

1 The outcomes studies that Geoff discussed also
2 support the fact that the readers do understand and
3 follow the instructions, and our user experience
4 also supports that people understand the labeling.

5 [Slide.]

6 TheraSense and its medical advisors
7 believe that our studies adequately define the
8 potential risk and device performance for the
9 purposes of regulatory clearance of alternate site
10 testing systems. We also believe that our proposed
11 labeling provides adequate information about the
12 potential difference in blood glucose measurements
13 between different body sites and provides adequate
14 instructions for managing the potential risk.

15 TheraSense does not believe that
16 additional studies are required for the purpose of
17 regulatory clearance.

18 [Slide.]

19 That our labeling and educational efforts
20 are effective is borne out by our experience with
21 adverse events. Since the product was first
22 commercially distributed, as I mentioned earlier,
23 we have approximately 400,000 users, and 100
24 million tests have been conducted. In that same
25 time period, our Serious Adverse Event Report rate

1 has been one event per 3 million tests.

2 In March of 1997, this Advisory Panel
3 concluded that that was an acceptable MDR rate for
4 blood glucose monitors, and more importantly, we
5 have had no sequelae and no deaths as a result of
6 any of these events that have been reported.

7 Now I would like to turn the podium over
8 to Dr. Abrahamson, who will give you a brief view
9 of his experience with alternate site testing.

10 Dr. Abrahamson?

11 DR. ABRAHAMSON: Good morning, Mr.
12 Chairman, members of the panel, ladies and
13 gentlemen.

14 I am Martin Abrahamson, Chief of Adult
15 Diabetes Section at the Joslin Clinic in Boston,
16 and Assistant Professor of Medicine at Harvard
17 Medical School.

18 As a clinician and teacher, I am actually
19 delighted to be here to talk about some of my
20 experience in treating patients with diabetes.

21 [Slide.]

22 Home blood glucose monitoring with
23 finger-stick devices has provided a major advance
24 in the management of patients with diabetes and has
25 led to significant improvements in glycemic control

1 for many patients.

2 Despite its major benefit, finger-stick
3 home glucose monitoring has its drawbacks. It is
4 painful, and this precludes many people from either
5 testing their blood sugars at all or performing
6 tests frequently, sometimes three or four or even
7 more times daily.

8 Indeed, we know that the frequent testing
9 of blood glucose reduces significantly the risk of
10 hypoglycemia as well as hyperglycemia and provides
11 patients and their providers with invaluable
12 information regarding glucose excursions that allow
13 rational changes that can be made in lifestyle
14 and/or pharmacologic therapy.

15 Alternate site testing represents a major
16 advance in home blood glucose monitoring. It is
17 less painful, and it provides an alternative for
18 people who are unwilling to test on their fingers.
19 It is especially valuable for parents testing
20 children, who often balk at the thought of having
21 their fingers pricked frequently.

22 In the trenches or in the field, where we
23 see many patients with diabetes, there is no doubt
24 that many patients prefer alternate site testing
25 and check their blood glucose levels more

1 frequently as a result of this option.

2 The question is is this as accurate as the
3 so-called gold standard, which is finger-stick
4 testing. I believe there is good data that has
5 been presented that shows that alternate site
6 testing is as accurate as finger-stick testing
7 under the following circumstances--under steady-
8 state conditions when blood glucose levels are not
9 changing rapidly and under conditions when blood
10 glucose levels are changing at a physiologic rate,
11 for example, after meals when blood glucose levels
12 are rising and then falling, provided subjects
13 follow their testing in accordance with the
14 manufacturer's instructions, which are easy to read
15 and understandable.

16 Even finger-stick glucose measurements are
17 not always 100 percent accurate when compared to
18 laboratory measurements of venous plasma glucose.
19 Indeed, as you have seen, the measurement error
20 present in alternate site testing is no greater
21 than the measurement error in some finger-stick
22 devices currently available on the market. And
23 serious adverse events from glucose monitoring are
24 rare in day-to-day clinical practice where the
25 testing is by finger-stick or at alternate sites.

1 Given the fact that the research in
2 alternate site testing has shown that there is some
3 lag between alternate site and finger-stick glucose
4 levels, it is appropriate to point out that
5 alternate site testing should not be utilized when
6 patients complain of symptoms of hypoglycemia. And
7 to take this one step further, alternate site
8 testing would not be appropriate for patients who
9 have hypoglycemic unawareness.

10 In summary, therefore, alternate site
11 testing represents a major advance in diabetes
12 management. It facilitates adherence to
13 therapeutic regimens, makes testing of glucose more
14 frequently an achievable and more realistic goal
15 for patients, and allows more rational adjustments
16 to therapy for patients, thereby improving overall
17 metabolic control without increasing the risk for
18 serious adverse events such as hypoglycemia.

19 Thank you for your attention.

20 DR. KROLL: Thank you.

21 Now we'll hear from Luann Ochs from Roche
22 Diagnostics.

23 DR. CONNER: Could I finish with my
24 conclusions very quickly? It will be less than a
25 minute.

1 DR. KROLL: You have 30 seconds.

2 DR. CONNER: Okay.

3 [Slide.]

4 With regard to the alternate site issues
5 that we have been discussing here today, TheraSense
6 believes that the data required for alternate site
7 testing should follow current guidelines but that
8 additional time series or other appropriate studies
9 should be conducted, depending on the claims that
10 the manufacturer wishes to make.

11 The data analysis should also follow the
12 current guidelines and should include evaluating
13 time series or other studies to determine the
14 physiologic effect.

15 Labeling should follow current FDA
16 guidelines for patient labeling, but it should also
17 advise patients about the alternate site testing
18 difference and include device-specific cautionary
19 statements based on data collected.

20 TheraSense has complied with all of these
21 requirements, and the data support our proposed
22 labeling.

23 510(k) applications should include
24 performance data to support alternate site claims.
25 Alternate site testing devices should remain on the

1 market as over-the-counter devices. I believe that
2 labeling comprehension and our outcomes studies
3 demonstrate that the product is being used safely.
4 And manufacturers should be responsible for the
5 timely and appropriate educational activities for
6 end-users and health care professionals.

7 Finally, I think we are all concerned
8 about the public health and the risks in alternate
9 site testing have been identified and managed
10 through labeling. We have seen no serious adverse
11 health effects--

12 DR. KROLL: Thank you.

13 DR. CONNER: --and there is no credible
14 evidence that supports the need for a public health
15 advisory.

16 Thank you for your time.

17 DR. KROLL: Now we'll hear from Luann Ochs
18 from Roche Diagnostics.

19 MS. OCHS: Good morning, distinguished
20 panel members and FDA scientist.

21 I am Luann Ochs from Roche Diagnostics
22 Corporation, where I am Director of Regulatory
23 Submissions for Near Patient Testing Products.

24 Thank you for allowing me to address you
25 today.

1 [Slide.]

2 As you may be aware, Roche does not
3 currently have a product with AST on the market.
4 Last year, Roche became very interested in having a
5 product with an AST claim. That interest stemmed
6 from market demand. There is a perception of less
7 pain. There is a desire to move away from
8 fingertip testing. There is a potential for better
9 compliance with prescribed monitoring programs.
10 People may test more frequently.

11 The consumer demand for products with AST
12 already on the market is strong. Clearly, AST
13 appeared to have its benefits.

14 However, internal R and D studies raised
15 concerns about patient safety when using alternate
16 site testing that were not being addressed in the
17 market. The concerns stemmed from evidence that
18 there could be significant differences between
19 fingertip test results and alternate site test
20 results. There could be risks.

21 So we decided to study the situation
22 further and clarify our understanding of any risks.
23 We needed to be able to answer this question: Can
24 glucose monitoring using AST be reasonably safe and
25 effective?

1 [Slide.]

2 The outcome of these studies revealed
3 first of all that measurements from an AST site are
4 equivalent to fingertip results if the person is in
5 a steady-state.

6 Secondly, there can be a difference
7 between AST and fingertip results. It appears to
8 be caused by the physiological differences between
9 the fingertip and the forearm, and these
10 differences are variable between patients.

11 We concluded from our analysis of the data
12 that alternate site testing as a technique can be
13 accepted provided that appropriate labeling
14 instructions are offered to the consumers and their
15 caregivers.

16 [Slide.]

17 This conclusion is reflected in our
18 position statement. "AST is safe and effective for
19 most people with diabetes most of the time.
20 However, health care providers and consumers need
21 education in order to understand when to
22 appropriately use AST."

23 We believe that it can be appropriate to
24 introduce AST into some diabetes monitoring
25 programs as long as the consumers and their health

1 care providers understand the new risks.

2 Subsequently, we evaluated AST with one of
3 our AccuChek products, confirmed our initial
4 findings, and filed a 510(k) for an AST claim on
5 that product in July of 2001. You have all
6 received copies of our data and the proposed
7 labeling, and you may have recognized some of that
8 data presented here today. I would just like to
9 briefly hit the highlights of our studies and then
10 move on to our recommendations.

11 [Slide.]

12 Our first study was to determine if the
13 differences seen in the results were simply due to
14 dilution of the forearm samples by interstitial
15 fluid. We wanted to look at another analyte
16 besides glucose. Is it the same in both samples?
17 If the sample is being diluted, then we should
18 expect the same magnitude of differences in other
19 analytes.

20 We decided to look at iron content and
21 relate that to the hemoglobin level in the samples.
22 These are whole blood samples; therefore, the
23 hemoglobin level should be constant if the sample
24 is not being diluted.

25 We measured the iron level by atomic

1 absorption spectroscopy. This study used a 2
2 microliter sample size. We found that, comparing
3 forearm samples to fingertip samples, the iron
4 content and therefore the hemoglobin content was
5 the same.

6 Our conclusion: Forearm samples are not
7 being diluted by interstitial fluid.

8 [Slide.]

9 Our second study looked at the correlation
10 of fingertip and forearm samples in a large
11 population of people with diabetes over a period of
12 10 days. For this study, we used the TheraSense
13 FreeStyle system. Our product was not yet
14 available, and the TheraSense product was the only
15 system that was readily available at that time that
16 allowed the use of both forearm and fingertip
17 testing using the same meter.

18 We believe that the data we collected
19 points to a physiological cause for the differences
20 and therefore probably applies equally to any AST
21 system. We have certainly seen the same trends
22 when using our own AccuChek system.

23 Four external sites and 190 subjects
24 participated in the study. All of the participants
25 measured their BT levels as part of their therapy,

1 routinely testing their blood glucose from one to
2 12 times per day. Ninety-eight of the subjects
3 were insulin-dependent, using either injected
4 insulin or insulin pumps, and 92 were not insulin
5 users.

6 For our study, each subject performed a
7 forearm stick and an immediate finger-stick test 10
8 times a day for 10 days. This testing was in
9 addition to any testing they would normally do with
10 their own SMBG system.

11 The 10 times a day were: before each
12 meal, 1 hour after each meal, 2 hours after each
13 meal, and also at bedtime. A total of 18,036 data
14 pairs were collected and analyzed.

15 [Slide.]

16 The point of this study was to determine
17 if forearm results are significantly different from
18 fingertip results under normal conditions of use.
19 We have just heard the criticism that Drs. Jungheim
20 and Koschinsky's study did not reflect real world
21 conditions, that they stressed the systems too far.

22 I personally believe that that study was
23 an appropriate research challenge. But what
24 happens during a normal day?

25 In our study, we did not influence the

1 subjects' diets, medication, or exercise. Except
2 for the added testing, they went about their normal
3 routines. We captured their forearm and fingertip
4 results during the course of 10 normal days.

5 [Slide.]

6 You have already seen the Clarke Error
7 Grid today. You have already seen data displayed
8 that way. Now, you may ask why use the Clarke
9 Error Grid. We use it because it is a well-
10 understood analysis tool that can help us make a
11 decision and then explain that decision to others.
12 We use the fingertip result as the reference result
13 because it is what people with diabetes are using
14 in their homes today. With our study being home
15 use and with the number of sticks involved, it was
16 not practical to use a lab reference. Our study
17 couldn't be done with a lab reference.

