after exercise--may be a time
7 of rapid drop, and it is not always as predictable
8 as is suggested by the labeling that says "when you
9 expect a rapid change"; you can't always expect it.
10 That's a basic concern, and I'm not sure anybody
11 has an answer for that.

12 DR. KROLL: All right. I'd like to thank
13 all the sponsors, presenters and the panel members.
14 We'll hold any other questions until later.

15 We'll take a break now and resume at
16 10:15.

17 [Recess.]

18 DR. KROLL: At this time, we're going to
19 continue with the sponsor presentations. Would
20 everyone please take their seats?

21 The next presenters are Drs. Eve Conner
22 and Martin Abrahamson, and they are going to be
23 speaking for TheraSense.

24 DR. CONNER: Dr. Kroll, ladies and
25 gentlemen, good morning. My name is Eve Conner. I

1 am Vice President of Quality Assurance and
2 Regulatory Affairs at TheraSense.

3 I would like to thank the agency for
4 giving us an opportunity to speak this morning.

5 After my brief overview, Geoff McGarraugh,
6 Director of Chemistry at TheraSense, will present
7 our clinical data; then I will discuss the labeling
8 based on that data.

9 Dr. Abrahamson, Chief of Adult Diabetes at
10 the Joslin Diabetes Center, will give a brief
11 summary of his experience with alternate site
12 testing; and I will conclude with my remarks on
13 alternate site testing based on the alternate site
14 issues raised by the FDA in their questions to the
15 panel.

16 [Slide.]

17 Our key messages this morning are that
18 there is substantial data to demonstrate the safety
19 and effectiveness of alternate site testing.
20 Alternate site testing has benefits and meets
21 important patient needs. The rapid adoption of
22 alternate site testing demonstrates, I think, that
23 there was a need and that that need is being filled
24 by alternate site devices.

25 More frequent testing, especially for

1 children and the elderly, is very important, and
2 less painful testing as well.

3 Our user experience for the last 18 months
4 that the product has been on the market supports
5 the safety of the product. We have over 400,000
6 users, and we have shipped at least 100 million
7 test strips. In that same period of time, we have
8 had a serious adverse event rate reported of one
9 per 3 million tests. And we define a serious
10 adverse event as any event requiring medical
11 intervention or the assistance of another.

12 We believe that our product is properly
13 labeled, that the labeling is supported by data,
14 that potential risks are identified and are
15 adequately managed through the labeling.

16 Labeling comprehension studies show that
17 the users do understand the labeling, and the
18 labeling meets the FDA requirements.

19 We believe that our product FreeStyle is
20 safe and effective and that the benefits of
21 alternate site testing far outweigh any risks
22 associated with the devices.

23 Now I would like to turn the podium over
24 to Geoff McGarraugh, who will present our clinical
25 data and summarize the conclusions.

1 DR. McGARRAUGH: Good morning. My name is
2 Geoff McGarraugh, and I am the Director of
3 Chemistry at TheraSense. I am here to describe the
4 extensive clinical studies we have conducted to
5 evaluate the accuracy and safety of the FreeStyle
6 monitor.

7 We have a large body of data, and I will
8 only touch on the highlights.

9 [Slide.]

10 This slide demonstrates the broad scope
11 and depth of the studies we have undertaken. These
12 studies deal mainly with the forearm as the
13 alternate site for the purpose of example.

14 We found that forearm, upper arm, thigh,
15 calf, and back of the hand behaved the same.

16 Beyond the accuracy studies necessary for
17 a 510(k) submission, these studies were conducted
18 under a variety of situations, and non-steady-state
19 conditions were thoroughly assessed. These include
20 time course studies where glucose changes are
21 monitored very frequently over many hours. These
22 studies were done to explore physiological
23 differences. They include arm/finger studies where
24 direct comparisons of arm and finger tests were
25 made with a large number of subjects which were

1 done to confirm hypotheses developed in the time
2 course studies; and they include field studies
3 where the product is placed in the uncontrolled
4 environment of home use for several weeks. These
5 were done to demonstrate that people could perform
6 the test properly and follow the labeling
7 correctly.

8 And to determine the effectiveness of
9 FreeStyle in detecting hyperglycemia, outcome
10 studies were conducted that include hemoglobin A1c
11 levels as a measure of the subjects' long-term
12 blood glucose control.

13 [Slide.]

14 I will begin the discussion with a time
15 course study.

16 Patients with Type I diabetes were studied
17 in a clinic, but other conditions were kept as
18 normal as possible. Normal meals, insulin therapy,
19 and exercise were maintained.

