

## FOOD AND DRUG ADMINISTRATION

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CENTER FOR DEVICES AND RADIOLOGICAL HEALTH

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MEDICAL DEVICES ADVISORY COMMITTEE

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CLINICAL CHEMISTRY AND CLINICAL TOXICOLOGY  
DEVICES PANEL

+ + + + +

MEETING

+ + + + +

MONDAY,  
DECEMBER 6, 1999

+ + + + +

The meeting was held at 9:00 a.m., in the Grand Ballroom of the Gaithersburg Marriott, 9751 Washingtonian Boulevard, Gaithersburg, Maryland, Dr. Henry C. Nipper, Chairperson, presiding.

PRESENT:

HENRY C. NIPPER, Ph.D., Chairperson  
 JOSEPH D. ANDRADE, Ph.D., Temporary Voting Member  
 STEPHEN CLEMENT, M.D., Temporary Voting Member  
 JOHN J. DiGIOVANNA, M.D., Temporary Voting Member  
 BASIL T. DOUMAS, Ph.D., Temporary Voting Member  
 JAMES EVERETT, M.D., Ph.D., Temporary Voting Member  
 BEVERLY HARRINGTON-FALLS, M.D., Voting Member  
 ROBERT L. HABIG, Ph.D., Industry Representative  
 JANINE E. JANOSKY, Ph.D., Temporary Voting Member  
 DAVIDA F. KRUGER, M.S.N., Consumer Representative  
 BARBARA R. MANNO, Ph.D., Voting Member  
 JAMES J. REED, B.S.E., Patient Representative  
 NADER RIFAI, Ph.D., Voting Member  
 ARLAN L. ROSENBLOOM, M.D., Voting Member

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ALSO PRESENT:

VERONICA J. CALVIN, Executive Secretary  
STEVEN I. GUTMAN, M.D., M.B.A., Division  
Director

SPONSOR PRESENTERS:

JOHN C. HODGMAN  
NEIL R. ACKERMAN, Ph.D.  
KENNETH PITZER, D.V.M.  
RUSSELL O. POTTS, Ph.D.  
STEVEN V. EDELMAN, M.D.  
LOIS JOVANOVIC, M.D.

FDA PRESENTERS:

PATRICIA BERNHARDT, B.S., M.T.(ASCP)  
KRISTEN MEIER, Ph.D.  
JEAN I. FOURCROY, M.D., Ph.D., M.P.H.

PUBLIC SPEAKERS:

MARY AYD  
LAURA BILLETDEAUX  
SONIA COOPER  
RYAN HARVEY  
JACK KEATING  
MICHAEL KOMONDY  
LAUREN LANNING  
SUE PALANDRI  
VIVIAN SKINNER

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## C-O-N-T-E-N-T-S

Call to Order, Chairman Nipper .....	4
Opening Remarks, Veronica Calvin .....	4
Introductions .....	5
Conflict of Interest Statement .....	7
Veronica Calvin	
Presentations, Steven Gutman .....	10
Open Public Hearing .....	12
Sponsor Presentation	
Greeting, John Hodgman .....	49
Introduction, Neil Ackerman, Ph.D. ....	51
Device Description .....	53
Kenneth Pitzer, D.V.M.	
Review of Safety and Effectiveness .....	66
Studies, Russell Potts, Ph.D.	
Clinical Perspective .....	96
Steven Edelman, M.D.	
Clinical Experience .....	111
Lois Javonovic, M.D.	
Question and Answer Period .....	119
FDA Presentation	
Patricia Bernhardt, BS, MT (ASCP) .....	120
Kristen Meier, Ph.D. ....	126
Jean I. Fourcroy, M.D., Ph.D. M.P.H. ....	144
Question and Answer Period .....	152
Open Committee Discussion .....	159
Open Public Hearing .....	296
Final Recommendations and Vote .....	315
Closing Remarks .....	354
Adjourn	

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

(9:06 a.m.)

CHAIRMAN NIPPER: May I have your attention, please?

I'm Henry Nipper, the chair of the panel. This meeting of the Clinical Chemistry and Clinical Toxicology Devices Panel will come to order.

I'll call on our Executive Secretary, Veronica Calvin, for comments.

MS. CALVIN: Good morning. As Dr. Nipper stated, I am Veronica Calvin, Executive Secretary of the panel, and I'd like to welcome you to this meeting. Today the committee will discuss, make recommendations, and vote on a pre-market approval application for a device indicated for frequent, automatic, and non-invasive monitoring of glucose levels in adults with diabetes.

Before we move into today's agenda, I will provide brief summary minutes of the last panel meeting. The Clinical Chemistry and Clinical Toxicology Devices Panel last met on October 28, 1999, to discuss a pre-market notification for the BioScanner T over-the-counter triglycerides test manufactured by Polymer Technology Systems, Incorporated.

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1           The panel concluded that appropriate  
2 precision and interference studies had not been  
3 performed, appropriate claims for the device had not  
4 been captured in the labeling, performance was not  
5 adequate to support the intended use, and the risks of  
6 the device outweighed the benefits. There was a  
7 consensus that the device was not yet ready for the  
8 market.

9           I would like to take this time to formally  
10 introduce the chairman of the panel, Dr. Henry Nipper.

11         Dr. Nipper is Assistant Dean for Admissions at  
12 Creighton University School of Medicine, Associate  
13 Professor of Pathology at Creighton, and Associate  
14 Director of Clinical Chemistry and Toxicology at St.  
15 Joseph's Hospital in Omaha, Nebraska.

16           I would also like to acknowledge some  
17 guest panelists. We welcome Mr. James Reed, who will  
18 be serving again as the patient representative; the  
19 statistician, Dr. Janine Janosky, from the Dental  
20 Products Panel; and Dr. John DiGiovanna, from the  
21 Drugs Advisory Committee.

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

24           DR. HABIG: I am Dr. Robert Habig. I am  
25 Vice President of Clinical Operations at Cytometrics,

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1 Incorporated.

2 MS. KRUGER: I'm Davida Kruger, a  
3 certified nurse practitioner in the area of diabetes  
4 at Henry Ford Health Systems in Detroit, Michigan.

5 MR. REED: I'm Jim Reed. I'm a patient  
6 representative, Type 1 diabetic, representing  
7 diabetics and Educating and Empowering Diabetics, a  
8 nonprofit group dedicated to helping diabetics learn  
9 to cope with their disease.

10 DR. ANDRADE: I'm Joe Andrade, Co-Chair of  
11 the Department of Bioengineering at the University of  
12 Utah.

13 DR. HARRINGTON-FALLS: Good morning. I'm  
14 Beverly Harrington-Falls, OB/GYN with Cornerstone  
15 Healthcare, High Point, North Carolina.

16 DR. ROSENBLOOM: Arlan Rosenbloom,  
17 academic pediatrician, from Gainesville, Florida.

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

22 DR. CLEMENT: Steve Clement, a clinical  
23 endocrinologist and diabetes specialist here in  
24 Washington, D.C., at Georgetown University.

25 DR. DOUMAS: Basil Doumas, Professor of

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1 Pathology, Medical College of Wisconsin.

2 DR. MANNO: Barbara Manno, Professor,  
3 Department of Psychiatry, and Co-Director of the  
4 Clinical Toxicology Lab at the LSU School of Medicine  
5 in Shreveport, Louisiana.

6 DR. EVERETT: James Everett, Medical  
7 Director at Madison Memorial Healthcare in Madison,  
8 Florida.

9 DR. JANOSKY: Janine Janosky, University  
10 of Pittsburgh School of Medicine, a biostatistician.

11 DR. DIGIOVANNA: I'm John DiGiovanna,  
12 Director of Division of Dermatopharmacology at Brown  
13 University, and I'm a consultant to the Dermatologic  
14 and Dental Drugs Advisory Committee.

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

18 MS. CALVIN: Thank you.

19 I will now read the conflict of interest  
20 statement, followed by the appointment to temporary  
21 voting status memo.

22 Conflict of interest. The following  
23 announcement addresses conflict of interest issues  
24 associated with this meeting and is made part of the  
25 record to preclude even the appearance of an

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1       impropriety. To determine if any conflict existed,  
2       the agency reviewed the submitted agenda and all  
3       financial interest reported by the committee  
4       participants.

5               The conflict of interest statutes prohibit  
6       special government employees from participating in  
7       matters that could affect their or their employer's  
8       financial interests. However, the agency has  
9       determined that participation of certain members and  
10      consultants, the need for whose services outweighs the  
11      potential conflict of interest involved, is in the  
12      best interest of the government.

13             A waiver has been granted for Ms. Davida  
14      Kruger, for her interest in firms at issue that could  
15      potentially be affected by the committee's  
16      deliberations. The waiver allows this individual to  
17      participate fully in today's deliberations. A copy of  
18      this waiver may be obtained from the agency's Freedom  
19      of Information Office, Room 12A-15, at the Parklawn  
20      Building.

21             We would like to note for the record that  
22      the agency took into consideration certain matters  
23      regarding Dr. Stephen Clement, John DiGiovanna, Basil  
24      Doumas, Nader Rifai, Arlan Rosenbloom, and Ms. Davida  
25      Kruger. These panelists reported current and/or past

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1 interest in firms at issue, but not in matters related  
2 to what is being discussed today.

3 Since these matters are not related to the  
4 specific issues of this meeting, the agency has  
5 determined that they may participate fully in today's  
6 deliberations. In the event that the discussions  
7 involve any other products or firms not already on the  
8 agenda for which an FDA participant has a financial  
9 interest, the participant should excuse him or herself  
10 from such involvement, and the exclusion will be noted  
11 for the record.

12 With respect to all other participants, we  
13 ask, in the interest of fairness, that all persons  
14 making statements or presentations disclose any  
15 current or previous financial involvement with any  
16 firm whose product they may wish to comment upon.

17 Appointment to temporary voting status.  
18 Pursuant to the authority granted under the Medical  
19 Devices Advisory Committee charter, dated October 27,  
20 1990, and as amended August 18, 1999, I appoint the  
21 following individuals as voting members of the  
22 Clinical Chemistry and Clinical Toxicology Devices  
23 Panel for this meeting on December 6, 1999. Joseph  
24 Andrade, Ph.D.; Stephen Clement, M.D.; Basil Dumas,  
25 Ph.D.; James Everett, M.D., Ph.D.; John DiGiovanna,

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1 M.D.; Janine Janosky, Ph.D.

2 For the record, with the exception of Dr.  
3 John DiGiovanna, these individuals are special  
4 government employees and consultants to this panel or  
5 other panels under the Medical Devices Advisory  
6 Committee. Dr. John D. DiGiovanna is a special  
7 government employee and consultant to the Dermatologic  
8 and Ophthalmic Drugs Advisory Committee.

9 They have undergone the customary conflict  
10 of interest review and have reviewed the material to  
11 be considered at this meeting.

12 Signed, David W. Feigal, Jr., M.D.,  
13 M.P.H., Director, Center for Devices and Radiological  
14 Health.

15 Thank you.

16 Now I would like to call Dr. Gutman  
17 forward. He has some remarks to make.

18 DR. GUTMAN: Good morning. This is a  
19 milestone meeting because three active members of this  
20 panel will have completed four years of loyal service  
21 to our agency as special government employees and will  
22 be changing their status with regard to this panel.  
23 And I would like to formally recognize them with a  
24 letter from our commissioner, Dr. Haney, and a plaque.

25 First, is Dr. Harrington-Falls, who has

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1 been with us for four years and has provided ongoing  
2 high-quality work, insight, attendance, and all of the  
3 things one would long for in a model scientist helping  
4 in the regulatory process.