18 It is appropriate to use the finger-stick
19 reference because that is the patient standard of
20 care for decisionmaking today, and based on
21 information given in TheraSense's labeling for the
22 FreeStyle system, it is sufficiently accurate to
23 justify the fingertip result as a reference result.

24 [Slide.]

25 Here is the data from our study, all

1 18,036 data points. Eighty-seven percent of the
2 results fall within the A Zone. For normal
3 fingertip compared to lab reference study, we would
4 expect at least 95 percent. Twelve percent of the
5 results are in Zone B. The Zone D results are the
6 ones that we are most concerned about; about one-
7 half percent of the time, the forearm result would
8 not detect hypoglycemia, and about one-half percent
9 of the time, the forearm result would not detect
10 hyperglycemia.

11 [Slide.]

12 Let's look at the data in a different way.
13 This is a 3-by-3 table to look at the results by
14 category. Using the finger-stick results, the data
15 pairs are divided into bins of hypoglycemic values,
16 euglycemic values, and hyperglycemic values.

17 Then you look at the AST results. How
18 many times did the AST results agree with the
19 fingertip result bin and fall into the green boxes?
20 How many times did the tests at least agree enough
21 to categorize the result into the appropriate bin?

22 [Slide.]

23 Let's populate this chart. The
24 overwhelming majority of the data fall in the green
25 boxes. Agreement is achieved.

1 [Slide.]

2 Focus in on the hypoglycemic category.

3 The fingertip result says that the glucose is less
4 than 70 mg/dL--hypoglycemic. Fifteen percent, or
5 86 out of 580, of the hypoglycemic occurrences are
6 missed by the AST result. These 86 results
7 occurred in 44 different subjects. Twenty-three
8 percent, or 44 out of 190 of the subjects in our
9 study, had at least one missed hypoglycemic event.
10 Of the 8 results, 57 occurred in Type I individuals
11 and 29 occurred in Type II's. The hypoglycemic
12 events are not limited to only Type I's.

13 You may say, come on, now, we are only
14 talking about one-half percent of the data. That
15 level gets lost in the noise of the system. All
16 glucose meters have much more error than that.

17 Let's put this in perspective. One-half
18 percent of the data, 15 percent of the hypoglycemic
19 events, 23 percent of the subjects. One-half
20 percent of the data means that 5 out of every 1,000
21 AST tests could be an undetected hypoglycemic
22 result if the users are allowed to test using AST
23 whenever they want. The users need to understand
24 when AST is appropriate and when it is not
25 appropriate. The users clearly need education in

1 order to avoid these undetected hypo events.

2 We are not talking about random error
3 here. This is a physiologically induced
4 difference. This error is on top of any other
5 analytical errors such as lot-to-lot or strip-to-
6 strip variability. This error is on top of any
7 pre-analytical errors.

8 In 1997, the Clinical Chemistry and
9 Toxicology Panel reviewed those other kinds of
10 errors and determined that the benefits of home
11 glucose monitoring outweighed the risks. With AST,
12 they still do, but we need to understand and
13 communicate the risk.

14 This is a new risk. Let's think in terms
15 of risk management principles. Ask these
16 questions. First, is there a pattern? Second, can
17 we understand the pattern? And third, can
18 understanding the pattern lead to a mitigation of
19 the risk?

20 Let's look at the data again.

21 [Slide.]

22 This first graph shows data collected
23 preprandially. At this time frame, 0.3 percent of
24 the data appears in Zone D. Generally, the data
25 looks pretty tight.

1 [Slide.]

2 The next graph shows one hour
3 postprandially. Now we have gone up to 1.2 percent
4 of the data in Zone D. The scatter is much
5 greater.

6 Let's look at some of these differences.
7 If I can focus on that up there, that point is
8 about an 80 on the AST result and nearly a 300 on
9 the fingertip.

10 [Slide.]

11 The next graph shows data 2 hours
12 postprandially. The glucose is stabilizing. We
13 are back down to one-half percent of the data in
14 Zone D. The scatter is coming back down. The
15 results are much closer.

16 We conclude that when you do something to
17 change your glucose level rapidly, such as eating,
18 you get more variability between the fingertip
19 result and the forearm result.

20 [Slide.]

21 Here are the conclusions from our study.
22 Most of the time--87 percent--the results are in
23 Zone A. Ninety-nine percent of the time, they are
24 in either A or B. The results tend to match best
25 during times when glucose is not changing rapidly.

1 At times, the forearm results were
2 dramatically different from the fingertip results.

3 We conclude that rapidly changing glucose
4 concentrations--for example, from carbohydrate
5 intake--may result in undetected hypo or
6 hyperglycemic events.

7 So we conclude that AST can be safe and
8 effective most of the time, but what can we do to
9 manage this risk?

10 [Slide.]

11 Education. Manufacturers must provide an
12 appropriate educational message to the consumers
13 and to the health care providers. That message
14 must be tested. Can the users understand the
15 message?

16 Messages are tested following human
17 factors testing guidance documents available from
18 FDA's Office of Health and Industry Programs, or
19 OHIP. You may ask: What is human factors testing?

20 Quoting from FDA's website, "Human factors
21 is a discipline that seeks to improve human
22 performance in the use of equipment by means of
23 hardware and software design that is compatible
24 with the abilities of the user population and by
25 preparing labeling instructions that are

1 appropriate for the intended readers." The terms
2 "human engineering," "usability engineering" and
3 "ergonomics" are often used interchangeably for
4 this process that is utilized to achieve highly
5 usable equipment.

6 Here is how it works. To determine if
7 users can understand the message, give it to them,
8 and give it to them in exactly the way that you
9 intend to provide it really--labeling, videos,
10 face-to-face--whatever you intend to put into the
11 marketplace. Let the users acquire the message by
12 reading the materials, watching the video, or
13 getting trained. Then, quiz them. Can they answer
14 the questions correctly to show that they
15 understand the materials?

16 We did this for our AccuChek product. In
17 our case, we provided labeling, the same labeling
18 that was provided to you in the FDA Panel packet.
19 We do not intend to provide a video or face-to-face
20 training, so all we gave them was the written
21 material.

22 They read it; they answered the questions.
23 Did they get the message? Yes, they got it. One
24 hundred percent understood that there can be
25 differences. Ninety-two percent could list the

1 factors that cause the differences unprompted. One
2 hundred percent understood to use fingertip testing
3 when hypoglycemia is suspected.

4 [Slide.]

5 Our study demonstrates that manufacturers
6 can provide educational material that consumers can
7 understand. Manufacturers can deliver the message
8 even with just written materials. It is not
9 necessary to provide the message with face-to-face
10 contact.

11 Of course, Roche Diagnostics is not going
12 to rely solely on labeling to get out the message.
13 We are prepared to do much more. We have already
14 informed health care providers of the results of
15 our study, telling them that there is risk that
16 they need to understand. We have professional
17 brochures and consumer brochures. We plan peer-
18 reviewed journal articles and white papers. We
19 have our 1-800 Call Center and AccuChek.com.
20 You'll see us at trade shows and symposia,
21 informing the public. We will take every
22 opportunity. We can get the message across.

23 [Slide.]

24 Let's switch gears for a minute to our
25 recommendations for future 510(k) review

1 requirements. There should be two paths forward--
2 one if you agree to strong labeling precautions and
3 another if you feel they are not necessary for your
4 device.

5 In the first case, the review criteria
6 should be the same as for a fingertip test. But
7 for the second type, you should provide valid
8 scientific evidence proving that the precautions
9 are not needed.

10 Challenge the systems during times of
11 rapidly changing glucose. Look at the kinetics of
12 changing glucose versus the AST result. Give FDA
13 the scientific explanation and the validation of
14 that explanation for how your product overcomes the
15 physiological phenomenon.

16 Other precautionary statements may be
17 necessary as well. For example, our studies have
18 been performed with an adult population. Since our
19 device will most likely be used by persons under 18
20 years old, we intend to revise our proposed
21 labeling to indicate that the study was limited to
22 adults and the results may not reflect performance
23 with children. We believe this is truth in
24 labeling.

25 Studies need to be conducted to understand

1 the use of AST in children. At Roche, we have
2 begun the process to look at AST in children, but
3 the studies are not yet complete.

4 Finally, the labeling message must be
5 tested. Can the users understand the message?

6 So here are the Roche recommendations.
7 Manufacturers need to get the message out. Roche
8 will continue to educate the diabetes community in
9 anticipation of offering a product with an AST
10 claim. FDA needs to continue to clear the products
11 with the appropriate labeling and instructions for
12 use.

13 FDA also needs to ensure level regulatory
14 requirements to allow the users to compare
15 performance claims--apples to apples.

16 More studies are needed to fully
17 understand the physiological effects of diet and
18 exercise and the impact of AST testing in children.

19 AdvaMed and FDA need to work together to
20 amend the FDA 510(k) review criteria guidance.

21 In closing, please remember this: AST is
22 safe and effective for most of the people most of
23 the time. It presents the potential for more
24 frequent testing, therefore, better control. AST
25 adds a new level of risk, but that risk does not

1 exceed its potential benefit. The risk can be
2 minimized with education. Roche is prepared and
3 positioned to deliver the necessary education.

4 Thank you.

5 DR. KROLL: Thank you.

6 At this point in the meeting, we now have
7 an Open Public Hearing. The first part will be
8 public attendees who have contacted the Executive
9 Secretary prior to the meeting, and these people
10 will be allowed to address the panel.

11 The speakers are to state whether or not
12 they have any financial involvement with
13 manufacturers of glucose test systems, and we also
14 request that they please state their names.

15 The first speaker is Professor Theodore
16 Koschinsky.

17 **Open Public Hearing**

18 DR. KOSCHINSKY: Mr. Chairman, ladies and
19 gentlemen, my name is Theodore Koschinsky. I am
20 working at the Clinical Department of the German
21 Diabetes Research Institute, and I am an Associate
22 Professor at the University of Dusseldorf.

23 For more than two decades, my group has
24 been involved in the technical and clinical
25 evaluation of test systems for spot as well as

1 continuous glucose monitoring, and we have
2 developed standardized evaluation tests. We have
3 in this context cooperated and contracted with all
4 companies and distributors that have presented
5 their products to the German market, so we have
6 been in a relationship with all manufacturers
7 except for Amira, which has not entered the German
8 market up until now.

9 As an outcome of these studies, we have
10 presented the results at different scientific
11 meetings and workshops, and have been supported in
12 these activities by honoraria and travel expenses
13 from the related companies.

14 [Slide.]

15 To start with, our starting point has been
16 the concern of patients who approached us at the
17 end of last year, presenting us data like these and
18 asking for advice how to explain the differences at
19 the arm versus the finger, for the hypoglycemic
20 range, 153 to 232, to give you an example, showing
21 at the same time during the course of the day well
22 agreement and then starting disagreement as well
23 and agreement as well.

24 After excluding all kinds of handling and
25 technical issues, we turned to the question whether

1 the rapid blood glucose changes had the
2 contribution. And to avoid artificial situations,
3 we used an independent group of 17 Type I diabetic
4 patients that we had studied during a continuous
5 glucose monitoring developing project and analyzed
6 the data from 17 Type I diabetic patients up to 72
7 hours according to the rate of change of blood
8 glucose and divided them into three sections--below
9 1.0 mg/dL per minute; intermediate 1.0 to 2.0; and
10 greater than 2.0 mg/dL.

11 In these intensified treated Type I
12 diabetic patients, the majority has been 74 percent
13 in the below 1.0 mg/dL, and a small segment of 7
14 percent of this population has demonstrated greater
15 than 2.0 mg/dL per minute. And we focused from
16 this our study protocol and developed an
17 experimental protocol to examine the question to
18 what degree these changes could contribute.

19 The population that we have studied--23
20 insulin treated Type I and Type I diabetic
21 patients; a wide range of age; BMI, normal to 37
22 BMI; 2 weeks duration to 28 years; HbA1c complete
23 normal until completely deranged; impaired
24 awareness of hypoglycemia involved in 5 patients.

25 [Slide.]

1 The study design that we used has been
2 standardized in the way that we started aimed at
3 normal glycemia, keeping the basal rate either from
4 insulin pump or long-term insulin overnight;
5 omitted the fast insulin and replaced the first
6 breakfast by 75 gram oral glucose load.