20 FreeStyle readings from the arm and finger
21 were taken simultaneously every 10 to 20 minutes
22 for 6 to 8 hours. These studies allowed us to
23 observe time lags and find ways to mitigate them.

24 [Slide.]

25 This slide shows the response of a single

1 patient but is representative of the kind of
2 results we saw in other subjects. The finger
3 readings in red first increase, then come back down
4 and stabilize. The arm readings in blue lag in
5 time, both going up and coming down. This was a
6 very significant discovery. It explained the
7 subtle differences between arm and finger tests
8 observed in accuracy studies.

9 We discussed the implications of these
10 findings with our medical advisory board, who
11 thought that increasing circulation by rubbing a
12 site could decrease or eliminate the lag. Rubbing
13 was added to the procedure, and we repeated the
14 time course studies.

15 [Slide.]

16 This is the same patient I showed you
17 previously. As you can see, the lag time is
18 effectively eliminated. This phenomenon was
19 observed in a majority of subjects.

20 [Slide.]

21 To confirm the results we saw in the time
22 course studies, we repeated the arm/finger
23 comparison studies on a large number of subjects.
24 Without rubbing, the intercept was greater than
25 zero and the slope less than 1. The effect of not

1 rubbing is subtle, but it could be clinically
2 significant at low glucose. This is an example of
3 the dampening effect that was discussed earlier.

4 But when the arm was rubbed, the bias was
5 completely eliminated. The intercept is nearly
6 zero, and the slope is nearly 1--an almost perfect
7 regression line.

8 [Slide.]

9 In the arm/finger comparison studies, we
10 included a laboratory reference measurement with
11 capillary blood from the finger. When we compared
12 arm and finger FreeStyle measurements to the
13 capillary reference method, there was slightly more
14 scatter in the arm data than in the finger. Given
15 the additional scatter, we wanted to know if this
16 subtle difference had any clinical implications, so
17 we expanded the scope of our time course studies.

18 [Slide.]

19 While rubbing eliminated or substantially
20 reduced the lag in the majority of subjects, here
21 is a worst case example where rubbing did not
22 sufficiently reduce the lag. There was a small
23 window in time when the lag could be clinically
24 significant. It is important to treat hypoglycemia
25 as soon as possible, so the time lag of

1 approximately 20 minutes could be important. For
2 this subject, the finger measurements provided the
3 necessary information sooner. Under these
4 conditions, the finger should be used when testing
5 for hypoglycemia.

6 [Slide.]

7 To evaluate the effectiveness of the
8 FreeStyle system in detecting hyperglycemia, an
9 outcomes study assessing hemoglobin A1c as the
10 measure of long-term glucose control of patients
11 using finger-stick testing and arm-stick testing.
12 The study was a crossover design where every
13 subject used FreeStyle and their finger-stick meter
14 for 3 months each.

15 [Slide.]

16 This slide shows the results of that
17 study. There was a clear improvement in A1c for
18 subjects who used FreeStyle meter on the arm, and
19 that improvement was comparable to the improvement
20 for subjects using the finger-stick meter. No
21 adverse events were reported for either finger-
22 stick or FreeStyle meters, and the FreeStyle meter
23 was highly preferred.

24 This long-term study confirms that glucose
25 control is maintained with arm testing, that

1 FreeStyle is effective in monitoring and
2 controlling hyperglycemia, and that FreeStyle was
3 preferred by three-quarters of the subjects.

4 As you can see, we have made a concerted
5 effort to conduct thorough, rigorous, and well-
6 controlled studies from which valid conclusions can
7 be drawn. There are two studies not sponsored by
8 TheraSense that may seem to contradict our
9 findings, but these studies lack the scientific
10 rigor necessary to support their conclusions.

11 You may already be familiar with these
12 studies, so we felt it important to point out the
13 flaws and explain why the conclusions reached are
14 not appropriate.

15 [Slide.]

16 The first study reported in a Letter to
17 the Editor of Diabetes Care concluded that
18 alternate site testing is potentially dangerous and
19 would unnecessarily endanger the lives of diabetic
20 patients. In fact, it was this study that
21 precipitated the events leading to the calling of
22 this panel meeting.

23 It was done on a very small study, 6
24 subjects, using FreeStyle contrary to its
25 instructions, under unrealistic, nonphysiological

1 conditions. Using a glucose tolerance test without
2 the required insulin to induce hyperglycemia,
3 followed by IV insulin to plunge the patient into
4 hypoglycemia does not correspond to normal
5 physiological conditions.