5 (Applause.)

6 The second is our industry rep, Dr. Habig.  
7 Bob has been an industry member of the panel for the  
8 past four years and has provided the perspective we've  
9 come to know, love, and, frankly, need, which is an  
10 iconoclastic and grounded industry perspective, and  
11 we're really grateful to have had his help.

12 (Applause.)

13 Last, but certainly not least, this is a  
14 swan song for our chair. Dr. Nipper has brought the  
15 ideal qualities of a chair, which, frankly, are not  
16 only that he is a good scientist, a good ear, and that  
17 he grounds us, but he keeps us on time. We'll see if  
18 he's able to end on that note.

19 He has taken us through some very  
20 challenging, very complicated submissions, some fairly  
21 tense times. He has personally bailed me out on more  
22 than one occasion, so I am particularly grateful to  
23 Dr. Nipper.

24 (Applause.)

25 And then, as a coda, we have a sort of

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1 special and different kind of an award, and this is to  
2 recognize Dr. Janosky. Dr. Janosky has become such a  
3 standard member of our committee it's as though she is  
4 a member of our committee. She, in fact, is not.

5 We have stolen her from the Dental  
6 Committee, but she has provided wonderful insights on  
7 some of our most complex products. And so we have a  
8 certificate of appreciation to note how grateful we  
9 are for her ongoing help on a panel that she wasn't  
10 actually recruited to.

11 (Applause.)

12 It shows you that we're a versatile  
13 organization, and you'd better be careful when you say  
14 yes to FDA.

15 (Laughter.)

16 CHAIRMAN NIPPER: Well, I appreciate the  
17 recognition. And on behalf of the other members of  
18 the committee and the panel, I appreciate the fact  
19 that the FDA has remarked on our service. I had no  
20 idea four years had gone so quickly. When you're  
21 having fun, it's wonderful.

22 At this time, we are ready to move to the  
23 open public hearing portion of the panel meeting.  
24 Panel attendees who have contacted the Executive  
25 Secretary prior to the meeting will address the panel

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1 and present information relevant to the agenda.

2 Speakers are asked to state whether or not  
3 they have any financial involvement with the  
4 manufacturer of the product being discussed, or with  
5 their competitors. So we, at this time, will call on  
6 Sonia Cooper to address the panel.

7 MS. COOPER: Good morning. It's an honor  
8 to be here.

9 I'm speaking not only for myself this  
10 morning, but I'm also taking up the time for Jeff  
11 Hitchcock, who is Editor-in-Chief of  
12 childrenwithdiabetes.org, and I'm also speaking for  
13 Margaret Himelfarb, who is a friend of mine whom I've  
14 known through the Juvenile Diabetes Foundation and is  
15 a very active participant in the diabetes community  
16 and is currently working on the diabetes awareness  
17 stamp.

18 Each year, in the Rocky Mountain region, I  
19 host a research update, and people come from about a  
20 five-state area. What happens at this research update  
21 is before this occurs we get the chance to ask people,  
22 what do you want to hear about each year? Every year  
23 the number one request is that they want to hear about  
24 the GlucoWatch.

25 They have three requests. We want a

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1 device that has a continuous, alarmable, and accurate  
2 method of preventing our loved ones from having these  
3 severe episodes of hypoglycemia. Continuous,  
4 alarmable, and accurate. We emphasize that at the  
5 JDF/NASA conference as well, and Cygnus is the company  
6 that's listening.

7 I think it's interesting because this  
8 request is even more frequent than requests on a cure  
9 in the form of beta cell transplantation. It's that  
10 important to people.

11 I'm here to ask for your help and your  
12 trust today. My sister is losing her sight and her  
13 kidneys. During pregnancy, the damage to her body was  
14 quite severe, and she had a child born that needed a  
15 heart transplant at birth. Because of her frequent  
16 hospitalizations, seizures, and ambulance rides, her  
17 ex-husband was able to successfully argue that he  
18 could provide a safer and a stress-free environment  
19 for her children.

20 My son was diagnosed at age one. I have  
21 an older son who we've been told has up to a 90  
22 percent risk of getting it in the next couple of years  
23 because he is auto-antibody positive. My daughter has  
24 the same high-risk genetics and has a 50 percent  
25 chance. I know parents who have three children with

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1 diabetes, and they need some help, and they need a  
2 tool. It's a lot to ask.

3 My son was recently able to borrow a mini-  
4 med continuous glucose monitor, and I thank each of  
5 you that were involved in the approval of that  
6 product, because although it's rather invasive and may  
7 not have a widespread applicability, that information  
8 that we obtained was absolutely invaluable in getting  
9 his basal rates at a correct level for his pump, so  
10 that he doesn't have to face the same complications my  
11 sister now sees.

12 The first graph up here shows that I  
13 thought I was a pretty good parent the first time we  
14 used this. We had four tests, and I decided I was  
15 safe to go to bed. You can see the numbers are  
16 between 100 and 150. The correlation is fabulous.  
17 And even though, you know, he had to go to bed with a  
18 pump sticking out of one side of his stomach, and a  
19 monitor out of the other side of his stomach, I felt  
20 like I was safe to go to bed.

21 If we can see the next overhead.

22 Look what happened after I went to sleep.  
23 The monitor only reads to 40. I don't know how much  
24 lower he was. He was there. Then I wake up at 4:00  
25 in the morning, a little bit after that, and test him.

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1 He's over 100 again because the somogyi effect has  
2 kicked in. I didn't do anything to help raise his  
3 blood sugar. We're blessed with an angel that helped  
4 that blood sugar get back up.

5 What's interesting is if I hadn't had that  
6 monitor, I might have actually raised his basal rate,  
7 thinking that he was perfectly safe during those four  
8 hours.

9 You can see, then, what happens after you  
10 have a somogyi effect. The rest of the day is pretty  
11 much a disaster.

12 So can I see the next slide? Thank you.

13 Here is another example. I go to bed at  
14 midnight, everything looks great. I think everything  
15 is going to be fine. Wake up at 4:00 a.m., and his  
16 pump had disconnected. If we had had an alarm, or if  
17 I had been able to go in and check his wrist, he  
18 wouldn't have been up above 400. This meter only  
19 reads to 400. He could have been 550, 600.

20 Finally, we come back down again you can  
21 see the correlation is fabulous in these devices using  
22 interstitial fluid. But look at how out of control  
23 the rest of his day is because of getting these wild  
24 fluctuations and swings.

25 Anyways, I urge your help with this

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1 matter. Even if my son never uses this type of device  
2 again, look at how invaluable it was in making  
3 decisions with our physician about his basal rates.  
4 It was absolutely invaluable. So I thank you for  
5 approving it.

6 I guess we can go on to the next one now.  
7 I'm honored to be able to help represent Jeff  
8 Hitchcock, who couldn't be here today. But I think  
9 his letter is really kind of terrific. Jeff reaches  
10 more people through his internet nonprofit site than  
11 any other web site in the world, and the awards speak  
12 for themselves that the site has obtained. And he  
13 reaches just about everybody in the world at this  
14 point. All of the dark portions on this are countries  
15 where we get hits from all over the world.

16 Anyways, Jeff writes to say, "Please take  
17 an imaginative journey with me as I paint a picture of  
18 what living with diabetes is like. I want you all to  
19 pretend that you are at the Kennedy Center for a night  
20 out at the symphony. You and your spouse have the  
21 best seats in the house, and the people who would be  
22 in front of you didn't make it, so you have a clear  
23 view of the stage and it's a perfect night.

24 The director lifts his baton, pauses, and  
25 begins. You see the baton flow through the air, see

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1 the bows pressed against the strings, but you hear  
2 nothing. You are confused. Then, a few minutes into  
3 the piece, you hear a fleeting note and then return to  
4 silence. A few minutes later, you hear one more note,  
5 but frustratingly return immediately to silence.  
6 Again, in a few minutes, you hear another note, and  
7 then the piece ends.

8 This is the life of a person with  
9 diabetes. Each day, through finger stick blood tests,  
10 a person with diabetes hears but a few notes of his  
11 body's symphony. From those very few notes, he must  
12 make decisions about how much food to eat, how much  
13 insulin to inject, and how to integrate exercise into  
14 the day.

15 With but a few blood sugar values to go  
16 by, he is essentially deaf to his body. If only he  
17 could hear more often, he could make better choices.

18 The management of diabetes is as much  
19 about information as it is about insulin and  
20 nutrition. The last 20 years have seen a revolution  
21 in the quality of diabetes self-management through the  
22 availability and affordability of in-home blood  
23 glucose monitors. These wondrous devices allowed the  
24 first fleeting notes of the body's symphony to be  
25 heard. But like a deaf person regaining his hearing,

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1 we who live with diabetes hungered to hear more.

2           The Cygnus GlucoWatch offers us the  
3 opportunity to hear more of our body's symphony.  
4 Instead of four to six notes a day, we can hear  
5 dozens. And what a difference that will make. With  
6 more information, we can and will make better  
7 decisions about our care. And with better decisions  
8 will come improved blood sugar control, and, as a  
9 result, a reduced risk of complications.

10           I urge the committee to understand the  
11 importance of the GlucoWatch to the millions of people  
12 with diabetes who manage their own care and make their  
13 own decisions, based on the few blood tests they  
14 perform each day.

15           By approving this device, you will not  
16 only open their ears to more of their body's symphony,  
17 but you will also lay the foundation for even better  
18 technology that will one day allow people with  
19 diabetes to hear the entire symphony of their body all  
20 day long. That will be sweet music to the ears of  
21 everyone who lives with diabetes."

22           Margaret Conn-Himelfarb writes to say that  
23 she is the mother of a 23-year old son who next month  
24 will mark the 20th anniversary of his diagnosis.  
25 Despite his diabetes, Michael has to his credit many

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1 wonderful accomplishments, including a degree from  
2 Princeton, magna cum laude.

3           Among his most remarkable achievements is  
4 the recent report from his ophthalmologist that  
5 revealed no evidence of retinopathy. Michael is  
6 beating the odds, the doctor proclaimed.

7           Testing your blood sugar four to six times  
8 a day is an endless, frustrating intrusion. As  
9 Michael said when he was seven years old, you never  
10 get to take a vacation. At one end of the continuum  
11 lurks the fear of blood sugars, seizures,  
12 unconsciousness, brain damage, and death. At the  
13 other end, high blood sugars that over time can  
14 destroy virtually every organ in the body.

15           Despite your best efforts, you cannot  
16 conquer the wild fluctuations that not only put you at  
17 risk for insulin shock and complications, but also  
18 cause headaches, blurred vision, dizziness, nausea,  
19 and fatigue.

20           Michael's still healthy retinas come at a  
21 cost. While most young adults believe they are  
22 invulnerable, Michael is acutely aware of his  
23 mortality. He has known since far too young an age  
24 that he controls his own destiny. His future depends  
25 in large measure on how he manages his disease. He's

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1 a veteran, with over 20,000 insulin shots and 35,000  
2 blood tests.

3 But Michael is not the norm. Most people  
4 with diabetes resist testing their blood sugar because  
5 they don't want to be conspicuous about their  
6 diabetes, continually interrupt what they're doing,  
7 prick their fingers or carry paraphernalia.

8 Others test religiously, many times a day.

9 But in spite of their good readings, many of them  
10 succumb to complications.

11 The explanation for that seeming paradox  
12 is that snapshot readings do not portray the full  
13 picture. And I think our slides represented that in  
14 my son's case.