7 We then stabilized the values at about 300
8 to 350 mg/dL, and then used an individually derived
9 insulin dose from the treatment schedule of the
10 patient, given i.v., to produce a fast decrease,
11 and followed that up over the next 45 to 150
12 minutes until hypoglycemia, defined as 60 mg/dL or
13 below, and then glucose has been given.

14 That is the standard design. All devices
15 have been tested.

16 [Slide.]

17 Blood glucose was measured in parallel
18 every 15 minutes by the same blood glucose monitor
19 at the fingertip and at the alternate site. We
20 used forearm, base of thumb, and abdominal sites.
21 Additional samples from the fingertip were analyzed
22 at the Clinical Chemistry Lab. All procedures were
23 performed by trained research nurses.

24 [Slide.]

25 The rubbing procedure that has been

1 mentioned in this regard, we have put in two
2 different groups. If not stated otherwise, forearm
3 skin was not manipulated before lancing in order
4 not to disturb normal regional circulation. In a
5 subset of patients, additional blood samples were
6 taken from the other forearms; there, a local
7 rubbing procedure was performed on the skin area,
8 about 20 square centimeters, for about 10 seconds,
9 reaching at least a difference of 1 degree
10 Centigrade with hyperemia, which was subsequently
11 used. The procedure was done by a research nurse,
12 not by the individual patient.

13 [Slide.]

14 The statistics were a two-sided Wilcoxon
15 matched pair signed rank test and a Bonferroni
16 procedure where appropriate, and the statistical
17 significance was P smaller than 0.05.

18 [Slide.]

19 Now, without going through all the
20 details, starting from a normal glycemic point, in
21 this sample of FreeStyle, the finger site faster
22 decreased lag time during the increase. The
23 crossover, the insulin, and the faster decrease in
24 lag time demonstrates a longer lag time, but the
25 patient was requesting not to take glucose and just

1 wanted to know; he was interested in how to follow
2 that up. So, starting from a hypoglycemic range,
3 the same applied as well.

4 Actually, we have calculated the rate of
5 glucose change from the maximum to the minimum, so
6 this differs from some calculations that have been
7 presented at this meeting where peak values have
8 been obtained. So if we are talking about these
9 ranges, this has to be kept in mind.

10 [Slide.]

11 One-Touch Ultra, we have examined three
12 devices which showed practically the same behavior;
13 and Soft-Sense or Sof-Tact as it is called in the
14 U.S. practically showed the same behavior, and we
15 couldn't really see any particular difference.

16 [Slide.]

17 These types of results are not only
18 produced by our own lab, should this slide
19 demonstrate. It has been shown by Dr. Pfitzner--an
20 independent consultant group in Germany that has
21 been contracted by Abbott/MediSense--he has
22 performed, using the SoftSense device in 10
23 patients, using an OGT as described in typical
24 form, and what is demonstrated in these 10 patients
25 is average values reaching a level of about 250

1 versus about 350 at the finger site.

2 During the decline part, he used
3 subcutaneous insulin and achieved a rate below 2
4 mg/dL per minute, and probably this explains the
5 missing differences.

6 [Slide.]

7 The next slide that Dr. Pfitzner provided
8 to me was from an individual patient from this
9 group demonstrating again a difference from 200
10 stabilizing over here during the OGT postprandial
11 state and differences up to 300.

12 So differences between 190 mg/dL blood
13 glucose belong to Zone B. And I would like to focus
14 your attention that there is actually no
15 difference; it is a difference of perspective how
16 you approach the data and how to interpret them.

17 Error grid analysis from my point of view
18 is not an ideal instrument, really, to focus on
19 these types of situations, and I think with all
20 devices that we had in our hands, and it is
21 obviously in other groups as well, we find similar
22 differences in the postprandial state. For the
23 decline, there is an issue of methodology, how fast
24 we really induce that.

25 [Slide.]

1 If we took the first hypoglycemic value at
2 the finger and compared the parallel value at the
3 arm from all patients tested, you see the wide
4 range of glucose differences that we observed, and
5 this is certainly an alerting type of letter. I
6 think it is reasonable to raise concern and to
7 alert the public and all parties involved.

8 [Slide.]

9 The next slide just summarizes the
10 comparison between forearm and finger. The
11 significant differences occurred always less
12 increase in the forearm and less decrease in the
13 forearm as well.

14 [Slide.]

15 Now I turn to the rubbing procedure. In
16 the group we applied--and I'll show you three
17 different examples--it is just the same group that
18 I showed you with the finger and arm, and then the
19 rubbing procedure showed the obvious result that
20 many values showed a smaller difference than
21 without rubbing.

22 What was of concern to us was that within
23 the same patient, we could find values that had no
24 difference to the finger, that had no difference to
25 the arm, and that this could be demonstrated at the

1 hyperglycemic, an increase as well as a decrease.
2 In this particular state, they did not approach the
3 finger at all. It was unpredictable in this
4 patient.

5 [Slide.]

6 The next slide demonstrates for the One-
7 Touch Ultra a more intermediate effect of the
8 rubbing procedure, again showing no difference to
9 the arm at one point, no difference to the finger
10 at another point.

11 [Slide.]

12 This slide demonstrates that SoftSense has
13 perfect data with the rubbing as well, independent
14 of the fact that they recommended it. We could
15 eliminate the difference with rubbing in this
16 particular case quite nicely. So we had a whole
17 variety of results with the rubbing procedure.

18 [Slide.]

19 This slide summarizes that. Without
20 rubbing, we had a difference of 81 mg. After
21 rubbing, it was about halved, and during the
22 increase as well as during the decrease part, but
23 it was a considerable range of results.

24 [Slide.]

25 We turned to another alternate site, and

1 that was the base of the thumb. The slides
2 demonstrate for all devices we have checked what
3 you have already seen from the Amira company.
4 There is a complete overlap between the finger and
5 the thumb side during stable as well as during
6 dynamic blood glucose changes, and we can confirm
7 from our study protocol the conclusions that have
8 been drawn by the Amira company.

9 [Slide.]

10 This slide simply demonstrates that it
11 works with One-Touch and with SoftSense as well.

12 [Slide.]

13 We concluded from our data that the
14 observed differences are not device-specific--for
15 example, not related to sampling mechanism or blood
16 volume per sample; and instead, observed
17 differences are site-specific.

18 [Slide.]

19 The base of thumb kinetics would be
20 identical to the finger during all stages of blood
21 glucose changes.

22 The effects of exercise--I can show you
23 the first observational results. They are not a
24 standardized protocol; we just observed.

25 [Slide.]

1 It demonstrated in 9 of 10 patients that
2 no differences occurred during this type of
3 decrease during the exercise phase as well as
4 during the recovery; but again, one out of 10
5 patients showed, despite a common starting point, a
6 delay and a small decrease at the arm site versus
7 the finger. We have no particular explanation for
8 that. We expected something different. But I
9 think it is important to share with you what we
10 observed in this observational part of the study.

11 [Slide.]

12 The physiological considerations--and skin
13 blood flow at various AST regions has been the
14 focus in this regard.

15 It is well-known that capillary blood is
16 derived from upper dermal plexus within 2 mm.
17 These plexus get inflow from capillaries and from
18 arterioles via arterio- venous shunts.

19 [Slide.]

20 The papillary capillary density differs
21 between the finger and the calf, and the AV shunts
22 are numerous in the hairless skin of the finger and
23 the palm, but nearly absent in hairless skin.

24 [Slide.]

25 So we embarked on a study using laser-

1 Doppler imaging technique, the infrared 780 nm,
2 penetration depth exactly where we are lancing, and
3 measured to flux.

4 This is the qualitative picture. The
5 color-coding for high flow for the finger and the
6 base of the thumb are very similar, expressing in
7 the 500-600 PU range. The forearm is significantly
8 less colorful, with below 100 perfusion units. And
9 the rubbing--and this is the thing I would like to
10 draw your attention to--rubbing as extensively
11 performed as we did results in the inhomogeneous
12 picture. And you could imagine that depending on
13 where you finally lance the capillaries--over here
14 or over here--you might have different results, and
15 this is part of the explanation that we offer for
16 the discrepancies that we have observed within the
17 same patient.

18 [Slide.]

19 This slide summarizes from 68 patients
20 finger and thumb are significantly higher than the
21 forearm. Forearm after rubbing, even with this
22 procedure, doubled on average, but certainly did
23 not reach the quality of the finger and palm. The
24 abdominal sites were not different from the
25 forearm, and pilot studies point to similar results

1 for the different lag times that were observed.

2 [Slide.]

3 So our hypothesis is that blood in dermal
4 plexus is exchanged at a far lower velocity at
5 hairy skin areas; and changes in arterial blood
6 concentrations of a certain solution like glucose
7 can produce a transient gradient between arterial
8 and capillary blood, and the transient gradient is
9 unmasked if change-velocity is sufficiently rapid.

10 [Slide.]

11 This simply demonstrates as a picture the
12 i.v. shunts exchange certainly faster, and you have
13 more capillaries than at the arm site.

14 [Slide.]

15 This is something to demonstrate that
16 during metabolic change as we demonstrate in our
17 study protocol, the finger flux and the and the
18 thumb flux are not affected by the rapid blood
19 glucose changes or the insulin dose, and the same
20 is true for the abdominal and forearm flux data.
21 So whatever concern we have and what we know about
22 deeper arterial effects, deeper layers, at this
23 very upper layer, we probably have not to discuss
24 too many other effects.

25 [Slide.]

1 Now, conclusions and perspectives.

2 Conclusion: The observed transient BG differences
3 between forearm and finger during rapid BG changes
4 could be explained sufficiently by anatomical and
5 physiological site-specific differences.

6 [Slide.]

7 We recommend from that that capillary BG
8 monitoring at the arm is safe at metabolic steady-
9 state and should not be recommended during rapid BG
10 changes, and never should exclusion of hypoglycemia
11 be aimed at; and at the base of the thumb, it is as
12 safe as it is at the finger.

13 [Slide.]

14 Objectives for further AST studies--yes, I
15 think it is in a standardized experimental design
16 for each BG monitor and for each alternate site
17 recommended as differences between the AST sites
18 can be demonstrated, and the incidence of an AST
19 failure under daily life in powerful population-
20 based observational design is a completely
21 different issue. Daily life, we have studied under
22 daily life conditions, and experimental studies
23 have to be done to focus on particular questions to
24 answer in functional respects.

25 [Slide.]

1 Objectives for further AST studies:
2 Characterization of patient-specific risk factors--
3 age, micro-angiopathy, autonomic neuropathy, dermal
4 diseases; and the effects of various types of
5 exercise under standardized experimental studies
6 and daily life observational studies are certainly
7 necessary, and I haven't seen any data on this
8 particular subject.

9 [Slide.]

10 Finally, consequences for other SMBG
11 devices. Any other glucose monitoring technology
12 which depends on blood or interstitial fluid
13 kinetics within the upper dermal compartment--
14 optical approaches, NIR infrared spectroscopy, and
15 transdermal approaches, reverse iontophoresis as an
16 example--have to be examined for the effects or
17 rapid BG changes as well.

18 Thank you for your attention.

19 DR. KROLL: Thank you.

20 I want to let the panel members know they
21 will have an opportunity for questions later.

22 Next we will hear from Dr. Russell Potts.
23 Please remember to state name, affiliation, and if
24 you have any financial involvement.

25 DR. POTTS: My name is Russell Potts, and

1 I am Vice President of Research and Development at
2 Cygnus.

3 I would like to thank the FDA for the
4 invitation to speak today.

5 On a personal note, it is a pleasure to be
6 back in front of this panel under a substantially
7 less personally stressful situation.

8 [Slide.]

9 The Biographer, which you see in front of
10 you, is very different from what you have heard
11 about earlier today. This is a prescription device
12 worn on the arm and measures interstitial fluid
13 glucose. It provides frequent and automatic
14 measurements that are not practically easily
15 obtained with any other technology. This is not
16 your typical meter.

17 [Slide.]

18 As you know, the GlucoWatch Biographer is
19 a monitoring device intended for detecting trends
20 and tracking patterns in glucose levels in adults
21 with diabetes. The device is intended for use by
22 patients at home and in health care facilities.