6 The rate of change of 5-8 mg/dL per minute
7 in this study is well beyond what is normally seen.
8 And the study conclusions were not supported by any
9 studies conducted under real life situations.

10 [Slide.]

11 The second study was performed using our
12 product, FreeStyle, in an uncontrolled field
13 environment without a suitable control. As I will
14 demonstrate, it is not possible to make reliable
15 conclusions from this type of study design.

16 With this study design, you cannot
17 determine how much of the error is attributable to
18 system and user error and how much is attributable
19 to arm/finger physiology.

20 We have also conducted field studies, but
21 the design of our studies allows for meaningful
22 interpretation. The key difference is the use of
23 duplicate samples in our studies. By using
24 duplicate measurements, it is possible to assess
25 the measurement error independently of the

1 physiological difference.

2 [Slide.]

3 This graph shows the deficiencies of an
4 uncontrolled study. The scatter in the data is the
5 difference between duplicate finger-sticks. You
6 can see there can be considerable differences in
7 two finger-stick measurements taken at the same
8 time by the same person with the same device.

9 Without controlling for this variable, the
10 uncontrolled study made unsupportable conclusions
11 about physiological differences.

12 [Slide.]

13 To quantify this type of data, we looked
14 at the frequency of obtaining large discrepancies
15 between duplicate measurements--30 mg/dL at low
16 glucose or 30 percent at high glucose. A
17 discrepancy this large would not be inspected in
18 light of the reported reproducibility of these
19 products.

20 The data in white is the discrepancy rate
21 of duplicate tests from the same site. This is
22 measurement error. The FreeStyle arm/finger
23 differences in red are due to physiological
24 differences and measurement error combined. The
25 total discrepancy rate in the FreeStyle system,

1 including physiologic difference, is less than the
2 measurement error alone in two of the most popular
3 finger-stick products.

4 When this study was done, these two
5 systems accounted for over half of the products
6 being sold.

7 The uncontrolled field studies ignored the
8 existence of user error and attributed all
9 arm/finger discrepancies to physiological
10 differences. But more significantly, they didn't
11 make the importance comparison to finger-stick
12 products that are currently used safely in the
13 field despite their technological limitations.

14 Therefore, the conclusions drawn in these
15 studies are not valid.

16 [Slide.]

17 Let me conclude by showing you a Clarke
18 Error Grid analysis of FreeStyle accuracy comparing
19 FreeStyle to a laboratory reference method.

20 This is an appropriate and well-accepted
21 method for assessing clinical utility, and 99
22 percent of the FreeStyle alternate sites are
23 clinically acceptable by this analysis.

24 Although there can be a physiological lag
25 in glucose changes at some alternate sites, it can

1 be minimized by rubbing the site vigorously before
2 lancing. Even with rubbing, there is an infrequent
3 but real possibility for delayed detection of
4 hypoglycemia, so fingertip testing is recommended
5 when testing for low blood sugar.

6 Long-term glucose control can be
7 maintained or improved using alternate site tests,
8 and by the accepted measures of accuracy, FreeStyle
9 alternate site tests are safe, effective, and
10 accurate.

11 Now I'd like to turn the podium back to
12 Eve Conner. Thank you for your attention.

13 DR. CONNER: As you saw in Geoff's
14 presentation, we have done extensive studies to
15 support our labeling. We have developed a test
16 method that includes rubbing the test site before
17 lancing to minimize any physiologic lag.

18 [Slide.]

19 In developing our labeling, we looked to
20 FDA guidance documents and concluded that good
21 labeling requires that we be able to motivate the
22 user to read the labeling, that it be simple and
23 clear, and more importantly, that it be supported
24 by appropriate data.

25 [Slide.]

1 This is a sticker that we put on the
2 outside of our labeling materials in our system kit
3 to encourage people to read the labeling to
4 understand that alternate site testing is different
5 from finger-stick testing.

6 [Slide.]

7 Our labeling informs the user about the
8 physiologic lag. That is, we tell them that arm
9 and finger values can be different, that this is
10 not an accuracy issue with the system, it is a
11 physiology issue; we explain when the lag might be
12 expected, that is, at times when glucose is
13 changing rapidly; we provide the user with very
14 simple instructions for minimizing or eliminating
15 the lag, and that is rubbing the site vigorously
16 for a few seconds until it is warm; and we
17 recommend fingertip testing when testing for
18 hypoglycemia or if the user has hypoglycemic
19 unawareness.

20 [Slide.]

21 Our evidence supports that users do
22 understand the labeling. Labeling comprehension
23 studies were done before we launched the product.
24 They were included as part of our 510(k) support
25 data. We also conducted subsequent user studies.