15 How many more times can a person be  
16 expected to prick their fingers? A device like the  
17 portable, unobtrusive, non-invasive GlucoWatch  
18 monitor, with its continuous automatic features and  
19 warning alerts would promote increased compliance and  
20 dramatically improve control.

21 Not enough has changed since Michael's  
22 diagnosis 20 years ago. The monitor would ultimately  
23 prevent tremendous human suffering and save countless  
24 dollars in health care expenditures. Its importance  
25 cannot be overestimated. If your investigation

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1 determines that this device is both accurate and safe,  
2 I urge you to expedite its approval, so that 16  
3 million Americans with diabetes can begin to benefit  
4 from its usage.

5 If you can -- I'm speaking for three  
6 people, so I apologize for being long. But this last  
7 letter I think is critically important. It's from Dr.  
8 Peter Chase, who is my son's physician. And, frankly,  
9 he has allowed us to have a life, so I am proud to  
10 read this letter in particular.

11 And Dr. Chase writes that, "As a physician  
12 who has cared for thousands of patients with Type 1  
13 diabetes over the past 30 years, and as the parent of  
14 a son with Type 1 diabetes, and as Clinical Director  
15 of the Barbara Davis Center for Childhood Diabetes at  
16 the University of Colorado, I would like to ask for  
17 your support of the GlucoWatch.

18 Your assistance in allowing this device to  
19 be made available to patients with the alarm and  
20 readout functions intact will be invaluable.

21 I am familiar with the alternatives. I  
22 was present at the NASA/JDF conference on non-invasive  
23 blood glucose monitoring, and currently have patients  
24 wearing the mini-med continuous glucose monitoring  
25 system.

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1 Patients with diabetes are taught to  
2 review many variables and consider several external  
3 and internal factors when making insulin adjustment  
4 decisions. Unfortunately, the tools available today  
5 are inadequate. The GlucoWatch Biographer's 20-minute  
6 measurement cycle and resulting moving average effect  
7 can accommodate clinical use by allowing review of a  
8 series of results before making management decisions.

9 You may set low glucose alert levels, even  
10 if these are somewhat above the level at which  
11 treatment of hypoglycemia is needed. Safety protocols  
12 are often prescribed for younger patients or those  
13 with extremely active lifestyles. Even with today's  
14 blood glucose meters, if there is any doubt about a  
15 reading, patients are taught to reconfirm by retesting  
16 and considering other factors.

17 I was the senior author of one of the  
18 first papers published on the clinical use of the  
19 GlucoWatch in diabetes care, so I'm quite familiar  
20 with its use. I'm aware that iontophoresis can cause  
21 transient mild skin irritation.

22 This can be managed by rotating the  
23 wearing site as needed until irritation is resolved.  
24 The number of sites required will depend on individual  
25 patient response and the frequency with which the

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1 device is used. Both forearms can be used to provide  
2 multiple sites at which the device may be worn.

3 Most patients will not require constant  
4 wear. But the value of having numerous readouts on an  
5 intermittent basis could be an important tool for  
6 patient-physician care decisions. Frequent,  
7 automatic, non-invasive measurements obtained with  
8 this biographer would provide access to previously  
9 unavailable information about glucose levels.

10 This information will allow patients and  
11 their health care team to make better decisions about  
12 all aspects of diabetes management. Detection of  
13 impending hypoglycemia and hyperglycemia will allow  
14 early treatment of these frequent complications,  
15 providing greater confidence to pursue more aggressive  
16 control of their care -- or control of their disease.

17 Fear of lows is the greatest obstacle in  
18 achieving tight control in euglycemia. Low blood  
19 sugars can impair brain function in child and can even  
20 lead to death." And he refers to the "dead in bed"  
21 syndrome papers that are recently published.

22 "The fear of hypoglycemia is amplified  
23 after many years of living with diabetes. Many  
24 patients who previously had good control are now  
25 experiencing hypoglycemic unawareness. Approximately

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1 half of low blood sugars in children occur during the  
2 night when finger stick glucose levels are not being  
3 done.

4 The insulin pump can be a wonderful tool,  
5 but without an alarm to signal high glucose levels  
6 when the infusion catheter is partially blocked, the  
7 patient's blood glucose levels increase dramatically."

8 You saw that in one of our slides.

9 "An alarm for high sugar levels would  
10 alert the patient, so they could change the pump site  
11 or correct for a missed bolus.

12 My experience from patient visits is that  
13 the GlucoWatch is one of the most anxiously awaited  
14 advancements. This information is confirmed in a  
15 recent poll taken on the [www.childrenwithdiabetes.org](http://www.childrenwithdiabetes.org)  
16 web site. The site is a nonprofit neutral forum for  
17 patient and parents, and the results show that at  
18 least 91 percent want this device.

19 In closing, I would like to reiterate that  
20 insulin dose decisions are based upon many factors,  
21 including food intake, exercise, stress, growth  
22 patterns, and previous experience. Unfortunately,  
23 these tools are not adequate today to achieve the  
24 control needed to significantly lower the risk of  
25 complications and eliminate suffering and expenses

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1 associated with nephropathy, retinopathy, neuropathy,  
2 stroke, heart disease, and 'dead in bed' syndrome.

3 The GlucoWatch would be a tool that could  
4 be used in conjunction with other factors that people  
5 with diabetes consider every day, just to improve  
6 their ability to meet the extraordinary challenge of  
7 living with Type 1 diabetes.

8 I have no financial interest in Cygnus. I  
9 don't own any stock. I just want to take out my  
10 checkbook and buy one of these things."

11 Thank you.

12 CHAIRMAN NIPPER: Thank you very much. We  
13 appreciate your comments.

14 Our next speaker is Sue Palandri. I hope  
15 I've pronounced your name correctly.

16 MS. PALANDRI: Good morning. Thank you  
17 for this opportunity. I am the Director of Finance  
18 for the Children's Diabetes Foundation. More  
19 importantly, my husband and my daughter have diabetes.

20 Diabetes entered into the life of my  
21 family in 1974, 25 years ago, when our four-year old  
22 daughter was diagnosed. We were devastated. Our  
23 perfect child was not perfect anymore. But we  
24 realized that we could learn to give her insulin  
25 shots, control her food, make sure that she had lots

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1 of exercise, and try to keep her life free of stress.

2 That one always amused me.

3 And check her urine at least four times a  
4 day. In order to do this, at age four, we had to have  
5 her double void, so that we could see what color her  
6 urine would turn to. Blue was good. It was a color  
7 of happiness in our household. And orange was bad.  
8 It was a color of discouragement.

9 We kept charts. We colored charts. We  
10 put charts on the refrigerator. We put happy faces  
11 and sad faces on them. And we took these charts to  
12 the doctor.

13 From this information, we attempted to  
14 adjust her insulin. You know, when I think back, it's  
15 amazing that we didn't kill her in the process. We  
16 truly had no idea what was going on in that little  
17 body of hers.

18 Throughout the years, many, many wonderful  
19 products have been developed to aid the diabetic.  
20 Home glucose monitoring -- that was a red letter day.

21 Even though it required more finger pokes, we were  
22 all like kids in a candy shop. Our family of four  
23 gathered around that first meter, and we watched  
24 Christy prick her finger.

25 We went through all of the required steps

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1 and the timing and waited for the reading. It was  
2 110. We cheered. This was amazing.

3 Since then, more meters have come on the  
4 market, smaller meters, meters with memories, meters  
5 that can slip into a pocket. Yet they all require  
6 blood. Now there is an opportunity to advance to the  
7 next level -- a GlucoWatch, a non-invasive instrument  
8 that will give blood sugar readings on a continuous  
9 basis.

10 Do you have any idea what this will mean  
11 for my daughter and the millions of others like her?  
12 She can manage even tighter control of her disease,  
13 not worry about severe hypoglycemic reactions at  
14 night, because if her blood sugar drops, the  
15 GlucoWatch will alarm. It will alarm when the blood  
16 sugar levels are too low. It will provide information  
17 that has never been available to her, information that  
18 she must have.

19 I implore you, as a mother and a wife of  
20 Type 1 diabetics, to take this next giant step  
21 forward. Give people suffering from this devastating  
22 disease the opportunity to know what is going on  
23 inside their bodies.

24 The GlucoWatch will alarm and read out  
25 functions as a tool, an exciting tool that we have

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1       been waiting and waiting and waiting for.     Please  
2       understand its importance and don't make us wait any  
3       longer.

4                     Thank you very much.

5                     CHAIRMAN NIPPER:   Thank you.

6                     I have to do the housekeeping and ask you  
7       to state whether you have any interest in the --

8                     MS. PALANDRI:   I do not have any interest  
9       in the company.

10                    CHAIRMAN NIPPER:   Vivian Skinner is next.

11                    MS. SKINNER:    Thank you.    I do not have  
12       any financial interest in Cygnus or any of its  
13       competitors.

14                    My name is Vivian Skinner.   My husband and  
15       I are the parents of four children.   Our youngest son  
16       Michael has Type 1 diabetes.   He was diagnosed five  
17       years ago at the age of nine.   We have no family  
18       history of diabetes, so we were totally unprepared for  
19       the impact this disease would have on our son and on  
20       our entire family.

21                    But Michael is a real trooper.   Since day  
22       one, we have been amazed at his attitude toward his  
23       diabetes.   He does the tests.   He does the shots.   He  
24       follows his plan, and he rarely complains.   But in  
25       spite of his best efforts and ours, Michael's diabetes

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1 is not well controlled.

2 Let me tell you about a typical day in his  
3 life. Like every other diabetic child, he tests his  
4 blood sugar four or five times a day -- before lunch,  
5 before breakfast, after school, before supper, at  
6 bedtime, during the day. He frequently has low blood  
7 sugars during the day.

8 He gives six shots a day in an attempt to  
9 achieve tight control. And every meal or snack is, of  
10 course, tightly scheduled and measured, 60 grams of  
11 carbohydrate for breakfast, 15 grams at his 9:00  
12 snack, and so forth. Not much out of the ordinary in  
13 that.

14 But Michael has a history of severe  
15 hypoglycemia in the night. So in addition to the  
16 blood tests that I've already mentioned, we must check  
17 his blood sugar every two hours all night long. Many  
18 nights when we've had a particularly unstable day we  
19 check his blood sugar every hour. And, of course, if  
20 he tests low, then we treat and we retest every 20  
21 minutes until he stabilizes. I've spent many a night  
22 on the floor in his room.

23 Thankfully, he is able to sleep through  
24 the finger sticks. Otherwise, he'd be totally non-  
25 functional at school the next day. But dad and I have

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1 two alarms, each with backup features, just in case we  
2 sleep through the first two rings.

3           Maybe you remember bringing your newborn  
4 babies home from the hospital and how those first few  
5 weeks when baby had daytime and nighttime mixed up,  
6 and you thought you'd never sleep through the night  
7 again and you just dragged through the days. Well,  
8 it's been four years at our house since we've had the  
9 luxury of a full night's sleep, but to sleep through  
10 the night at our house is to court disaster.

11           That's because Michael has severe  
12 hypoglycemic unawareness. Most diabetics will wake in  
13 the night. They'll have physical symptoms or  
14 nightmares that wake them up if they drop low, but not  
15 Michael. If he drops low, there are no warning signs.

16           He just continues to drop low, lower, and lower, and  
17 then we can't wake him and he begins to twitch and  
18 then jerk and then the full-blown seizure.

19           Fortunately, to this date, we've been able  
20 to interrupt that cycle and treat him. But we realize  
21 that the next step, if we don't intervene, is coma and  
22 we could lose him. Needless to say, he never spends  
23 the night away from home. Dad has to go on every  
24 school trip, every church trip. Otherwise, Michael  
25 simply cannot go.