23 In addition, it is intended for use as an
24 adjunctive device to supplement, not replace,
25 information obtained from standard home blood

1 glucose monitoring devices.

2 [Slide.]

3 Finally, it is indicated for use in the
4 detection and assessment of episodes of hyper- and
5 hypoglycemia, facilitating both acute and long-term
6 therapy adjustments. Interpretation of the results
7 should be based on trends and patterns seen with
8 several sequential readings over time.

9 [Slide.]

10 The glucose sample is collected using a
11 process of reverse iontophoresis. This involves
12 the application of a very low electric current
13 across intact skin, and the sample that is obtained
14 is an extract of interstitial fluid from beneath
15 the skin.

16 [Slide.]

17 The Biographer provides a reading every
18 20 minutes, and that process is shown schematically
19 here. The glucose sample is collected over 3
20 minutes. The collected glucose is then measured in
21 the next 7 minutes. This process is repeated, and
22 data integrity checks are completed at the end of
23 that. The glucose value that is displayed is based
24 on the total signal from two 10-minute measurement
25 periods. This 20-minute cycle is repeated

1 throughout the 12-hour monitoring period.

2 This procedure creates an integrated, or I
3 should say time-averaged, glucose measurement in
4 contrast to the instantaneous measurement provided
5 by a traditional blood glucose meter.

6 [Slide.]

7 The performance of the Biographer,
8 however, has been judged by comparison to blood
9 glucose values. This comparison can lead to
10 differences due to both inherent error as well as
11 procedural and physiological differences.

12 First, there are differences due to the
13 inherent error of the calibrating device, the
14 comparative device, and the Biographer.

15 There are also differences due to sampling
16 and measurement. In particular, the comparison
17 involves differences in the sample source--namely,
18 blood glucose versus an extract of interstitial
19 fluid--and differences in timing of that sample, an
20 instantaneous in the case of blood and a delayed
21 and time-averaged in the case of the Biographer
22 value.

23 Finally, there are also physiological
24 differences. All of these differences combine to
25 yield an apparent error--and I emphasize the term

1 "apparent"--that underestimates the Biographer
2 performance.

3 [Slide.]

4 Let me show you in this slide. Here is an
5 example of a comparison of the Biographer values
6 versus blood glucose values as a function of
7 elapsed time. On the right here, I have shown the
8 various statistical measures that we have used in
9 our FDA submission--mean difference, mean relative
10 difference, and the mean absolute relative
11 difference. Down on the bottom are the values for
12 this particular run. The mean difference is about
13 minus 6.0 mg/dL; the mean relative difference is
14 about minus 2.0 percent; the mean absolute relative
15 difference is about 7.0 percent, and the
16 correlation coefficient is 0.97. Clearly, there is
17 close tracking, close agreement.

18 Note, however, large differences can
19 occur, especially during periods of rapidly
20 changing glucose. Look, for example, at the time
21 periods a little bit after 8 hours elapsed time in
22 the middle, and you will see that there is as much
23 as 100 percent difference between the Biographer
24 and the blood glucose values.

25 These differences are real and reflect

1 physiological and sampling differences between the
2 two techniques.

3 [Slide.]

4 This slide shows quantitatively what some
5 of those differences are, and we have done this by
6 comparing Biographer versus blood glucose monitor
7 and Biographer versus itself.

8 In the left two columns is clinical data
9 obtained by Cygnus on the Biographer versus two
10 blood meters. If you look at the third row down,
11 the mean absolute relative difference for these 400
12 or so points is around 17 to 20 percent.

13 Note that the lower value in the extreme
14 left is obtained with a YSI, which is a much more
15 accurate meter. So hence, error of the comparative
16 meter can affect the outcome.

17 A comparison between two Biographers--
18 where each subject wore two Biographers--is shown
19 in the third column there, and the mean absolute
20 relative error is about 9.9 or about 10 percent.

21 Shown in the last column are the values of
22 the meters one to the other in the same clinical
23 trial, and there again you see the mean absolute
24 relative error is a little bit less, about 9.0
25 percent.

1 Thus, the results show that the inherent
2 error of the Biographer is actually similar to that
3 of blood glucose meters. However, physiological
4 sampling and timing differences lead to an
5 overestimate of the Biographer error as shown in
6 the first two columns.

7 [Slide.]

8 This apparent error notwithstanding, the
9 frequent automatic measurements possible with the
10 Biographer provide a potential warning for low
11 blood glucose, or just low glucose in the case of
12 the Biographer.

13 Using current blood glucose measurement
14 technology, it is difficult if not impossible to
15 detect low blood glucose events. The Biographer
16 provides a method to alert users to instances of
17 low glucose levels. In addition, the user and
18 health care team can control the Low Glucose Alert
19 setting used in this warning system; the user can
20 adjust it. The adjustable Low Glucose Alert level
21 then determines the circumstances and frequency of
22 alerts as well as the number of true positives and
23 false positives.

24 I will demonstrate some of those data in
25 the next slide.

1 [Slide.]

2 These are an analysis--these data have
3 been published in Diabetes Care this summer--of the
4 low glucose alert. Hypoglycemia is defined here as
5 a blood glucose less than 70 mg/dL.

6 The top two rows show analysis just using
7 self-monitoring blood glucose values. If you
8 measure twice per day, pre-breakfast or pre-dinner,
9 we find that you detect about one in seven
10 hypoglycemic events. If you up that to four times
11 a day, before meals and at bedtime, you detect
12 about 40 percent of all hypoglycemic events. These
13 are similar values that you'll find in literature
14 from other studies.

15 In contrast, the lower three rows show by
16 setting the Biographer alert level at about 90
17 mg/dL, you will detect over 60 percent of all
18 hypoglycemic events with the penalty of 6 percent
19 of false-positive.

20 Of course, increasing the low alert level
21 setting, as could be done by the user, results in
22 detection of even greater numbers of low glucose
23 events and at the cost of greater false alarms.
24 The bottom row shows if you set it at 110, you can
25 detect close to 90 percent of all hypoglycemic

1 events at the cost of 15 percent false-positives.

2 These results clearly demonstrate that the
3 Biographer can detect a greater number of low
4 glucose events than conventional measurements taken
5 even as frequently as four times per day.

6 [Slide.]

7 To conclude, the differences between the
8 Biographer and blood glucose are real. The sources
9 of these differences are error in the calibration
10 device, error in the comparison device, error in
11 the Biographer, sampling and measurement
12 differences and physiological differences.

13 [Slide.]

14 As I have stated, the Biographer is a
15 unique device that provides truly unique
16 information. The frequent and automatic nature of
17 the Biographer provides trends and tracks glucose
18 patterns.

19 Moreover, the Biographer provides better
20 detection of hypoglycemia than is available with
21 existing blood meters even if they are used as many
22 as four times per day.

23 In summary, then, in spite of differences
24 between the Biographer values and blood glucose,
25 the device's ability to detect trends and track

1 patterns provides for hypoglycemia--and I haven't
2 presented the data, but also hyperglycemia--
3 detection that cannot be achieved with any other
4 existing meter.

5 Thank you.

6 DR. KROLL: Thank you.

7 Next we will hear from Clare Rosenfeld.

8 MS. ROSENFELD: Hello. My name is Clare
9 Rosenfeld. I am 15 years old, and I am the former
10 National Youth Advocate for the American Diabetes
11 Association. For the record, I don't have a
12 financial connection to any of these companies,
13 although LifeScan was gracious and paid the way of
14 me and my mother so that I could appear here today.

15 I have had Type I diabetes for 8 years,
16 and I am very happy to be here today so that I can
17 share with you how important this is. I am very
18 honored to be able to share my personal testimony
19 with you.

20 Eight years of testing on my fingers four
21 to six times a day is painful. Until recently, I
22 did not have a choice in that. Alternate site
23 testing has changed that for me. This positive
24 change has given me the freedom and the choice for
25 a less painful alternative which has encouraged me

1 to test my blood sugar more frequently, whereas
2 before I was testing four to six times a day. Now,
3 not only do I follow manufacturers' directions; I
4 tend to go a step further and continue to figure
5 out how products will affect me personally. I
6 experiment and document those results.

7 When I first tried the One-Touch Ultra
8 alternate site testing program, my parents and I
9 chose to compare blood glucose levels between the
10 finger and the arm. For nearly 6 weeks, almost
11 every time I tested, I tested twice, on both the
12 finger and the arm. For me, alternate site testing
13 proved virtually the same as fingertip testing even
14 before and after meals.

15 Now I always test on my fingers during
16 times when my blood sugar might be changing
17 rapidly, such as before speaking here. For me and
18 for those youth whom I work with who are also
19 alternate site testing, it is simple. We
20 understand--when we are in doubt and when we are
21 feeling strange, we test on our fingers.

22 People with diabetes learn how their own
23 bodies work, and we want to be healthy. We know
24 how awful we feel when we are not in control of our
25 diabetes. Because of alternate site testing, I am

1 now testing 8 to 10 times a day, which allows me to
2 make more precise changes in my blood sugar
3 management, and I am in much better control of my
4 diabetes. My recent Alc was 7.2--better than it
5 was.

6 Better control of my diabetes means that I
7 can live a normal life. I can participate in
8 activities that other teens do and even do
9 extraordinary things like backpacking with my
10 father.

11 Living a normal life means appreciating
12 the little things. For the first time in 8 years,
13 because the callouses are disappearing, I am able
14 to feel the texture of a page when I turn it when I
15 am reading--and I love reading, so that is a
16 wonderful experience.

17 Being normal means being healthy and
18 living my life to its fullest. As a representative
19 of our Nation's youth with diabetes, I have
20 listened to people around the country, and I have
21 heard many kids speak in favor of alternate site
22 testing. This their message: If it doesn't hurt
23 as much, kids will test more often. And if teens
24 especially are given a choice, they will stay in
25 better compliance because they have freedom.

1 I respectfully urge you to please not make
2 changes in the policy of alternative site testing.
3 It is very important to us. Please allow others to
4 experience this wonderful advancement as it stands
5 and provide them the opportunity to better manage
6 their diabetes with safe and accurate alternate
7 site testing.

8 You will be providing 16 million people
9 with diabetes the chance to attain better health
10 and perhaps even be a little more normal.

11 Thank you.

12 DR. KROLL: Thank you very much.

13 Next, we'll hear from Dr. Craig Orłowski.

14 DR. ORŁOWSKI: Mr. Chairman, panel
15 members, thank you for allowing me to appear. I
16 don't have any slides.

17 I am Craig Orłowski from the Department of
18 Pediatric Endocrinology at University of Rochester.
19 I have no financial interest in any of the
20 companies. I have no consulting agreements or
21 anything like that; TheraSense is paying my way
22 today, and that is the only connection.

23 I come here representing nobody else but
24 myself and the patients that I take care of, and I
25 would like to essentially reiterate what Clare just

1 said. I didn't realize she would be saying what
2 she said. But I would like to give you the
3 perspective of a practitioner who follows
4 approximately 600 children with Type I diabetes and
5 a smaller group with Type II diabetes.

6 I don't know exactly how many of our
7 patients are using alternate site testing, but it
8 is approximately 100 by our count, and we started
9 immediately after the FreeStyle became available
10 last summer. So I am estimating that we have
11 someplace around 50,000 to 100,000 blood sugar
12 determinations that have been done on alternate
13 site testing.

14 My bottom line is that in our practice, we
15 have not come across as of yet a single instance
16 where there was what we could call a reportable
17 event, a severe low or an out-of-control high, that
18 has been the result of alternate site testing. So
19 at least on our 100 or so patients over the last 15
20 months, it seems to be a perfectly safe method of
21 testing.

22 One thing I did not hear--well, I haven't
23 heard several things until Clare just spoke. I
24 have heard what was being called clinical data as
25 really very carefully controlled clinical trials

1 and not real life. One thing that we do with blood
2 sugars is not just use blood sugars--and people
3 with diabetes don't use blood sugars to make
4 insulin determinations on the spot, but also to
5 recognize patterns.

6 We realize that even if systematically
7 blood sugars are under- or overestimated--what we
8 do, for example, at a normal clinic visit is look
9 over 30 days or more of blood sugar tests. There
10 should be no systematic bias in the average of
11 those blood sugars even if the blood sugars are
12 being over-read or under-read when the blood sugar
13 is rising or falling, since the rise and the fall
14 is essentially independent of the time that the
15 blood sugar is being tested.

16 So one of the main usefulness of alternate
17 site blood sugar testing is, just as Clare had
18 said, we have really had this perception that there
19 has been more testing going on because of the
20 decrease in the pain.

21 Since this topic has come up, since I saw
22 the letter first in Diabetes Care, I have been
23 making it a point to ask my patients about
24 alternate site testing, and what I have found is
25 that for the patient and family, the response has

1 been that they probably or definitely would be
2 doing less blood sugar testing if they had switched
3 back to finger testing rather than alternate site
4 testing. And after explaining what the concerns
5 were, I had no family say they wanted to abandon
6 alternate site testing; in their minds, the
7 positives far outweighed any of the disadvantages
8 that we have been hearing about earlier this
9 morning.

10 The concerns about real-time hypoglycemic
11 detection and the way we have handled that is
12 exactly as the previous speakers have suggested.
13 Our population, our children--the children can
14 actually be up to college students, from infants to
15 college students--so we do have a subgroup of our
16 population who drive. We have had it a point to
17 urge them to make sure they use fingertip testing
18 even if they are using a FreeStyle or some other
19 alternate site testing meter. Everybody has
20 acknowledged that and again as a clinician, what I
21 have really looked for more is more data and more
22 testing.

23 Even with some chance of being falsely
24 reassured by hypoglycemia, the fact that the meters
25 use less blood sample, and people have adopted the

1 use of those meters far outweighs the potential
2 disadvantages.

3 So as I said, nobody really wishes to
4 abandon this whom I have asked in my practice. And
5 the practicality of it is that people do talk to
6 each other. There are chat groups on line,
7 diabetes camp, parent support groups. I think that
8 if there were a change in the indication, people
9 who were using alternate site testing now would
10 continue to do so, and in fact other people would
11 find out about it, and instead of decreasing the
12 lines of communication by restricting the
13 indication, I think what we need to do is what is
14 happening today, that is, understand the process
15 more and incorporate that into our daily practices.

16 DR. KROLL: Thank you.

17 Next, we will hear from Laura Billetdeaux.

18 MS. BILLETDEAUX: And Sam. Hello,
19 everybody. This is Sam. We have a great picture
20 of Sam we'd like to put up.

21 Sam was not going to come with me in
22 September, and then, when we moved to October, he
23 decided that this was very important, and he wanted
24 to come, so we drove the 9 hours here yesterday, a
25 very long 9 hours. He wanted to stand up with me

1 today on behalf of alternate site testing.

2 I do want to say that I personally have no
3 financial involvement with any of the companies
4 here today, although Children with Diabetes, which
5 I do represent, gets advertising funds and
6 conference sponsorships from all of the companies
7 that have been here today, regardless of their
8 positions.

9 I also want to say--you have been watching
10 us here over in the corner, getting up, walking
11 back and getting water. Sam walked in this morning
12 and looked at everybody and said, "I'm the only kid
13 here." I think he has probably never seen so many
14 people in suits in one place in his whole life--and
15 his blood sugar went from in range to 380 within
16 about 5 minutes, up to 410, at which point, we
17 said, "Hmm, we just gave a 6-unit bolus; why is it
18 still going up? Are we stressed out, or what's
19 going on here?"

20 So we went outside in the hallway, and he
21 did do fingertip testing, and he was 450, and we're
22 thinking, "Oh-oh, we're really, really going up."

23 So we went up to the room and did an
24 injection of 4 units and came back down, and he is
25 now about 250 or so. But we did test 10 times

1 since we got up this morning, and it was a
2 combination of fingertip testing and alternate site
3 testing.

4 And I think--and I am going to read you my
5 speech--that is really what it boils down to--as an
6 informed parent, you need to understand what
7 alternate site testing can and cannot do, and when
8 your child is going high and going low--in a
9 teenage boy, there is no such thing as a steady
10 state--you have to know what the next step is. I
11 was ready to grab Davida and say, "Come outside and
12 help us figure this out."

13 This is not a steady state. This is a
14 teenage boy--right? Right. Okay.

15 I'm going to start my speech now, and you
16 can take that picture down. I just wanted you to
17 see how handsome Sam was this summer.

18 This is what Sam looks like the other
19 three seasons of the year. Sam is a hockey player;
20 he is a very good defense man, and last year, his
21 team took first place in the Ann Arbor House
22 League. He is a straight A student in 7th grade
23 and a pretty decent tenor sax player.

24 Sam has been wearing an insulin pump for 2
25 years, and he has used alternate site testing since

1 it was approved. He is also a very healthy kid.
2 He is healthy largely because he takes very good
3 care of his diabetes, as you could see this
4 morning. He tests his blood sugar on the average
5 day about 6 to 10 times, and he follows the
6 guidelines of his diabetes pump team.

7 Sam's personal meter choice is the
8 FreeStyle, and we own six of them. I guess I said
9 I had no financial investment, but maybe I do. We
10 own six of them, because Sam will test literally
11 anywhere, so I have meters literally everywhere.
12 He tests in the classroom, he tests in gym, he
13 tests in the lunch room, in band practice. He
14 tests at least three times during each hockey game.
15 He tests in the car. He tests in restaurants. He
16 is a young man who wants control over his health
17 and his future.

18 Sam's A1c is usually around 7 and never
19 over 7.9. He goes through 300 strips each month,
20 and he usually calls me at least once a day from
21 school to have a conversation about his blood
22 sugar. He does not hesitate to test his fingers if
23 he feels his sugar is dropping and his forearm
24 blood sugar is in range. Sam loves alternate site
25 testing. It has made a huge difference in how he

1 accepts having diabetes and how he takes care of
2 himself.

3 Fingertip pokes were painful for him. I'm
4 not saying they are painful for everybody, but they
5 were very painful for him. His fingers peeled and
6 bled, and I was concerned about infections with
7 these open areas that never seemed to heal and
8 always came in contact with the dart and the bike
9 and the basketballs and all the junk in the yard.

10 Although he has always been a good kid
11 about testing when we asked him to, the overall
12 number of tests that he did in a day was far less
13 than what he does now.

14 I am not here to say that one meter is
15 better than another, that alternate site testing is
16 better than fingertip testing, or to point fingers
17 at this company or that company because of what
18 they do or don't have. I am here as a parent who
19 supports alternate site testing and who has seen
20 tremendous improvement in the health and mental
21 well-being of somebody whom I love very much.

22 I want to make sure this technology stays
23 available to our family and to Sam.

24 I am also speaking on behalf of hundreds
25 of families in the Children with Diabetes Network

1 who use alternate site testing. CWD, for those of
2 you who don't know, is a support and education
3 system for families with Type I diabetes that
4 operates entirely on the internet. It is the
5 largest support network for families with Type I
6 diabetes, and it reaches literally thousands of
7 children and their families all over the world.

8 I am a CWD parent, and I have been asked
9 by other CWD parents who use alternate site testing
10 to speak on their behalf, so when I speak about
11 Sam, I am also speaking on behalf of hundreds of
12 other children who are just like him.

13 Alternate site testing is so very
14 important to our families. Quite simply, it takes
15 the pain out of diabetes management for our
16 children. It has revolutionized how many of us
17 manage our children's disease day-to-day. We now
18 have children who are eager to participate in their
19 testing and who don't mind testing 6 to 10 times
20 each day.

21 Clearly this give us better information to
22 keep tighter control on the diabetes and hopefully
23 to minimize the occurrence of later complications.
24 We don't want complications for Sam.

25 These things are important to us. We

1 parents are a smart group of people--we have to be
2 for our kids. We read the research. We listen to
3 our medical professionals. We read directions. We
4 learn how to operate the various diabetes gizmos
5 before we use them. When alternate site testing
6 came along, we learned how to use the different
7 meters--and they are different. We didn't test
8 legs before legs were approved; we only tested
9 arms. When we were instructed to "rub the site
10 vigorously," we rubbed vigorously.

11 When our children say they feel low and
12 shaky, which Sam often does, we know to trust those
13 feelings and complete the fingertip testing to
14 verify the blood glucose reading.

15 It is so important to our families to be
16 able to do alternate site testing and to spare our
17 children pain while keeping tight control on their
18 disease.

19 Children with diabetes completed two
20 online surveys this summer that focused on
21 alternate site testing. We wanted to know what our
22 families were thinking about this new approach to
23 testing and how many families actually had begun to
24 use alternate site testing.

25 The first survey in July asked readers:

1 How important is alternate site testing for you or
2 your child? Of a total of 606 responses, 47
3 percent indicated that it was very important, and
4 an additional 21 percent indicated it was somewhat
5 important. That is a total of 68 percent of
6 respondents online who felt that alternate site
7 testing was important.

8 In a follow-up survey asking readers which
9 blood test meter out of all the meters on the
10 market they used, the One-Touch Ultra had the
11 largest percentage at 23 percent, followed by the
12 FreeStyle meter at 15 percent. That was out of a
13 total of 1,098 readers.

14 To conclude, I'd like to read you just a
15 couple of pieces from letters that I received from
16 parents who wanted me to share with you their
17 strong support of alternate site testing. Clearly,
18 they are fearful that with proceedings like this,
19 alternate site testing may be taken away from their
20 families, and their children will need to go back
21 to using finger pokes, which clearly did not work
22 well for them or the daily diabetes management.

23 The first letter is from Sonia Cooper, who
24 is president of the Children with Diabetes
25 Foundation, and mom to Matthew, who is 11.

1 "I would like to thank you for the
2 opportunity to discuss this topic. The Foundation
3 strongly supports alternate site testing. One of
4 our Foundation's top priorities is to limit severe
5 complications of hypoglycemia, including the 'dead
6 in bed' syndrome. The goal is to have alarmable,
7 continuous, and accurate blood glucose measurement
8 systems available to patients. Please provide
9 companies and products working toward that end your
10 highest level of support. One of the first steps
11 is limiting the pain of testing."

12 From the Frankert family in Finley, Ohio:
13 "As parents of clinically ill children, we are very
14 cautious, and we read everything. Before I even
15 allowed my daughter to take FreeStyle out of the
16 box, I read over every, single piece of information
17 that came with it. The reason we purchased the
18 FreeStyle was because of problems with low blood
19 sugar reactions, therefore, it was a very serious
20 concern for us. When I read that TheraSense
21 advised to test on the fingers of low blood sugar
22 was suspected, I recorded that in my mind, and
23 since then, I test my daughter's fingers when I get
24 up during the night to check her blood sugar. The
25 reason for this is because I know this is a

1 critical time for my daughter, and I am following
2 the directions that the company has given me. If
3 they say check on the fingers when a low may be
4 suspected, then, by God, I'm going to test on the
5 fingers. Why would I take a chance otherwise?"

6 I'm sure you get the idea. I am not going
7 to read all these letters. There are many, many
8 more emails and letters that have been sent to your
9 board to review--I believe there were over 50 of
10 them--and I hope you get the opportunity to read
11 each and every one of them. Please give our
12 parents an opportunity to be heard. If you don't
13 have all 50 in hand, I can get them to you.

14 Sam, like all the kids whose parents have
15 spoken on their behalf, just wants to be healthy
16 and be a kid. He doesn't want to look pain in the
17 face a dozen times a day. Please continue to
18 support our children and our families by continuing
19 to endorse alternate site testing.

20 Thank you for taking the time to hear us
21 and consider our thoughts.

22 DR. KROLL: Thank you very much. We
23 appreciate Sam coming, too.

24 The next speaker is Dr. Paul Madden.

25 DR. MADDEN: Good day, everyone.

1 My name is Paul Madden. And Sam and
2 Laura, I hope it helps that I did not put my suit
3 coat back on--a little less formal.

4 I do not benefit in any way directly from
5 any of the companies that are here today or any of
6 the others that are not here, except that I did get
7 a free dinner last night, so that should be noted.

8 Thanks so very much for this opportunity
9 to speak and talk about the importance of alternate
10 site testing for blood glucose monitoring.