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1           During waking hours, Michael recognizes  
2 his low blood sugars about 50 percent of the time.  
3 And, again, his symptoms are very subtle, and they are  
4 very inconsistent. So unless the teacher or a friend  
5 or a family member recognizes that he is behaving  
6 strangely, he is headed for loss of consciousness and  
7 seizure. One Sunday he just collapsed over the pew in  
8 front of him, no warning signs.

9           His doctor says Michael is also extremely  
10 sensitive to his insulin. He is on an extremely low  
11 dose. Case in point, recently he went to bed with a  
12 blood sugar of 386. That was too high, but we don't  
13 give sliding-scale insulin at night. I set the alarm  
14 for 12:30 -- that was two hours later -- but woke up  
15 at 12:15. I've learned if I wake up for no reason,  
16 I'd better get in his room.

17           And I could tell as soon as I looked at  
18 him that he was in trouble. His blood sugar was 36.  
19 He suffered a grand mal seizure. After two tubes of  
20 glucose gel and an injection of glucagon, he dropped  
21 to 30. And needless to say, we had a 911 ride to the  
22 hospital that night.

23           In the emergency room with dextrose  
24 running into his arm, he dropped again to 48. It's a  
25 scenario that repeats itself, and nobody can tell us

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1 why.

2 Another example. On Thanksgiving Day,  
3 with relatives coming and so forth, and all of the  
4 excitement, he forgot his morning shot. So when he  
5 tested his blood sugar at lunch, he was horrified to  
6 discover he was 590. We gave the prescribed insulin  
7 sliding scale, as the doctor ordered, and in two  
8 hours, after Thanksgiving dinner, he had dropped to 52  
9 -- 540 points in two hours with no exercise.

10 These factors -- his hypoglycemic  
11 unawareness, the subtlety of his symptoms, and the  
12 unpredictability of his blood sugars -- make managing  
13 Michael's diabetes an unusual challenge.

14 I don't suppose I even need to say I'm  
15 here to ask you to approve the GlucoWatch. I've made  
16 a 1,200-mile trip from Dallas, Texas, to tell you  
17 this. Michael needs the GlucoWatch. His fingers are  
18 already calloused from over 300 blood tests a month.  
19 But we don't have good control.

20 Imagine his frustration. He is becoming  
21 discouraged, and I cannot say that I blame him.  
22 Perhaps the GlucoWatch's continuous monitoring would  
23 give us the information that's lacking, the crucial  
24 bit of information that would help us achieve the  
25 illusive goal of tight control.

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1           The alarm function would be an absolute  
2 God-send, a lifeline, for Michael. During the day, it  
3 would enable him to catch a blood sugar at its -- a  
4 low blood sugar at its onset and treat it promptly.  
5 During the night, it would provide an invaluable  
6 safety net, a backup to the alarm clocks that  
7 sometimes don't wake his sleep-deprived parents.

8           Please, I urge you to recommend approval  
9 of this device as soon as possible. The need is truly  
10 urgent. The technology is available that could give  
11 diabetics the information they need to effectively  
12 manage their disease. It could enable my son and  
13 others like him to find real success in controlling  
14 his diabetes, and thereby forestall the dreaded  
15 complications. And it could save Michael's life.

16           Thank you for your time.

17           CHAIRMAN NIPPER: Thank you.

18           Our next person is Laura Billetdeaux. I  
19 hope I pronounced your name correctly.

20           MS. BILLETDEAUX: You did. Thank you.

21           I am truly a mom living on the edge this  
22 morning. This is not how I usually start my day, and  
23 I'm a little bit on the nervous side. I wanted to  
24 show you my son Sam. I'll be talking about him, and I  
25 wanted you to have a face to go with the name. Sorry

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1 it's not bigger. He's doing his favorite thing,  
2 playing hockey.

3 I'd actually like to talk with you about  
4 two people who are very special to me. The first one  
5 is my son Sam, who you just saw. Sam was diagnosed  
6 with Type 1 diabetes the first day of school, a little  
7 over a year ago, when he was eight years old. The  
8 second person is my friend David, and I'd actually  
9 like to tell you his story first.

10 Three years ago, David was a 35-year old,  
11 bright, young professional, a rising star in the field  
12 of computers. He graduated from college with honors  
13 and had everything to look forward to -- a wife, a  
14 family, a great career, a wonderful life. He was a  
15 handsome, outgoing guy, and liked to describe himself  
16 as six foot one and full of fun.

17 David was also a brittle diabetic, and he  
18 experienced frequent wide swings in blood glucose  
19 levels. One evening David was alone when he became  
20 hypoglycemic. He suffered a severe seizure and was  
21 comatose when his father found him on the floor of his  
22 apartment many hours later.

23 At the time, his blood glucose level was  
24 zero. David was resuscitated and taken to a trauma  
25 center, and this was the beginning of his new life.

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1 David spent two years in intensive rehabilitation.  
2 His brain had suffered extensive damage, and this was  
3 evident in both his life functions and his cognitive  
4 functions.

5 David looked and acted sometimes like an  
6 animal. He screamed. He clawed. He chewed and bit  
7 anything that came near him. He also had a feeding  
8 tube because, although he ate things like shirts and  
9 bed sheets, he was unable to swallow food.

10 Very slowly David got better. He began to  
11 communicate by grunting, then saying single words.  
12 Mostly, he asked for dad. About 14 months into his  
13 recovery, David picked up a marker and he wrote his  
14 name. This added another dimension to his recovery.

15 Today, nearly three years later, David is  
16 still six foot one and full of fun, but when he says  
17 it you need to listen hard to be able to understand  
18 the words. His eyes still sparkle with fun, but the  
19 humor is on a 10-year old level. He is a delightful  
20 friend, and I love visiting him, but I am struck by  
21 what has become of his future.

22 Instead of a loving wife and family,  
23 travel, a great job, David will live out his days in a  
24 nursing home as a handsome young man, six-foot-one and  
25 full of fun, but with contractures. And he will

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1 always require caregivers.

2 If David had the GlucoWatch, this would  
3 not have happened.

4 My son Sam has everything to live for. He  
5 is a bright, friendly kid, with a neighborhood full of  
6 buddies. He loves to play hockey, and he loves those  
7 Red Wings. He is also clear-headed and realistic when  
8 you ask him about his diabetes management. Some days  
9 are pretty steady.

10 Most days, however, his blood glucose  
11 varies from the 50s to nearly 400. He usually feels  
12 the lows coming on, but when it happens fast he'll  
13 tell you he just feels bad and he can't act quickly  
14 enough to reverse the low. With the GlucoWatch alarm,  
15 we could respond to these lows in their initial stages  
16 before Sam feels and acts sick.

17 When his blood glucose rises over 275, he  
18 sometimes can't even tell you something is wrong. He  
19 just stares off or he cries or he starts a fight.  
20 When he plays hockey, Sam's glucose may start in  
21 range, but within 30 minutes he might be 350; and by  
22 the end of the game, 450.

23 I can tell how high he is by watching his  
24 response time on the ice. A slow, foggy brain is not  
25 a good thing in a defenseman. The point here is that

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1 Sam is never able to identify highs coming on. They  
2 are always identified by an adult, and way after the  
3 fact. If Sam had a GlucoWatch, the alarm would alert  
4 an adult to these highs as they happen, and they could  
5 be treated much earlier with far less risk.

6 In closing, I think of my son, and I think  
7 of my friend. I don't even want to entertain the  
8 notion that there is the possibility something like  
9 David's experience might happen to Sam. But I know  
10 that it is a possibility with all kids who have  
11 Type 1. And as a parent, I must advocate for  
12 something better.

13 The GlucoWatch is that something better,  
14 and you can make it available to families like mine.  
15 I urge you to approve the GlucoWatch and make it  
16 available to consumers quickly.

17 Thank you.

18 CHAIRMAN NIPPER: Before you leave, would  
19 you do the statement, please?

20 MS. BILLETDEAUX: The statement? I have  
21 no financial interest in this.

22 CHAIRMAN NIPPER: In either company or  
23 competitors?

24 MS. BILLETDEAUX: No, I do not.

25 CHAIRMAN NIPPER: Thank you very much.

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1 MS. BILLETDEAUX: Thank you.

2 CHAIRMAN NIPPER: Our next speaker is  
3 Lauren Lanning.

4 MS. LANNING: Good morning. My name is  
5 Lauren Lanning. I have no interest in Cygnus or any  
6 of its competitors. Please forgive me; I'm not much  
7 of a public speaker, but I feel passionate about this.  
8 That's why I'm here today.

9 The reason I'm here this morning is to ask  
10 that you please approve the GlucoWatch with all of its  
11 features intact. Most importantly, patients need  
12 access to the readouts and alarms to improve control,  
13 reduce costs, and prevent severe hypo and  
14 hyperglycemia.

15 Diabetes care is very individual and  
16 changes daily. It's the individual who is balancing  
17 the daily diet, insulin, and exercise. We need a tool  
18 that is continuous, alarmable, and accurate. From  
19 what I've read, the GlucoWatch is that tool.

20 My daughter Monica has been living with  
21 diabetes for three years. My challenge is to maintain  
22 a normal lifestyle, good control, so she can live a  
23 long, healthy life. Blood tests, exercise, insulin,  
24 and a strict diet are critical pieces to good control,  
25 but balancing them, it -- balancing them all is not

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1 easy.

2 My good friend Linda was diagnosed with  
3 diabetes at the age of 11. She was diagnosed with  
4 diabetic retinopathy in her teens and legally blind by  
5 the age of 36. Now, at the age of 41, she has kidney  
6 disease, heart problems, and neuropathy. This is  
7 someone who has struggled all of her life for good  
8 control, always testing, exercising, and watching her  
9 diet.

10 After living with diabetes for 30 years,  
11 she still gets baffled by the numbers. She can never  
12 predict a low or a high coming on.

13 The current tools -- the lancet and meter  
14 -- are fast and accurate, but lack two critical  
15 features -- trends and alarms. It's just a snapshot.

16 We're constantly making educated guesses based on  
17 exercise, diet, insulin, and that snapshot, trying to  
18 figure out if the level is going up, down, too  
19 quickly, and we make decisions from there, with  
20 nothing to warn us if we've made a poor decision.

21 Our doctor says we have good control. My  
22 graph shows that good control is not without its  
23 risks. These are Monica's numbers, but they could be  
24 anyone's. The left axis is the blood glucose level.  
25 The bottom axis is the time of day.

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1           There are 206 readings that were taken  
2 during the month of November, an average of six-and-a-  
3 half readings a day. The green area is our target  
4 range. It has 92 readings. The yellow area is the  
5 high range. There are 80 readings. The red area is  
6 low. You can see they happen at any time during the  
7 day. There are 34 readings in the low range. This is  
8 not good. Each one of these is potentially life-  
9 threatening.

10           Just like many adults who try to keep good  
11 control, she has hypoglycemic unawareness. She has no  
12 idea if a low is coming on, so we usually don't catch  
13 it until it's too late. The lowest number there is a  
14 38, but Monica's 38 was seemingly nothing because she  
15 is an otherwise healthy, robust, girl. The same 38 in  
16 her grandmother, who also has diabetes, results in  
17 personal injuries, a 911 call, an ambulance, and  
18 emergency room care.

19           And this is at least a once-a-month  
20 occurrence for grandma. These represent a huge health  
21 risk and are very expensive. Avoidable, if only an  
22 alarm had warned the low.

23           The highest reading there is a 456. Was  
24 it a rebound? Was it just stress? If it was a  
25 rebound and we give extra insulin, is she going to

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1 crash? If we don't give enough extra insulin, will  
2 she go into DKA? If we had the GlucoWatch, there  
3 would be no mystery. If we had the GlucoWatch,  
4 Monica's grandmother could safely maintain lower  
5 numbers at night and avoid the emergency room.

6 I know the GlucoWatch is not the perfect  
7 tool, but it's miles ahead of what's currently  
8 available. All of the people with diabetes I've  
9 spoken to say they would take the skin rash, the long  
10 warmup times, and delayed readings, to get the kind of  
11 information that the GlucoWatch can provide.

12 Patients are an integral part of the  
13 diabetes team, making life and death decisions in a  
14 complex environment every day. They should be  
15 considered in the GlucoWatch approval. It's critical  
16 for patients to have access to the continuous  
17 readings, and it's critical that the patients have  
18 alarms.

19 Please approve the GlucoWatch, so we can  
20 do a better job, reduce emergency health care costs,  
21 and even save lives.

22 Thank you.

23 CHAIRMAN NIPPER: Thank you, Ms. Lanning.

24 I'd like to note that Ms. Lanning's name  
25 was inadvertently left off the speaker list through an

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1 administrative glitch. We apologize for that, and we  
2 thank you for your comments.

3 At this time, I would like to push the  
4 time just one little bit more because Mary Ayd is here  
5 to talk, and we'd like to move her to the morning  
6 talk.

7 Are you ready to talk, Ms. Ayd?

8 MS. AYD: Yes.

9 CHAIRMAN NIPPER: Yes. Good. Thank you.

10 MS. AYD: This is my daughter Megan.  
11 Megan was diagnosed with diabetes four years ago, but  
12 that wasn't the first time that it touched our lives.  
13 My mother was diabetic. She was diagnosed when I was  
14 in sixth grade. At the same time, I was introduced to  
15 diabetes from a friend named Bridgette that came to  
16 our school.

17 I was kind of amazed by the things that  
18 would happen with low blood sugars and the fact that  
19 she really had to like watch things, and you had to  
20 watch her carefully. I remember going to a concert  
21 once and having her have a low blood sugar and the  
22 nuns taking care of her by giving her candies, and  
23 just the slow thing that would happen, just letting  
24 her come back to life, because it's like a flower that  
25 wilts. It's such a scary thing to watch a low blood

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1 sugar.

2 My mother is no longer with us and neither  
3 is Bridgette. The year that my daughter was diagnosed  
4 I wanted to call Bridgette's mother, who I got such  
5 strength from, and tell her, "Thank you for allowing  
6 me to have that strength to go on and take care of my  
7 children." But I couldn't do that because Bridgette  
8 had died of heart failure at the age of 36.

9 She left a child of her own with a very,  
10 very difficult pregnancy. She was unable to maintain  
11 a marriage because of her health problems. I don't  
12 want this for my children.

13 The year that my daughter was diagnosed I  
14 had a hard time telling my mom about it because Megan  
15 was in the hospital with diabetes. She had been sick.

16 I couldn't tell what it was. But my mother was  
17 having her foot amputated at the time. She had  
18 suffered from diabetes since 1972, and it was very  
19 difficult for me because I kind of blamed her for it,  
20 even though I knew it wasn't her fault.

21 The complications that my mother has  
22 experienced, she died of renal failure in July of this  
23 year. She decided not to go onto dialysis, which  
24 would have prolonged her life, but she had lost  
25 another limb, she was blind. She depended on us for

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1 everything, and that just wasn't her way.

2 I was really happy that my sister and I  
3 were able to take her home and she was able to die in  
4 our arms. Megan was there, too. It was wonderful to  
5 be able to care for my parent. I don't want to have  
6 to do this for my child.

7 Megan is going to be going on an insulin  
8 pump. We've worked really, really hard for this. She  
9 tests six, eight, 10, 12 times a day. It hasn't been  
10 without some complications. This past spring she had  
11 two seizures. The first one was very -- it was very  
12 scary. I didn't realize it because blood sugars make  
13 your mood swings -- you have a lot of mood swings.  
14 And you're not sure whether it's a high blood sugar, a  
15 low blood sugar. A lot of times you are confused.

16 But my son who was six was the one that  
17 witnessed her first seizure. I had to count on his  
18 identification of it because I sent her down for  
19 breakfast. But she had fallen and she hit her head,  
20 and we had two sets of paramedics there that day.  
21 This could have been prevented if she had had a  
22 GlucoWatch. I would have known this was falling. I  
23 would have been able to tell that it wasn't that or  
24 maybe it wasn't epilepsy because we went through all  
25 of that screening afterwards, too. I have a cousin

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1 that's epileptic as well.

2 Megan's blood sugar, as soon as I took it,  
3 after I had given her -- I couldn't get the glucagon  
4 in because my glucagon had expired, and I had never  
5 experienced having to use the glucagon. You have to  
6 physically shoot it into the little container, and you  
7 have to mix it, and you have to make sure all of the  
8 crystals are gone. But you know what? When you have  
9 a kid having a seizure on the floor, you can't think  
10 straight. It's a really difficult situation. You  
11 want to help them, and you can't do it.

12 I ended up calling 911. I had the first  
13 set come out. We got her coming around, gave her  
14 glucose orally. She didn't ever get the glucagon. I  
15 didn't know if she was vomiting because -- she had  
16 never had glucagon. A lot of children have -- or a  
17 lot of people have reactions to the glucagon. I  
18 didn't know if she was vomiting because of that, but  
19 it ends up that she had hit her head on the way down  
20 from the seizure and she was having -- she had a  
21 concussion.

22 So we had another trip to the ER, another  
23 set of ambulance to our house, and she was fine,  
24 though, afterwards. So I'm really grateful for that.

25 Six weeks later, we were on vacation in

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1 Ocean City, Maryland, up here at Baltimore. We drove  
2 down here to see this lovely weather. And we were  
3 sitting at the table -- it was Easter morning -- and  
4 she came out. I had to stay on watch because the  
5 Easter bunny leaves all of that candy around. Well,  
6 you know, what? You have a 10-year old, you have a  
7 lot of candy around; they want to eat it. But that  
8 will kill my kid. She can't do that.

9 I had to sleep out on the couch, and I  
10 came out -- the kids all came out. We were with  
11 friends. And she sat down, she put an Easter egg in  
12 her mouth, was eating it, and fell down and had a  
13 seizure again, in front of all of her friends. I took  
14 her blood sugar. I gave her glucagon. She was 80; 80  
15 is not a blood sugar to have a seizure.

16 The problem is she was having a rebound.  
17 She had probably fallen all the way down to the  
18 bottom, and she had come back up because the regular  
19 -- her glucose -- the liver had put out that glucose  
20 for her, the glucagon, her natural glucagon. And it  
21 was a horrible experience for my son to see, her  
22 friends to see. We are a pretty social family.

23 I have some very good friends that I've  
24 traveled with over the years. I'm still friends with  
25 the girls that I went to high school with. And I only

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1 have one of my girlfriends that Megan can spend the  
2 night with, because my friends are afraid. They're  
3 afraid that something is going to happen.

4 She's a nice kid. She's got lots of  
5 friends. She's supposed to go to a birthday party  
6 today with a girl in her class, but I've never met her  
7 parents, so I'm a little apprehensive about sending  
8 her to a four-hour party where I don't know whether  
9 she'd be cared for properly.

10 I'm asking you to approve the GlucoWatch.  
11 It will allow some normalcy in my life. Megan is  
12 scheduled to get an insulin pump the end of the month,  
13 assuming that our insurance will continue to approve  
14 it. It's going to help us a lot because she's going  
15 to be able to control things a little bit better.

16 But she is also going to be entering  
17 puberty, and puberty is going to end up raising and  
18 lowering her blood sugars for unknown reasons. And  
19 that's another issue that I have to deal with,  
20 regardless of whether the basal rates are set  
21 properly. But we're willing to deal with it. We're  
22 fighters, and we're not going to let diabetes get the  
23 better side of us.

24 Please give us the tools to be able to  
25 make those decisions. We make life and death

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1 decisions every day.

2 I've got a nine-year old who can do these  
3 algorithms practically. She is just -- it's amazing,  
4 if you could see these conversions that you do. If  
5 your blood sugar is 270, what is your coverage for  
6 your high? What's your food coverage? You're going  
7 out to exercise, so you'd better drop that a half a  
8 unit. She makes these decisions for every meal she  
9 has. Allow her to have the tools to make good  
10 decisions, so she doesn't put herself into situations  
11 that are harmful.

12 Thank you.

13 I have no interest in any companies  
14 associated with this GlucoWatch. I just have an  
15 interest from my heart and for my family, for each and  
16 every family that suffers from diabetes. Thanks.

17 CHAIRMAN NIPPER: Thank you very much.

18 At this time, we will close the open  
19 public hearing and move to the sponsor presentation.  
20 We are calling on John C. Hodgman, President,  
21 Chairman, and Chief Executive Officer of Cygnus,  
22 Incorporated, for opening remarks.

23 MR. HODGMAN: Good morning, ladies and  
24 gentlemen. I'm John Hodgman, President and CEO of  
25 Cygnus, Inc. I'd like to take this moment to thank

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1 the agency for the opportunity to present our pre-  
2 market approval application for the GlucoWatch  
3 Biographer.

4 We recognize and appreciate the agency's  
5 diligence and interactive participation with us, the  
6 company, in reviewing our application. I would also  
7 like to take this time to thank the large team of  
8 scientists and engineers at Cygnus who have worked to  
9 develop this device. It is only through their single-  
10 minded focus and commitment over seven long years that  
11 we are able to be here in front of this panel today.

12 We've been driven by the many letters and  
13 comments, similar to the ones you've heard this  
14 morning.

15 The GlucoWatch Biographer was developed to  
16 address a critical unmet need for additional  
17 information about glucose levels -- something that has  
18 been desperately needed but until now unattainable.  
19 We are pleased to provide this important new tool to  
20 the millions of Americans living with diabetes.

21 I've asked Dr. Neil Ackerman, our Senior  
22 Vice President of Research and Development and  
23 Scientific Affairs, to act as the moderator for this  
24 session.

25 Neil?

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1 DR. ACKERMAN: Dr. Nipper, Dr. Gutman,  
2 members of the panel, ladies and gentlemen, we'd like  
3 to thank the Division of Clinical Laboratory Devices,  
4 though we are especially appreciative for this  
5 division for scheduling this panel review only six  
6 months after receiving a very complex and voluminous  
7 PMA.

8 I would like now to introduce the members  
9 of the Cygnus team. They're on the screen behind you.

10 I will serve as the moderator for this  
11 team. Dr. Kenneth Pitzer, Vice President of Product  
12 Management, is a member of this team. He's a member  
13 of the company, as is Dr. Russell Potts, who is Vice  
14 President of Research at Cygnus.

15 In addition to these two employees, we  
16 have Dr. Steven Edelman, the Associate Professor of  
17 Medicine at UCSD School of Medicine, Division of  
18 Diabetes and Metabolism, with a joint appointment at  
19 the Veterans Administration Medical Center. Dr.  
20 Edelman is a consultant to the company.

21 And our last -- primary speaker will be  
22 Dr. Lois Jovanovic. She is a Director and Chief  
23 Scientific Officer at the Sansum Medical Research  
24 Institute and a clinical professor of medicine at the  
25 University of Southern California.

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1 I have listed the other members of the  
2 Cygnus team. I will not go through them individually,  
3 but they have all been major contributors to this  
4 program. We have a combination of both employees as  
5 well as consultants to the company. We'll rely on  
6 their skills later during the Q&A.