11 Let me give you a brief introduction as to
12 who I am and why I felt it is so important for me
13 to take time from my life to be here today.

14 Currently, I serve as special assistant to
15 the president of the Joslin Diabetes Center. I
16 also serve as a professional counselor at Joslin
17 and the administrator for the Joslin Diabetes
18 Center's camping and retreat programs.

19 Twenty-six years ago, I was chosen by Drs.
20 Priscilla White and Alexander Marble to serve as
21 the first resident mental health specialist at
22 Joslin and I believe at any diabetes specialty
23 clinic, and also as the first director of the
24 Joslin Camping Programs in 1975, who happen to have
25 diabetes. I remember vividly the discussion of

1 home glucose monitoring, washing strips, over-
2 washing, under-washing, and the debate that ensued
3 at the time, and I remember my early mentor Dr.
4 Priscilla White saying, "For goodness' sake, folks,
5 it's an advance, we are going to refine it." And
6 the spirit and tone of this discussion today talks
7 about refinement and protection of people with
8 diabetes, so I applaud the panel for that.

9 I also serve as a board member of the
10 Diabetes Camping Association and the American
11 Diabetes Association's Camp Task Force, and in
12 those capacities, I do serve as a voice for young
13 people with diabetes as well as their families.

14 Let me now share with you some of my
15 personal reasons to be here that have helped
16 strengthen me professionally.

17 I will be entering my 40th year of life
18 with diabetes on November 21. I remember it well
19 as if it were yesterday. When I travel throughout
20 the United States and the world speaking on
21 diabetes, I am increasingly introduced by others as
22 the man who has lived with more people with
23 diabetes than any other person in the world.

24 I believe this description may be true. I
25 have lived with over 20,000 people with diabetes

1 and have spoken, like many of you, in front of a
2 few hundred thousand people and loved ones who are
3 challenged by the multiple challenges of diabetes
4 each and every day.

5 Sadly, I also believe I may have attended
6 more funerals of people who were taken from this
7 world too early because of diabetes and its
8 devastating complications. I believe my
9 perspective is indeed quite unique. I believe
10 these personal qualifiers coupled with my
11 professional training and experience give me a most
12 formidable reason to be here today.

13 I am now going to weave my comments, so I
14 will speak today as a professional counselor, as a
15 person who knows so many people with diabetes, and
16 as a person who lives well and is challenged daily
17 by his own diabetes. We have all recognized--and
18 it is the prime reason we are here--that diabetes
19 is serious. We know that it is a crisis facing
20 America, with over 16 million people with diabetes--
21 --and this number continues to grow--and
22 unfortunately, diabetes also has the distinction of
23 being the most expensive medical condition in our
24 country, at approximately \$160 billion last year,
25 including direct and indirect expenses.

1 Adherence to a balanced diabetes
2 management program--helping people to reach and
3 maintain what is best for their health and their
4 diabetes will forever be a challenge for
5 professionals. At times for individuals and
6 families, to reach and maintain this challenge may
7 more be likened to an attempt to climb Mount
8 Everest. Dealing with complications, both real and
9 perceived, poor physical feelings from high or low
10 blood sugars, not enough time to attend to another
11 detail, routine detail of diabetes management, not
12 understanding a diabetes management program well
13 enough, feeling overwhelmed by their diabetes
14 management program, bored with the routine of
15 management, glorious food, limited choices with
16 some parts of the therapy--all these and other
17 issues work together to make diabetes a formidable
18 adversary.

19 Professionals are constantly look for ways
20 to make the multiple challenges of diabetes more
21 workable for their patients and their families. We
22 understand that the rigors and routines of
23 diabetes--at this point, diabetes does not go away--
24 --often make it difficult to care for so many of
25 these details that must be considered each day in

1 the life of a person with diabetes.

2 The varying parts of the diabetes
3 management program and offering choice remove some
4 of the boredom and help people to feel that they
5 are more in control of their own management
6 program. This is an important way to enhance
7 success for a number of our patients and their
8 families. Alternate site testing does clearly
9 offer this possibility.

10 We have heard some comments especially
11 from Clare and Laura and Sam about the pain. As
12 you look at Sam, clearly, pain is something that
13 relates to strapping, powerful young men, powerful
14 athletic young women; it is not just something,
15 discomfort and pain, that is only described by
16 people who would seem to be more mild-mannered and
17 meek.

18 Alternate site testing does substantially
19 reduce pain for a significant number of people.
20 Lancing the finger is at a minimum uncomfortable
21 for many people and described as painful by others.
22 We must continue to support alternate site testing
23 as it does remove a significant barrier, that pain,
24 to glucose monitoring for a large number of people.

25 There is no question in my mind that as

1 more people are aware of alternate site testing
2 that more people and families will choose this
3 method, and more people will be able to check blood
4 sugars more frequently.

5 Balancing diabetes to the best level is
6 optimal for short and long-term health. Many of
7 you on this panel have known that well before the
8 studies were starting to be announced 8 years ago,
9 the DCCT, studies in Great Britain. Thank goodness
10 many of us have known this for 40-plus years that
11 balancing blood sugars is crucially important.

12 Doing this safely has become a larger
13 concern as we have noted that as many people,
14 especially the folks with Type I diabetes, get
15 closer to and within the normal blood sugar range
16 more frequently, we have tended to see more serious
17 low blood sugars, including unconscious
18 hypoglycemic episodes.

19 Serious hypoglycemic episodes all too
20 often promote serious accidents which can be
21 disabling both mentally and/or physically. We know
22 that the best way to keep people with diabetes safe
23 is to couple good diabetes education and support
24 with frequent glucose monitoring. We must support
25 a therapy like alternate site testing that

1 significantly increases our patients' willingness
2 to check blood sugars more frequently, which does
3 enhance safety both short and long term for people
4 with diabetes. Any therapy that will allow an
5 enhanced number of people to check blood sugars
6 and/or check them more frequently will allow these
7 people to stay safe more often and within that
8 normal blood sugar range.

9 As people maintain more balanced health,
10 they will be able to more dynamically raise their
11 families, be around to nurture their grandchildren,
12 remain gainfully employed, which will allow them to
13 pay their bills and help us to decrease the
14 spirally costs of diabetes care that get so
15 aggressively eaten up by the all too often serious
16 complications.

17 One conservative estimate--and all of you
18 have seen other estimates, too, but I believe this
19 one to be conservative--has the cost of dialysis
20 and kidney care at over \$30,000 per year.

21 Alternative blood site testing is a
22 significant improvement in the total diabetes care
23 package that is and will continue to make a growing
24 positive difference in the well-being of families
25 living with diabetes and for our country as we stay

1 healthier.

2 Thank you so very much for this
3 opportunity to stress the value of this life-
4 sustaining and life-enhancing therapy.

5 Thank you very much.

6 DR. KROLL: Thank you.

7 We want to thank all the speakers.

8 I was informed that the FDA has received
9 over 30 emails from parents supporting alternative
10 site testing.

11 At this point, we're going to break for
12 lunch, and we'll resume exactly at one o'clock.

13 Thank you.

14 [Whereupon, at 12:05 p.m., the proceedings
15 were recessed, to reconvene at 1:06 p.m. this same
16 day.]

AFTERNOON SESSION

[1:06 p.m.]

DR. KROLL: The panel meeting is going to resume, and at this point, we're going to have an open committee discussion.

What I'd like to do is give our panel members over the next 10 minutes an opportunity to ask questions of the last two sponsors who gave sponsor presentations. That was TheraSense and Roche Diagnostics.

Dr. Henderson?

DR. HENDERSON: I was very impressed with the pediatric data; and the two young people who participated in this morning's presentations, I give kudos to.

I am still confused about the other end of the spectrum. My sense is that if we are talking about Type I and Type II diabetics, there is a certain amount of peripheral vascular disease that is almost inevitable, and I'm not sure if that isn't another group that we need to be concerned about. It sounds as though the pediatric kids are pretty well-educated, and their parents are well-educated, and that's good; they should have more options. Options are good. But I don't know if we

1 have data on the other end, and if they are going
2 to use it regularly, I think we should be concerned
3 about that spectrum also.

4 Also for my own interest, with pregnant
5 women, if this gets into the main milieu of
6 treating diabetics, eventually we are going to have
7 some pregnant women on it, which I am still okay
8 with, but we still don't have any data, and many
9 companies--not just in this area but every area of
10 pharmacy and FDA and everybody else who oversees
11 this are really, really hesitant to do testing in
12 pregnant women because they don't want the risk.
13 But that means that when we start to use it, and
14 they continue to use it if they have already been
15 on it, we are testing in everybody, every person is
16 an experiment, and we are not collecting that data.

17 I know it was suggested that some data may
18 be available in Europe, and if anyone has any
19 information about those two groups of patients,
20 that would be interesting.

21 DR. KROLL: Yes?

22 DR. CONNER: Eve Conner from TheraSense.

23 In the studies that we have done to
24 support our 510(k)s, we have actually had a very
25 broad range of people. I think the youngest person

1 in our studies was 5, and we had many patients over
2 70 and actually quite a few patients in their 80s.
3 So the results with those patients have actually
4 been quite good.

5 With regard to your question on
6 gestational diabetes, we have two studies--

7 DR. HENDERSON: Not gestational diabetes;
8 I am not even sure that's a disease--but with
9 pregnant diabetics, and the ones that I'm very
10 concerned about are those who are Type I and Type
11 II who have had longstanding diabetes. Those are
12 the ones who are going to come to us with new
13 agents, because the gestational diabetics, any
14 obstetrician will just put them on whatever they
15 can think of, and that's fine. It is those women
16 who are using things that we don't really know a
17 lot about, and we tend to just continue that during
18 pregnancy.

19 DR. CONNER: We actually have two studies
20 underway to look at the time series studies that we
21 showed earlier in pregnant women with diabetes. We
22 don't have the results yet, but we will certainly
23 have them very soon.

24 DR. HENDERSON: Thank you.

25 MS. KRUGER: I just wanted to comment on

1 your question about the elderly. I would say to
2 you, though, that if there is going to be an issue
3 in circulation, the issue is going to be at the
4 fingertips as well as at the arms, so you're going
5 to have to work with that patient and educate them
6 no matter what to get a good drop of blood. I
7 don't think it has anything to do with whether it
8 is an alternate site or a fingertip.

9 DR. ROSENBLOOM: I would wonder with the
10 elderly also with the skin fragility and the
11 bruising if the suction device might present a
12 special problem. Do we have any information about
13 that?

14 MS. CONNER: Eve Conner from TheraSense.

15 In our clinical study, there were some of
16 the elderly people who had some problems with
17 bruising. We certainly were able to get enough
18 blood from them to do the testing, but there were
19 occasional people who probably would not want to
20 use it long-term on their arm because they did have
21 problems bruising, but they did not have problems
22 using it on their finger.

23 MR. LOCKE: Paul Locke, U-Mass Medical
24 School.

25 I had the pleasure of being clinical

1 investigator for a number of Abbott Sof-Tact
2 studies. One-third of the population I studied
3 personally, with myself in attendance at all times,
4 were over 50 years of age, and even though people
5 on coumadin were excluded, we categorically did not
6 have in the elderly population any problems with
7 akinesis, bruising, or complaints. That was very
8 reassuring.

9 I say that as a medical investigator and
10 not in any way tied into the corporate entities.

11 Thank you.

12 DR. KROLL: We'll take one more question.

13 DR. CARA: Can I ask two?

14 MS. KRUGER: We were just curious over
15 here if 50 is really elderly.

16 [Laughter.]

17 DR. ROSENBLOOM: I sure don't think so.
18 Elderly is 10 years older than my present age,
19 whatever that may be.

20 DR. KROLL: I don't think the FDA takes a
21 position on that.

22 [Laughter.]

23 DR. CARA: I have a question for Dr.
24 Conner.

25 Dr. Conner, in this document that I guess

1 you provided us with before the meeting, there is
2 what you call an "outcomes study." I had a couple
3 of questions about that.

4 Number one, I was pleased to see that
5 there was no difference in glycosylated hemoglobins
6 or any change overall in the management of
7 patients, although I was very surprised about one
8 finding that you mentioned, and that is that even
9 though patients were using alternative site
10 testing, the willingness to test was no different
11 between the two groups--those using the standard
12 fingertip methods and those using the alternative
13 site.