7 These are the trademark devices that will  
8 be mentioned in the course of today's presentation.

9 The agenda for today is also presented on  
10 the screen. Firstly, Dr. Pitzer will provide a device  
11 description and will also provide the intended use.  
12 Dr. Russell Potts will review our safety and  
13 effectiveness studies. Dr. Edelman will then provide  
14 a clinical perspective on the use of the biographer.  
15 And, lastly, Dr. Jovanovic will describe her clinical  
16 experiences with this device. She is one of our  
17 clinical investigators.

18 As we will explain in our presentation,  
19 the GlucoWatch Biographer is fundamentally different  
20 from any of the present meters that are available.  
21 The differences introduce both new benefits and new  
22 risks. As a consequence, we are proposing three  
23 specific steps to address these risks.

24 Firstly, the device will be available only  
25 by prescription. Secondly, it will be labeled for

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1 adjunctive use with standard home monitoring systems.

2 And, lastly, we will be providing extensive education  
3 for both the professionals and the patients for the  
4 use of this device.

5 Dr. Pitzer will expand on these issues in  
6 his presentation of the device description.

7 Dr. Pitzer?

8 DR. PITZER: Good morning. I'm Ken  
9 Pitzer, Vice President of Product Management at  
10 Cygnus.

11 My presentation will address the intended  
12 use, the device features, procedures for use, and an  
13 overview of the technology used in the GlucoWatch.  
14 But, first, I'd like to discuss some context and  
15 provide one illustration of how the GlucoWatch  
16 Biographer can detect trends and track patterns in  
17 glucose levels.

18 Over the last 20 years, self-monitoring of  
19 blood glucose has become an integral part of diabetes  
20 management. The current practice is to perform  
21 several blood glucose tests per day, typically one to  
22 four. Self-monitoring, however, is not without  
23 limitations.

24 The report of a consensus conference  
25 convened by the American Diabetes Association in 1993

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1 noted a decrease in accuracy at both low and high  
2 glucose concentrations, a wide variety in device  
3 performance, a dependence on operator technique, and  
4 problems with quality assurance.

5 A critical limitation is that patients  
6 only obtain glucose readings when they remember to  
7 test and take the necessary time away from daily  
8 activities. Most current testing is performed before  
9 meals and at bedtime. These relatively infrequent  
10 measurements provide only limited information about  
11 glucose levels.

12 The limitations of current and frequent  
13 testing can be appreciated with a simple example.  
14 This chart shows the pre-meal blood glucose results.  
15 I don't know if this is going to reach. Here, 80  
16 before lunch and 121 before dinner. And these are  
17 from an actual subject during a home environment  
18 study.

19 Note that this subject appears to have  
20 relatively normal glucose results before both lunch  
21 and dinner.

22 With the GlucoWatch Biographer, readings  
23 are performed automatically and non-invasively after  
24 one finger stick test, which is used for calibration.

25 This chart shows the calibration blood glucose value,

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1 which is this purple dot here. If I can hold my hand  
2 steady, you might be able to see it.

3 (Laughter.)

4 Along with all of the GlucoWatch readings,  
5 which are shown in the blue line, which you can see  
6 here, up and down throughout the day. This is from  
7 the same subject on the same day in the home  
8 environment study.

9 The biographer results showed that this  
10 subject, in fact, has quite high glucose levels after  
11 lunch. You can see here consistently above 240  
12 milligrams per deciliter for several hours. This is a  
13 very different pattern than that seen with only the  
14 pre-meal blood glucose tests.

15 As shown in this example, the GlucoWatch  
16 Biographer provides information that is quite  
17 different from the testing results that patients and  
18 professionals are used to. For this reason, we have  
19 prepared initial device labeling in a conservative  
20 manner.

21 The intended use is shown on this slide,  
22 and I'd just like to read it verbatim. "The  
23 GlucoWatch Biographer is a glucose monitoring device  
24 intended for detecting trends and tracking patterns in  
25 glucose levels in adults, age 18 and older, with

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1 diabetes. This device is intended for use by patients  
2 at home and in health care facilities. The GlucoWatch  
3 Biographer is intended for use as an adjunctive device  
4 to supplement, not replace, information obtained from  
5 standard home glucose monitoring devices."

6           So what does this intended use mean?  
7 There are two key concepts to understand. First, is  
8 the idea of detecting trends and tracking patterns.  
9 Trends are acute changes in glucose level detected as  
10 an individual goes about their daily routine. At any  
11 time, the user can check the biographer readings from  
12 the last few hours with the touch of a button.

13           In addition, the device will sound an  
14 alarm to notify the user of trends in glucose levels  
15 that require their attention. Finally, by looking  
16 retrospectively at the readings from an entire  
17 biographer use, perhaps from several days in a row,  
18 patients and health care professionals can examine  
19 longer term patterns in glucose levels.

20           The second thing to understand is the  
21 concept of adjunctive use. This means that the  
22 biographer results are to be used in combination with  
23 information obtained with standard blood glucose  
24 testing. Specifically, patients using the biographer  
25 must perform a blood glucose test, first, to calibrate

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1 the GlucoWatch Biographer; if the patient has any  
2 symptoms of low or high blood glucose that do not  
3 match the biographer readings, before making an  
4 insulin dose determination based upon glucose  
5 monitoring results; and if the patient questions the  
6 results from the biographer.

7           How can we ensure that this unique device  
8 is used appropriately? First, as Dr. Ackerman  
9 mentioned, the biographer is proposed as a  
10 prescription device. Prescription status will  
11 restrict use to those patients selected by physicians.

12 Physicians and other health care professionals will  
13 also have an opportunity to determine the training  
14 needs of each patient and then individualize the use  
15 plan for the device based upon the unique patient  
16 situation. The health care team will also be able to  
17 follow up on device use by patients over time.

18           Second, Cygnus is committed to an  
19 extensive education program for both patients and  
20 health care professionals. Included in your briefing  
21 materials are proposed versions of a user's guide,  
22 instructional videotape, and quick reference guide.  
23 We have several other educational items already in  
24 development.

25           In addition, we have agreed to develop a

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1 mechanism to ensure that each patient understands the  
2 key safety information before they use the device.  
3 Such an approach has been used with other novel,  
4 first-of-a-kind, home testing products.

5 Finally, Cygnus will provide continuing  
6 support for patients and professionals, to answer  
7 questions and to reinforce appropriate use. This will  
8 take the form of both a technical services hotline and  
9 an interactive web site.

10 I would now like to turn to a description  
11 of the device features. With each application, the  
12 GlucoWatch Biographer provides automatic readings  
13 every 20 minutes for a 12-hour period. The monitoring  
14 period follows a three-hour warmup period and a single  
15 point calibration using a finger stick test result.

16 An audible alarm will sound in response to  
17 high, low, or rapidly declining glucose levels. Both  
18 the high and low glucose alert levels can be  
19 customized for each user and changed whenever  
20 appropriate.

21 The device will store the last 4,000  
22 glucose readings, including the date and time of each  
23 reading. This provides the opportunity for examining  
24 acute trends and long-term patterns in glucose levels.

25 The GlucoWatch Biographer is shown in

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1 these two photographs. The device is powered by a AAA  
2 battery, which goes here into the battery compartment.

3 And it's operated with four function buttons that you  
4 see on the face of the device.

5 The device uses a liquid crystal display  
6 with two rows of characters, the main display here,  
7 and the upper display, which is hard for me to see  
8 from here, but it's above the large numbers.

9 On the back of the biographer, there are  
10 two metal probes that serve as perspiration detectors.

11 Those are shown there. Two little metal probes.  
12 These detectors are part of an extensive system of  
13 data integrity checks that are incorporated into the  
14 device design and operation.

15 Each application of the GlucoWatch  
16 Biographer requires a single-use disposable component  
17 called the AutoSensor. This diagram shows the  
18 multiple layers that make up the AutoSensor. The base  
19 is a plastic tray that snaps into the back of the  
20 biographer. A series of electrodes are screen-printed  
21 on a plastic sheet that is anchored to the tray.

22 Two hydrogel collection discs are  
23 contained in an adhesive pad, which makes up the outer  
24 layer of the AutoSensor. Removable protective liners  
25 are placed in between the electrodes and the adhesive

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1 pad -- that's protective liner number one -- and on  
2 the outer skin contacting surface of the adhesive pad,  
3 number two here with the blue tab.

4 Next, I will show you how a patient will  
5 apply and operate the GlucoWatch Biographer. The  
6 first step is to remove an AutoSensor from the pouch  
7 in which it is provided. Next, an accessory device  
8 called the AutoSensor press is used to prepare the  
9 AutoSensor for use.

10 The AutoSensor shown here is inserted into  
11 the press, and the press is held closed for ten  
12 seconds. This leads to uniform contact between the  
13 gel discs and the electrodes.

14 The AutoSensor is then snapped into the  
15 biographer using the indexing tab. The biographer can  
16 be worn on the inner or outer surface of either  
17 forearm. An area without significant hair should be  
18 selected, or the hair shaved before application. An  
19 alcohol wipe is used to clean the selected site.

20 The biographer is then placed on the  
21 selected site, and the watchband secured, just like a  
22 wristwatch.

23 The user presses the start button, which  
24 is this lower left-hand button, to begin the three-  
25 hour warmup period. The warmup is required for

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1 equilibration of the interface between the skin and  
2 the device. This equilibration must occur before  
3 calibration can be performed. The length of the  
4 warmup period was determined based upon feasibility  
5 study results.

6 After three hours, the alarm will sound  
7 and the display will show the message CAL. During the  
8 next five minutes, the user must perform a finger  
9 stick test with a traditional meter and enter the  
10 results into the biographer. The calibration blood  
11 glucose value must be between 40 and 280 milligrams  
12 per deciliter.

13 This calibration procedure accounts for  
14 variability in skin permeability between individuals  
15 and between sites on the arms of each individual user.

16 If the user prefers not to calibrate at this time, or  
17 is unable to complete calibration within five minutes,  
18 the initial calibration period can be skipped. The  
19 five-minute window will then repeat every 20 minutes  
20 until the user completes the calibration. However, no  
21 glucose readings will be reported to the user until  
22 calibration is completed.

23 After calibration, the biographer will  
24 complete a reading every 20 minutes. This photo shows  
25 a glucose result of 95 milligrams per deciliter, which

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1 was completed at 10:55 a.m. The time is in the upper  
2 display.

3 The arrow here on the right pointing down  
4 notifies the user that this result was at least 18  
5 milligrams per deciliter, or one millimole per liter  
6 below the preceding result.

7 The measurement range for the device is 40  
8 to 400 milligrams per deciliter. Results outside this  
9 range will cause the alarm to sound, and the display  
10 will show less than 40 or greater than 400. At any  
11 time, the user can check the current trend in their  
12 glucose levels by simply pressing the up button, which  
13 is this button here in the upper right, to scroll back  
14 through the memory of glucose readings.

15 A series of data integrity checks are  
16 performed on each reading before the glucose result is  
17 calculated. Suspect readings are skipped, and no  
18 glucose value is reported to the user.

19 These photos show what happens if the  
20 perspiration detectors indicate excessive  
21 perspiration, as measured by a change in skin  
22 conductivity. The display will alternate between the  
23 message SKIP, shown here in the upper left, and the  
24 message PRSP, for perspiration, shown here on the  
25 lower right. The audible alarm will also sound

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1 because perspiration may be due to hypoglycemia.

2 This data integrity check is necessary  
3 because perspiration includes glucose and may confound  
4 the biographer readings. Once the skin conductivity  
5 returns to normal, glucose monitoring will resume.

6 The audible alarm will also sound if any  
7 reading is above the high alert level or below the low  
8 alert level, or if the reading is 35 percent or more  
9 below the preceding reading. These photos show a low  
10 glucose alert situation.

11 The display will alternate between the  
12 message LOW here in the upper left and the glucose  
13 result; in this case, 65 milligrams per deciliter.

14 I would now like to discuss the technology  
15 utilized in the GlucoWatch Biographer. The glucose  
16 sample is collected using the process of reverse  
17 iontophoresis. This entails the application of a low  
18 level electric current across intact skin. In  
19 response to this current, charged ions move through  
20 the skin towards the anode and cathode. We've tried  
21 to illustrate that here with these arrows.

22 Glucose and other neutral species are  
23 transported by convective or electro-osmotic flow and  
24 are collected primarily at the cathode.

25 Relative to a blood glucose meter, this

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1 procedure results in a lower glucose concentration,  
2 but in a much cleaner sample. Only small compounds  
3 pass through the skin, and many potentially  
4 interfering species are collected predominantly at the  
5 anode because they are negatively charged. You see  
6 that here with things like ascorbate or urate, which  
7 go only to the anode. The biographer glucose readings  
8 are based only on the signal generated at the cathode.

9 The glucose is collected in the gel  
10 collection discs, which consist of a hydrogel matrix  
11 containing the enzyme glucose oxidase. Using  
12 conventional electrochemical detection, the collected  
13 glucose reacts with oxygen in the presence of glucose  
14 oxidase to form hydrogen peroxide and gluconic acid.

15 When the platinum biosensor is activated,  
16 the hydrogen peroxide reacts and releases two  
17 electrons, which are measured by the biosensor. Thus,  
18 one molecule of collected glucose yields one molecule  
19 of hydrogen peroxide, and subsequently two electrons  
20 which are measured by the device.

21 As I described previously, the GlucoWatch  
22 biographer provides a reading every 20 minutes. The  
23 20-minute monitoring process is shown schematically on  
24 this slide. First, a glucose sample is collected over  
25 three minutes. The collected glucose is then measured

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1 over the next seven minutes.

2 This process is repeated, and, finally,  
3 the data integrity checks are performed. Only then is  
4 the glucose result calculated based on the total  
5 signal from the two seven-minute measurement periods.

6 An algorithm uses the user-entered  
7 calibration value and the total biosensor signal to  
8 calculate each glucose reading. This 20-minute cycle  
9 is repeated throughout the 12-hour monitoring period.

10 This procedure creates an integrated or time-averaged  
11 glucose measurement, in contrast to the instantaneous  
12 measurement provided by a traditional blood glucose  
13 meter.

14 I would now like to return to the 1993 ADA  
15 consensus conference on self-monitoring of blood  
16 glucose. The consensus report included a discussion  
17 of the future of self-monitoring. In this section,  
18 the authors commented that technology now on the  
19 horizon has the potential to monitor blood glucose  
20 levels on an almost-continuous basis. Such increased  
21 monitoring is likely to improve glycemic control while  
22 at the same time decreasing hypoglycemic risk.

23 Six years later, the GlucoWatch Biographer  
24 offers an important step towards achieving this  
25 vision. To appreciate the value of this device, it's

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1 important to understand six key aspects of the  
2 readings provided by the GlucoWatch. Think of these  
3 as design specifications.

4 The results provided by the GlucoWatch  
5 Biographer are frequent, automatic, non-invasive,  
6 time-averaged measurements of transdermally extracted  
7 glucose that are calibrated to blood glucose. Through  
8 these specifications, the GlucoWatch is able to detect  
9 trends and track patterns in glucose levels.

10 The result is more information, something  
11 that people with diabetes and the professionals who  
12 care for them have been seeking for many years.

13 This concludes the device description.  
14 The next speaker will be Dr. Russ Potts.

15 DR. POTTS: Good morning. I'm Russ Potts  
16 from Cygnus. I would also like to thank you for this  
17 opportunity to present our results. We've all looked  
18 forward anxiously to this day.

19 My presentation will be divided into three  
20 parts: a discussion of the non-clinical results,  
21 showing safety and linearity in the GlucoWatch  
22 Biographer. I will then cover the clinical results.  
23 The PMA which you've reviewed in front of you  
24 contained an extensive presentation of results from  
25 the pivotal clinical trials.

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1           Due to the time limitations of this  
2 presentation, I will focus my comments primarily on  
3 effectiveness results in the home environment study.  
4 Keep in mind, however, that the PMA contains  
5 information on such topics as biographer precision,  
6 comparison to home blood glucose meters, a six-week  
7 extended wear study, and irritation and sensitization  
8 studies. Finally, then, I will end with a summary and  
9 conclusion.

10           The biographer was subjected to an  
11 extensive battery of medical equipment tests. You see  
12 a list of them here. These included evaluations of  
13 the environmental characteristics as well as  
14 electronic and software performance. Time does not  
15 allow me to go into these studies. But, to summarize,  
16 the biographer exceeded standards in all of these  
17 tests.

18           The performance of the biographer was  
19 assessed by measuring linearity in response to  
20 changing glucose levels. This was determined by  
21 extracting glucose through human cadaver skin using a  
22 biographer and a benchtop apparatus as depicted here  
23 -- human skin with the watch and a glucose solution.

24           In these experiments, the biographer was  
25 placed against human skin that was profused on the

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1 dermal side with solutions of buffer containing  
2 glucose. Five concentrations were used. These are 0,  
3 50, 100, 300, and 500 milligrams per deciliter.

4 This study simulates human use under  
5 glucose clamp conditions without putting a subject at  
6 risk or discomfort. Shown in this slide are the  
7 results obtained with six different biographers, each  
8 with a different skin sample.

9 Each plot shows the biographer's signal,  
10 shown here as nC versus the subcutaneous or subdermal  
11 glucose concentration under the skin. As can be seen,  
12 these results are linear over the range tested. In  
13 all cases, R squared exceeded .96, and the intercept  
14 is zero.

15 Note, however, that the slopes differ by a  
16 factor of two to three. This reflects variability in  
17 glucose permeability in human skin. Skin variability  
18 from site to site and person to person is seen in all  
19 human subjects. It is the largest source of variation  
20 in the biographer's signal.

21 To account for this individual variability  
22 in skin permeability, a single-point calibration  
23 method is used. For example, for these studies, we  
24 used a value at 100 milligrams per deciliter to  
25 determine a calibration factor. Quite simply, this

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1 factor is the ratio of the glucose concentration to  
2 the biographer signal.

3 All other biographer measurements shown on  
4 here have then been scaled by that value. One can  
5 conclude from these results that the biographer  
6 response is linear from zero to 500 milligrams per  
7 deciliter, with a slop near unity and intercept near  
8 zero and R squared that exceeds .99. These results  
9 demonstrate clearly that the biographer readings are  
10 linear and accurate in this range.

11 Let me now turn to the pivotal studies. I  
12 will summarize results obtained in the pivotal  
13 clinical trials submitted in the PMA. Note that the  
14 results of earlier feasibility trials have already  
15 been published in peer review journals.

16 This part of my presentation will involve  
17 four parts. I will begin with a discussion of the  
18 clinical protocols. Then I will report the paired  
19 point results, with particular emphasis on analysis by  
20 glucose range. In addition, I will describe the use  
21 of frequent automatic readings to provide an early  
22 warning of low glucose levels. I will then cover  
23 safety evaluation involving skin irritation and  
24 sensitization. And, finally, I'll end with overall  
25 conclusions.

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1           Let me now describe the clinical protocols  
2 used in these pivotal studies, and there are a number  
3 of general aspects that are common among all of these.

4       These include, first, the biographer was applied, and  
5 iontophoresis was initiated, at elapsed time zero.  
6 After three hours, a single glucose value obtained  
7 with a traditional meter was entered into the  
8 biographer as a calibration point.

9           For the next 12 hours, the biographer  
10 produced up to three measurements per hour. In all  
11 studies, neither the patient nor we, the sponsor, saw  
12 the data. Furthermore, patients were required to make  
13 one or two blood finger stick measurements per hour at  
14 a time corresponding to the biographer measurement.

15          After operation, the biographer was  
16 removed and the skin was examined for irritation by  
17 the clinical staff. All biographer data were  
18 downloaded at an independent clinical data management  
19 company. These data were merged with the  
20 corresponding blood glucose values and then analyzed.

21       This independent company, not the sponsor, controlled  
22 the data.

23          The data were analyzed using an algorithm  
24 and data integrity checks that were predetermined by  
25 an independent set of data.

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1           Finally, all paired data are accounted for  
2           in this analysis. None were removed.

3           The pivotal study submitted in the PMA  
4           were obtained using a demographically broad group of  
5           test subjects, insulin-using diabetic patients. There  
6           were 473 unique subjects. These subjects provided  
7           over 1,400 biographer use applications. About two-  
8           thirds of the subjects were Type 1, and about one-  
9           third were Type 2.

10           Slightly more than half of the study  
11           population was female. It was a broad ethnic  
12           diversity, including representative populations of  
13           caucasians, African-Americans, Latinos, as well as  
14           Asians and Native Americans. This test population is  
15           large and demographically representative of Americans  
16           with diabetes.

17           There are four primary measures used to  
18           evaluate the biographer performance. They differ in  
19           the environment used, the calibrating and comparative  
20           device used, and the duration of study. These range  
21           from the accuracy protocol shown here in a controlled  
22           clinical setting, all the way to the home environment,  
23           which was actual home use.

24           We also evaluated the device in a  
25           simulated home environment where subjects were

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1 required to be in the clinic only at times where blood  
2 samples were obtained. The duration ranged from a  
3 single use to five days of consecutive use.

4 Note also in a separate study, which I  
5 won't discuss today, subjects wore the biographer  
6 every day for six weeks.

7 In addition, a variety of home meters and  
8 laboratory devices were tested, shown here. Note that  
9 in all studies measures of capillary whole blood were  
10 used for both calibration and comparison. The home  
11 environment study involved actual home use.

12 The One Touch Profile meter was used as  
13 both a calibrating and comparative device. Subjects  
14 were given one biographer to be used on five  
15 successive days, and there were no restrictions on  
16 activity or exercise.

17 Let us now turn our attention to how we  
18 measure the biographer performance. The biographer is  
19 different from standard home glucose meters. The  
20 glucose sampling method differs. As Dr. Pitzer  
21 explained earlier, the biographer results -- the  
22 biographer measures a time-averaged value of glucose  
23 in extracted interstitial fluid, while traditional  
24 devices have measured instantaneous blood values.

25 The nature of the results also differ.

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1 The biographer provides tracking, which results from  
2 frequent automatic glucose values. Traditional meters  
3 measure glucose at discrete, independent times. The  
4 lag time between the blood and corresponding blood  
5 biographer measurements must, therefore, be taken into  
6 account.

7 The performance standards differ.  
8 Standards are well established for discrete, paired  
9 glucose values. However, no standard exists for  
10 measuring trends. The benefit of frequent ratings  
11 must, therefore, be taken into account.

12 Let's start with a discussion of the  
13 paired metrics because that's what is traditionally  
14 used, and it's easiest to understand. Keep in mind  
15 there are some limitations to paired point analysis,  
16 however.

17 In all studies, accuracy was judged using  
18 paired biographer and blood glucose values. These  
19 paired points were analyzed using a variety of tools,  
20 and these include error -- error really defined as  
21 difference -- between the biographer and blood glucose  
22 value.