14 DR. CONNER: I think that in that
15 particular group of patients, they were actually
16 already in pretty good control. Many of them had
17 hemoglobin A1c's in the range of 7, so I think we
18 were not too surprised that compliance didn't
19 increase a lot in that group.

20 I think the important thing about that
21 study was that whether they actually tested more or
22 not--maybe it's more a quality of life issue--they
23 did prefer the FreeStyle because it was easier,
24 less painful, or whatever. So it may not have
25 increased the number of times per day they were

1 testing, but they certainly expressed a preference
2 for that. So I guess that's good news in our
3 opinion. I think sometimes we see perhaps people
4 who are already testing at a fairly high rate don't
5 increase their testing rate, but the alternate site
6 devices get people who refuse to test at all to
7 test, and that's probably as important as anything
8 else.

9 DR. CARA: Do you have any data about that
10 other than the anecdotal that we have heard about?

11 DR. CONNER: We are actually doing another
12 outcomes study that includes over 500 patients. We
13 are about halfway through that study now. In that
14 study, the requirement to be enrolled in the study
15 was a hemoglobin Alc over 8, so these people will
16 be in less good control, if you will, and we are
17 collecting the data on frequency of testing. So I
18 would hope that when that study is completed, we
19 will have more information.

20 DR. CARA: Great. Another sort of related
21 question--and I don't know if you have this data--
22 but I was just curious as to whether or not you had
23 looked at the correlation between symptomatic
24 hypoglycemia and hypoglycemia as established by
25 either fingertip testing or alternative site

1 testing.

2 DR. CONNER: We have not done that
3 correlation.

4 DR. AHMANN: Can I ask a quick extension
5 to the first part you were discussing? On the
6 comparator, you didn't give us any characteristics
7 of the comparator meter--how large, how fast, what
8 size droplet, whether it had capillary. When we
9 are comparing preferences, there is more involved
10 than just the site.

11 Can you tell us anything about the
12 comparator meter?

13 DR. CONNER: The meter that the individual
14 had been using before was the meter that they
15 continued with. We probably do have that data and
16 could look at the data by type of meter, if you
17 will, but I don't have that here with me today.

18 DR. KROLL: Thank you.

19 Now we'll have some discussion among the
20 panel members, and actually, Dr. Clement has an
21 organized discussion he wanted to present.

22 **Open Committee Discussion**

23 DR. CLEMENT: Thanks.

24 I am Steven Clement, clinical
25 endocrinologist.

1 Some of the issues that present to us as
2 clinical endocrinologists, diabetologists,
3 practicing and seeing patients are how to achieve
4 better glucose control. DCCT, as we all know,
5 changed things dramatically.

6 [Slide.]

7 This is a slide from the DCCT data that
8 came out in 1993. We all know this, we all have
9 this burned into our memory, that the lower their
10 A1c is, the better off they are, the lower their
11 risk for complications. Clearly, we are trying to
12 get people down in this range as much as we can.

13 However, there is a trade-off. As we get
14 closer to this level, the risk of what was termed
15 by the DCCT group of "severe hypoglycemia," which
16 was defined as requiring assistance to get out of
17 the reaction, which is quite a severe definition,
18 goes up dramatically as we reach that goal.

19 So clearly, as we are trying to achieve
20 over here, we have sort of a two-edged sword that
21 we work with patients on a day-to-day basis and
22 struggle with every day on where is the right
23 balance and how do we get there. And clearly,
24 glucose monitoring as a huge part to play in this.

25 [Slide.]

1 The therapeutic paradox that we are left
2 with is that intensive insulin therapy clearly
3 saves lives, reduces complications. New criteria
4 by the America College of Clinical Endocrinologists
5 is now 6.5, again, with the caveat that the risk
6 for hypoglycemia potentially goes up the lower we
7 get.

8 And clearly, as I mentioned, the risk of
9 hypoglycemia increases as we get closer to these
10 lower targets, which is a major concern.

11 [Slide.]

12 These are, as we have all seen over and
13 over again, the ADA standards, trying to approach
14 A1c's of 7 percent. Still it is recommended that
15 we use--ADA does not have specific postprandial
16 glucose levels. There is lots of controversy over
17 what is the meaning of postprandial glucose levels
18 and how they reflect in terms of how they add to
19 the increase in hyperglycemia that contributes to a
20 high A1c, but these are the numbers that we
21 currently use.

22 [Slide.]

23 So with the DCCT and the strategies that
24 were developed during this trial, clearly, self-
25 monitoring of blood glucose has a key role in all

1 of this so we can come up with flexible timing of
2 insulin to meet the needs of the patient, flexible
3 activity with exercise, and the patient uses this
4 data every day, as Sam mentioned, checking 10 times
5 a day or at least within a 4-hour period, to try to
6 make clinically relevant decisions on what to do.

7 [Slide.]

8 So the decisions that the patients make
9 all the time, 10, 15, 20 times a day as to what is
10 my blood glucose, which is crucial to what we are
11 talking about today; what insulin is currently
12 working. There has been lots of discussion about
13 stable and unstable times of the day when blood
14 sugars are occurring. Many of our Type I patients
15 are never stable; they are up all the time. A lot
16 of this is because they have insulins peaking at
17 different times of the day.

18 Perhaps the only quote-unquote "stable"
19 blood glucose is the fasting glucose level.

20 When am I going to eat; what am I going to
21 eat; what activity am I going to do--because
22 clearly, that has an effect on blood glucose as
23 well; and what was the past experience with this
24 situation. Jay Skylik gives great talks on this;
25 he is basically one of the major champions of

1 intensive insulin therapy.

2 So there are multiple decisions being made
3 all the time, primarily based on the accuracy of
4 that number.

5 [Slide.]

6 This is what we are trying to achieve.
7 This is Jeremiah Bulley's [phonetic] graph that
8 came out in Lancet just a couple of weeks ago in a
9 beautiful article about looking at different
10 insulins and different insulin analogs.

11 This is in millimoles--for the European
12 folks in the audience, this is more familiar to
13 you--basically multiply each number by 18. Normal
14 glucose variation is very small, peak about 140
15 mg/dL after a meal, and then it comes back down.
16 And this is endogenous insulin production; these
17 are nondiabetic patients.

18 Clearly, this is a fairly stable glucose
19 pattern, but I would love to come even close to
20 this in our patients.

21 [Slide.]

22 The reality that we do have is that in our
23 particular insulin-treated patients, we have wide
24 and rapid fluctuations in blood sugars. This is a
25 norm that we see, and most of our patients who are

1 completely c-peptide-negative, especially after
2 meals, insulin injection and during exercise.

3 [Slide.]

4 How does self-blood glucose monitoring
5 play into this? It is critical for intensive
6 diabetes therapy. We cannot practice, and patients
7 cannot make any of these kinds of decisions without
8 accurate glucose data.

9 Frequent testing has been found to be
10 strongly associated with better hemoglobin A1c
11 values. Dr. Laurie Lefell at Joslin proved this in
12 a group of adolescents a few years ago.

13 [Slide.]

14 Clearly, part of this whole process that I
15 am learning about is that just generating the data
16 is useless. Part of our job as clinicians and
17 educators is to instruct patients how to use that.
18 I think a lot of that came out in the discussions
19 about labeling. How do we teach patients--because
20 many of our patients may not have access to an
21 educator; they may not have access to this
22 information that they need.

23 [Slide.]

24 And clearly, this is critical for safe
25 driving.

1 And glucose meters, as we know, are
2 getting smaller and smarter, with memories,
3 downloadable capabilities, and so forth, so it
4 really is an exciting field right now.

5 [Slide.]

6 One thing that hasn't been talked much
7 about is the impact of exercise on glucose levels.
8 Exercise can drop glucose levels as much as 50 to
9 100 points, depending on the intensity of the
10 exercise and the duration of exercise.

11 This is a beautiful study published in
12 Diabetes Care in the spring where they actually
13 looked at the drop in blood glucose levels with
14 varying amounts of exercise based on degree of
15 exercise and intensity of exercise. This is
16 exercise, for example, 50 percent VO2 max, which is
17 running about a 9-minute mile--that's a pretty good
18 clip--for about 60 minutes. And you can see the
19 drop in blood sugars. This is in millimoles, but
20 that's a drop of about 80 points. So depending on
21 where the person started, they can drop
22 significantly, and if they start off here, as you
23 can see here, they start off at about 180 or so,
24 they clearly drop into the hypoglycemic range with
25 60 minutes of exercise.

1 What my patients tell me is that when they
2 are exercising, they cannot distinguish between
3 fatigue from exercise and symptoms of hypoglycemia;
4 it is absolutely impossible to do that.

5 [Slide.]

6 I think alternate site testing clearly
7 provides useful information regarding overall
8 glycemic control, and there is lots of useful
9 information. Because fasting glucose is clearly
10 the most stable, I think it is very, very useful
11 for measuring morning sugar, because we can titrate
12 either the insulin or sulphur ureas or whatever
13 oral agent they are on as a guide--use their
14 morning sugar and titrate the nighttime therapy to
15 achieve better morning glucose levels.

16 [Slide.]

17 But there are lots of issues on the other
18 times. If we look at fasting glucose levels,
19 fasting glucose levels to correlate to A1c data, so
20 getting an accurate fasting glucose level, which I
21 think alternate site testing is very, very useful
22 for, can give us a very good clue on what their
23 overall glucose control is.

24 [Slide.]

25 And again, adjusting bedtime long-acting

1 insulin I think is very useful; adjusting oral
2 agents, because patients with Type II diabetes tend
3 to be more stable.

4 [Slide.]

5 But I definitely have some concerns from
6 looking at this data. Clearly, as clinicians, we
7 use what we can get. The more the patient can
8 test, we'll use any information that is available
9 to us to help them adjust their regimen and live
10 with things. But there have got to be some caveats
11 in terms of accuracy. Accuracy clearly is
12 important.

13 I think the plus or minus 20 percent has
14 served us well for a long time, and I think the
15 burden of proof is really on the companies to show
16 that they can get this type of control even in a
17 dynamic state.

18 I think this technology has a wonderful
19 potential to help patients monitor more, get more
20 data that we can use. Clearly, I think the
21 accuracy issue can potentially be a problem based
22 on some of the studies we saw. I think dynamic
23 testing can help ferret out some of these
24 differences on whether using palm testing or
25 suction on rubbing, but I'll be very interested to

1 hear other panel members' viewpoints.

2 Thank you.

3 DR. KROLL: Thank you, Dr. Clement.

4 Now we'll have an opportunity for panel
5 members to voice their opinions, and what I'd like
6 people to do is think about what the FDA questions
7 are as they are trying to come up with opinions and
8 comments. I'll just reread these quickly for
9 people.

10 Question 1: "Should the FDA's review of
11 these devices include dynamic as well as steady-
12 state data, or are there more appropriate and less
13 burdensome ways to address this public health
14 issue?"

15 There are some additional points for
16 Question 1, for example, what are the appropriate
17 studies; what is the minimum data set to be
18 studied; what are appropriate analytical or
19 statistical tools to be applied to the data.

20 Question 2: "Should the FDA require
21 manufacturers to include strong cautionary labeling
22 about this problem unless they provide data
23 demonstrating that the discordance is unlikely to
24 occur with their particular device?"

25 Question 3: "Should the FDA rescind the

1 clearance for labeling for alternative site testing
2 if the 510(k)s do not address this new scientific
3 issue; make these products prescription home use;
4 require additional data and labeling changes?"

5 And finally, Question 4: "Are there other
6 activities or issues that FDA should consider with
7 regard to this important public health issue, such
8 as a public health alert, targeted postmarket
9 surveillance, educational outreach activities to
10 stakeholders and other Government and non-
11 Government entities to promote additional research
12 in this area?"

13 Unless somebody has a burning desire to
14 get up and say something, perhaps we could go
15 around the panel. Let's start with Dr. Rosenbloom.

16 DR. ROSENBLOOM: Well, typically, we
17 address these questions one at a time. Do you want
18 me to give my opinion on all of these questions?

19 DR. KROLL: We can do it one at a time.
20 Let's start with Question 1.

21 DR. ROSENBLOOM: So the first question,
22 then, is "Should FDA's review of these devices
23 include dynamic as well as steady-state data, or
24 are there more appropriate and less burdensome ways
25 to address this public health issue?"

1 I think it is abundantly apparent both
2 from the experience of the clinicians and patients
3 and others in the room that this is a dynamic
4 question that needs to be answered with dynamic
5 studies; that not only do we have variation related
6 to the absorptive state and how busy the liver is
7 and how busy the pancreas is, if there is anything
8 left of it, but how busy the insulin that is being
9 absorbed is. There are just so many variables
10 related to age, type of diabetes, duration of
11 diabetes, gender, and BMI and the physiologic state
12 that cannot be taken as an assumption to indicate
13 that any given individual will look like the model.

14 So I think we have seen enough data to
15 indicate that we definitely do need to consider
16 devices that are dealing with rapidly changing
17 metabolic substances--in this case, of course,
18 glucose--that it is appropriate for FDA to review
19 dynamic data before approving either the device,
20 the system, or the labeling.

21 DR. KROLL: Do you have any comments on
22 the second part of Question 1, what is the minimum
23 dataset, what study designs? Actually, if you
24 answer "yes" to the first part, the second set of
25 questions is probably the most important.

1 DR. ROSENBLOOM: I'd rather you go around
2 and come back and let everybody answer the first
3 part, and then I'd be willing to tackle the second
4 part. Otherwise, I'll waste time reflecting on it.

5 DR. KROLL: Okay. Dr. Henderson?

6 DR. HENDERSON: I absolutely agree with
7 Dr. Rosenbloom. I think it has been made clear
8 today that this is an excellent clinical tool that
9 has a wide number of uses, but I think we have also
10 seen that it is a tool that provides us with an
11 area for improvement. So I definitely think yes,
12 that dynamic-state studies should be evaluated.

13 DR. KROLL: Okay.

14 MS. KRUGER: I think we have seen a ton of
15 data that both says that the companies have been
16 very responsive to the concerns that we are all
17 dealing with today, and I applaud all of the
18 companies for that. I think they have given us a
19 lot of that data, and I think we need to ongoing
20 look at dynamic data and how it affects these
21 meters and how it will affect our patients, but I
22 think we also need to consider the fact that this
23 is an advancement for people with diabetes beyond
24 anything we have ever had before and keep that in
25 mind in terms of the demands that we place on the

1 companies.

2 DR. CLEMENT: I definitely think dynamic
3 testing is necessary to try to sort out how much
4 lag time there is, how much of an accuracy problem
5 there is. Some of the data presented to us from
6 Roche suggested that the difference between YSI
7 data in the arm data can be as much as 156 points.
8 That is clearly unacceptable for trying to make
9 decisions, particularly looking at the hypoglycemia
10 range.

11 We saw a lot of different presentations
12 about doing different types of dynamic testing. I
13 think the methodology that we saw many times over
14 of some type of glucose challenge followed either
15 by an injection of insulin, whether it is
16 subcutaneous or i.v., to help bring the sugars down
17 and then monitor doing PK samples every 15 to 20
18 minutes for 4 to 6 hours, I think is very, very
19 useful.

20 I have scribbled a couple of plots for
21 which I don't have overheads, but maybe I'll make
22 copies of them. Basically, we have all seen this
23 pattern over and over again where, during the up
24 slope, there is a lag, and during the down slope,
25 it tends to be higher. Somehow separating these

1 two periods of time into an up-slope period and a
2 down-slope period and even analyzing that data
3 separately using Bland-Altman plots to look for
4 bias one way or the other I think would be very,
5 very helpful.

6 If a company has a method to minimize this
7 error--and again, certain limits would have to set--
8 -I think it would be very useful to allow them to
9 say that it is substantially equivalent; but I
10 think it has to be challenged in a fairly rigorous
11 way to try to sort out that data, and just doing
12 kind of random testing for thousands of patients
13 and different types of the day, depending on what
14 time they are eating or not, is not quite as
15 rigorous as this.

16 And these fluctuations in sugars going
17 from 100 to 300 are not out of the realm of
18 reality. We saw this even this morning; sugars can
19 go up. So I think this is a fairly realistic and
20 reasonable test to measure.

21 DR. KROLL: Thank you.

22 I'll make my comments now. I concur with
23 all the other panel members that, yes, dynamic
24 testing is important. We have to remember that
25 diabetes is a dynamic disease, and you can't

1 evaluate dynamic disease or anything dynamic at
2 steady state.

3 To answer the other questions, what are
4 appropriate study designs--I think it is very
5 important to look at the data that we have seen
6 today where they look at time course data, and we
7 look for this like hypoglycemia as well as
8 hyperglycemia. I think some of the studies also
9 used oral glucose tolerance tests as well as
10 insulin challenges in addition to normal patients
11 eating and taking their regular insulin, I think
12 that's also very important. They need to evaluate
13 what happens if someone is challenged into the
14 hypoglycemic range.

15 What is the minimum dataset to be studied?
16 I think we ought to look at this in terms of the
17 time course and pick out times--in other words,
18 somewhere between every 15 or 30 minutes--collect
19 those data points, watch the rise, and it comes
20 back down into the fasting level and see what
21 happens, because that is getting into a dangerous
22 zone there for hypoglycemia.

23 In terms of how the data should be
24 analyzed and else should we be looking for, I think
25 one thing that was very interesting was that some

1 of the sponsors and some people presented
2 information that there were significant time lags,
3 but these time lags did not occur with all people.
4 As a matter of fact, it sounded as if sometimes the
5 time lags only occurred in one out of 10 people.
6 And that is very significant to identify that piece
7 of information--how significant are the time lags,
8 how often do they occur, maybe break them down by
9 groups, but have a very good idea, because the
10 important thing is if somebody doesn't have a time
11 lag problem, and they don't have a problem with the
12 difference between the values, you really don't
13 need to do a lot of additional testing. I think
14 that is important to figure out.

15 In terms of what type of statistics should
16 be used, I think we have to get away from the
17 stationary type of statistics--even like the
18 difference plots are fairly stationary--and begin
19 to look at things like series analysis, and also be
20 able to assess that time lag and assess it well and
21 have it well-characterized.

22 There is even the potential that some of
23 the data across time could be fit to, for example,
24 polynomial regressions, to get an idea of the
25 characteristics of those curves. They may end up

1 being very easy to characterize and may show actual
2 differences that could be used for predictiveness
3 later on.

4 Thank you.

5 DR. AHMANN: Like everyone else, I would
6 agree that dynamic testing is a necessary and
7 important feature of this whole thing. I think our
8 first priority is to have safety; the second
9 priority will be to have efficacy and reliability.

10 I do reject one statement or suggestion
11 that was made at least once during the time
12 earlier. I don't think there is any dynamic test
13 which would be considered nonphysiologic, because I
14 think what people with Type I diabetes in
15 particular get are things that will happen any day
16 at any time, without prediction. If you want to
17 talk about somebody who has gastroparesis and just
18 took their dose of short-acting insulin and the
19 potential for how much their level might change if
20 they don't get their food absorbed, or you take
21 somebody who took their dose and was interrupted
22 from having a meal, or you have somebody who went
23 out for the afternoon who does nothing and suddenly
24 spent the whole afternoon working in their yard,
25 those may not fit into some classification of

1 physiologic activities, but boy, they are the
2 things that will most impact the patients.

3 With regard to how one would look at the
4 hypoglycemic end, which I think is probably the
5 most important area to highlight, that is
6 difficult. I think we would have to have some sort
7 of provocative test that would create hypoglycemia.
8 You would want to do it relatively safely, and you
9 would want to do it in a reproducible manner that
10 everyone else could adhere to, and I think that
11 would take some studying on the part of the panel
12 or others to determine what the best test in that
13 situation would be. It would not necessarily be
14 the ones at least at doses and so forth that we
15 have seen today with insulin.

16 I think that the suggestion of the
17 highlighting of how often would you become
18 hypoglycemic and not recognize it is one important
19 feature of what we would be looking at, since that
20 is the area that is going to most threaten the
21 patient. And whether the suggestion of 15 percent
22 in one of the last technical presentations is true
23 would be very important. I think that is a
24 significant number if it holds true in multiple
25 studies.

1 So the minimum dataset I think does
2 include exercise as a very important issue. As Dr.
3 Clement said about exercise, it needs to be
4 highlighted. I think that that is a frequent place
5 where people will become hypoglycemic without
6 intending to and without really any forethought
7 about it, and I think it occurs in several
8 settings, including the one he mentioned where
9 someone would go out and do a set amount of
10 exercise that is fairly high-intensity--but I have
11 a patient on a pump who works for Nike who runs 5
12 or 6 miles every day, and he can go running without
13 ever turning down his basal rate because he is so
14 fit that there is no difference between his insulin
15 sensitivity with activity or not. I have other
16 patients who do nothing but go out and work in
17 their flower bed for a few hours, and they crash
18 and have severe hypoglycemic. We would need to
19 somehow take those sorts of things into account; we
20 couldn't just put some people on a treadmill and
21 expect that that is going to answer the questions.

22 So these are technical issues, but I think
23 we all agree that this is an advancement in
24 therapy, and if we can make it more comfortable for
25 people--this is a disease like no other disease in

1 terms of requiring patient management; they have a
2 lot of aspects of the misery index for all that
3 they have to do with their disease, and anything we
4 can do to facilitate their therapy safely would be
5 the optimum thing.

6 DR. CARA: I just want to make a couple of
7 comments before answering the question, if you
8 don't mind, and I'm going to echo some of the
9 sentiments that have already been mentioned.

10 To a large extent as a pediatric
11 endocrinologist, I am faced daily, as everybody
12 else is in their own practice, with the paradox of
13 children with diabetes having to perform blood
14 glucose monitoring. I think we would all agree
15 that blood glucose monitoring is probably, after
16 insulin, the most important discovery for the
17 management of Type I diabetes, certainly probably
18 for Type II diabetes. But on the other hand, there
19 are probably few other things--well, one of the
20 most important thing that people with diabetes
21 probably hate the most is blood glucose monitoring,
22 so oftentimes there is the paradox of the clinical
23 utility of the procedure and on the other hand how
24 it is viewed by the person who is actually doing
25 it.

1 As a result, it is oftentimes difficult
2 for us, especially in pediatrics, to get
3 information to be able to counsel patients
4 appropriately, either because they are not willing
5 to test or don't want to or do but don't write down
6 blood sugar levels or whatever.

7 I think this is an important technology
8 that really needs to be explored further, and I
9 would caution the FDA about moving backward in any
10 way.

11 I think we are essentially seeing the tip
12 of the iceberg here in terms of this phenomenon,
13 and I think we need more information in terms of
14 what is actually going on. I would specifically
15 encourage the FDA and the manufacturers of these
16 devices to look at different populations of
17 patients--what does happen in infants; what happens
18 in children; what happens with exercise. We assume
19 that with exercise perhaps there will be more
20 discordance with finger and alternative site
21 testing, but on the other hand, you could argue
22 that with exercise there is increased blood flow,
23 and maybe the difference will be less. We don't
24 know that.

25 I would encourage that dynamic studies be

1 performed, obviously, as everyone else has
2 mentioned.

3 I would encourage the manufacturers to
4 look at other procedures besides rubbing--perhaps
5 warming the area with a washcloth or a warm bag or
6 something; I'm sure you can be much more creative
7 in the procedures--might lead to less discordance.

8 And again, addressing some of the issues
9 that were mentioned earlier, maybe finding out why
10 some people have more discordance than others might
11 be important to look at.

12 That's all. Thanks.

13 DR. MANNO: Everybody has said everything
14 I was going to say, but I would add to Dr. Cara's
15 comments to the extent that in selecting broader
16 populations to study, I think we need to definitely
17 include people with vascular problems--and I'll say
18 why in a second--renal and hepatic.

19 I think we definitely have to look at not
20 only the different results that we're getting with
21 the different therapeutic agents for diabetes. I
22 think we have to look also at concomitant drugs
23 that are on board. An issue in point--the comment
24 about changing of absorption of food productions
25 and nutrients. With the number of stress-related