23 We also measured relative error and the  
24 mean -- or, excuse me, the absolute value of the  
25 relative error.

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1           Here is an example of an analysis from the  
2 home environment study, and you can see in this  
3 circled area here at about six hours the biographer  
4 value was about -- was 245 milligrams per deciliter,  
5 while the comparative value about 15 minutes earlier  
6 was 282. Hence, the difference between these two  
7 values is negative 37 milligrams per deciliter.

8           The relative error is determined by  
9 dividing that difference by the comparative value and  
10 resulting in a value of negative 15.1 percent. The  
11 absolute value of the relative error, therefore, is  
12 positive 15.1 percent.

13           The mean value for these parameters was  
14 then determined for all data pairs. For this  
15 particular subject day, the mean error was 18.1  
16 percent, the mean relative error was 9.6 percent, and  
17 the mean absolute value of the relative error was 14.9  
18 percent.

19           Accuracy was also judged using correlation  
20 techniques. These include a Deming regression  
21 analysis. We chose Deming because it accounts for  
22 variability in the comparative value. We also  
23 estimated the correlation coefficient and used the  
24 Clarke error grid analysis, which divides the  
25 correlation plots into regions of clinical

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1 interpretation.

2 The Clarke error grid divides a  
3 correlation plot into five regions. Region A, shown  
4 here in the center, represents glucose values that  
5 deviate from the comparative value by less than 20  
6 percent. Or are less than 70 milligrams per deciliter  
7 when the comparative value is less than 70 milligrams  
8 per deciliter.

9 The B region, outside of the A, represents  
10 values that deviate by greater than 20 percent, but  
11 lead to a benign or no treatment. To quote the paper,  
12 Regions A and B are considered clinically acceptable.

13 Region C are described as those regions --  
14 those points where -- that would overcorrect an  
15 acceptable glucose, shown here. And up above.

16 Region D is described as those values that  
17 would result in a dangerous failure to detect and  
18 treat. Region D values below 70 milligrams per  
19 deciliter, right down in here, are particularly common  
20 among all glucose devices. Many home meters have up  
21 to 20 percent of low blood glucose points in this  
22 region.

23 Region E is described as those points that  
24 would result in erroneous treatment. The data shown  
25 here, the red dots, are the same data that I've shown

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1 you on the previous slide. As you can see, the Deming  
2 Linear Regression for these results yields a slope of  
3 1.1, an intercept of 0.1 milligrams per deciliter, a  
4 correlation coefficient of 0.85.

5 In addition, 100 percent of the data or  
6 paired points fall within the AB region of the Clarke  
7 error grid.

8 We use a variety of different performance  
9 metrics, since no single statistic can adequately  
10 describe the accuracy of the biographer. In addition,  
11 very important, none of these metrics can capture the  
12 sequential nature of the readings, which provide  
13 information about glucose trends.

14 As I describe earlier, what is measured  
15 and how performance is assessed differs substantially  
16 from what is done with traditional meters. In studies  
17 using a conventional monitor, a single blood sample is  
18 divided between two test devices. Thus, this single  
19 split sample is obtained at one time.

20 By contrast, studies using the GlucoWatch  
21 Biographer require two different samples obtained at  
22 two different times. In these studies, an  
23 instantaneous blood glucose value is compared to a  
24 biographer value obtained from interstitial fluid,  
25 effectively averaged over approximately 15 minutes

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1 into a single value.

2 In addition, there are errors associated  
3 with the comparative device which do not reflect the  
4 true performance of the biographer.

5 The sources of difference between the  
6 biographer and blood glucose readings are summarized  
7 here. The first two are clearly relevant for the  
8 assessment of the biographer performance, and they  
9 include error due to the device itself and the  
10 calibration procedure.

11 There are also sources of error unrelated  
12 to in-use performance. Most notable among these are  
13 error associated with the comparative device, and I'll  
14 speak to this in a moment. In addition, the process  
15 of a comparison also includes effects of the kinetics  
16 between the blood and interstitial fluid glucose  
17 levels.

18 The comparison method also introduces  
19 error due to the difference between the time-averaged  
20 measurement and the instantaneous blood glucose test.

21 These latter, although important for understanding  
22 how to use the device, they experimentally obscure the  
23 actual analytical performance.

24 Thus, when results are reported as error,  
25 it should be more correctly described as difference.

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1 And only part of the error is due to the biographer.

2 I would now like to go into some details  
3 on the results of the home environment study, since  
4 this represents an evaluation under the intended use.

5 Following that, I will summarize results from some  
6 other studies.

7 Let me just briefly remind you of the  
8 protocol in the home environment study where subjects  
9 used the biographer at home for five consecutive days.

10 In this study, subjects were allowed full freedom of  
11 activity. They wore the biographer indoors, outdoors,  
12 sometimes even during sports activities.

13 In addition, these studies were performed  
14 at a geographically diverse series of clinical sites,  
15 including those in areas of high relative humidity as  
16 well as high altitude.

17 In this study, subjects were required to  
18 make their own blood glucose measurements using a One  
19 Touch Profile meter. One blood measurement was  
20 obtained at three hours and used for calibration. And  
21 one blood measurement was taken per hour thereafter.

22 Keep in mind that blood measurements had  
23 to be obtained within plus or minus a five-minute  
24 window to be paired with, and compared to, the  
25 biographer value obtained 15 minutes later.

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1           Subjects were required to apply, operate,  
2 and remove the biographer. Instructional materials  
3 and training were provided at the beginning of the  
4 study and a health hotline was available to answer  
5 questions anytime during the study.

6           There were no restrictions on activity  
7 other than not getting the device wet, such as  
8 swimming or bathing.

9           In this slide, I've selected six  
10 representative elapsed time profiles out of the 420.  
11 You have these in front of you. These results span a  
12 range of performance.

13           The plot shown here in the upper right  
14 shows mean absolute relative error of seven percent,  
15 correlation of 0.97, and 100 percent of the data are  
16 in the AB region. Clearly, everyone would agree that  
17 this is a very successful example of accuracy and  
18 tracking.

19           As you progress through these results,  
20 however, values for mean absolute relative error  
21 correlation in AB vary. For example, the graph in the  
22 lower left shows a correlation coefficient of 0.31,  
23 and 75 percent of the data in the AB region.

24           From these values alone, one would  
25 conclude that this was a poor performing biographer.

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1 Look at the graph, however, and this suggests that the  
2 biographer is closely tracking blood glucose.  
3 Similarly, look at the graph in the lower right here,  
4 which has a mean absolute relative error of 49  
5 percent.

6 Now, however, the correlation coefficient  
7 is 0.89, and 100 percent of these data fall in the A  
8 plus B region of the error grid, both of which are  
9 quite respectable numbers.

10 These examples clearly illustrate my  
11 earlier point that no single statistic can adequately  
12 capture the performance of the biographer. Rather,  
13 these various metrics, along with visual inspection,  
14 are necessary to judge tracking.

15 I'd now like to discuss an analysis of all  
16 of the paired data in the home environment study.  
17 This data set consists of nearly 3,000 data pairs. A  
18 correlation analysis of these data shows a Deming  
19 slope of 0.95, an intercept of 12.6 milligrams per  
20 deciliter, and a correlation coefficient of 0.80.

21 These results demonstrate that the  
22 biographer values correlate with the One Touch Profile  
23 measures of blood glucose. In addition, as you can  
24 see, these data are superimposed on the Clarke error  
25 grid.

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1                   The results of this error grid analysis  
2 show that 94 percent of the paired points are in the  
3 clinically acceptable A plus B regions, while only  
4 three out of nearly 3,000 points are found in the  
5 E region.

6                   An analysis of the error statistics is  
7 also useful, and it shows a mean error of 4.6  
8 milligrams per deciliter, and a mean relative error of  
9 seven percent. These values provide an estimate of  
10 the tendency to read high or low relative to the  
11 comparative meter.

12                   The scatter in the data is characterized  
13 by the standard deviation of the mean error, which is  
14 43.2 milligrams per deciliter, and the mean absolute  
15 relative error, which is 21 percent.

16                   Another means to determine the biographer  
17 performance is to measure the bias at various blood  
18 glucose concentrations. The bias hypothesis was  
19 established before beginning analysis of the results.

20                   Bias for this analysis was defined as the difference  
21 from the Deming regression line.

22                   The hypothesis tests whether the bias is  
23 less than 15 milligrams per deciliter, below 100  
24 milligrams per deciliter, and less than 15 percent at  
25 greater than or equal to 100 milligrams per deciliter.

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1 The results shown here for five different decision  
2 levels show that the bias and 95 percent confidence  
3 intervals are within the proposed limit at each blood  
4 glucose concentration. The bias was significantly  
5 less than that in the pre-specified limits.

6 Here are some details of the four studies  
7 used to judge performance. The mean error, the mean  
8 relative error, the slope and intercept, measure the  
9 tendency to read high or low relative to a comparative  
10 value. In total, more than 13,000 paired data points  
11 showed that the results were similar across all  
12 protocols.

13 Overall, the mean error is five milligrams  
14 per deciliter or less, and the mean relative error is  
15 seven percent or less. In addition, the slope is near  
16 unity, and the intercept was 13 milligrams per  
17 deciliter or less.

18 These results, I want to emphasize, are  
19 comparable to performance generally seen for home  
20 blood glucose monitors. For example, in home monitors  
21 used in our clinical studies, the mean relative error  
22 was in the range of three to 10 percent.

23 In addition, measures of data scatter were  
24 similar throughout the studies. For example, the mean  
25 absolute relative error was 21 percent or less, and

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1 more than 94 percent of the data were in the AB region  
2 of the error grid.

3 By contrast, only one-tenth of one percent  
4 -- that's one in 1,000 -- of the points, at most, were  
5 found in the E region. Note also a comparison between  
6 the YSI and HemoCue measurements uses comparative  
7 meters in these two home simulator trials. All  
8 measures of scatter are better with the YSI. If you  
9 look at the values here, compared to the HemoCue, all  
10 measures are better. This is due to the lower  
11 technique -- the lower error of the YSI technique used  
12 for the comparative values.

13 Note especially the MARE of 17 percent and  
14 the error grid of 98, compared to the values obtained  
15 with the HemoCue. In comparison, home meters -- home  
16 meters used alone -- show mean absolute relative error  
17 in the range of 11 to 13 percent when using split  
18 sample in a laboratory environment.

19 Finally, it's important to note that in  
20 these studies, on average, more than 25 measurements  
21 were obtained for each biographer use. This far  
22 exceeds what's obtained with blood meters.

23 So far, I've presented summaries of data  
24 using mean values. Of course, there is a distribution  
25 performance which is not obvious from mean values. Of

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1 primary concern to the sponsor and the reviewers is  
2 performance at the lower end of evaluation, which can  
3 be called poor tracking events.

4 In this slide, I've attempted to convey  
5 the results of various analyses of poor tracking.  
6 These analyses include both point and biographer use  
7 evaluation. For example, as shown earlier, six  
8 percent of the points lie outside the AB region of the  
9 error grid.

10 On the other hand, nearly 14 percent of  
11 the points have mean absolute relative error greater  
12 than 20 percent, and correlation less than .9, and  
13 A plus B less than 90 percent. Depending on the  
14 criteria selected, the values for poor tracking range  
15 from less than one percent to greater than 20 percent.

16 This slide shows three examples among the  
17 worst of the home environment study, based on the  
18 criteria listed below. And they are E greater than  
19 30, and R less than .8, and A plus B less than 90.

20 In the far left, we see a biographer that  
21 is reading high and shut off early. In the middle,  
22 the biographer reads a bit low.

23 The final slide actually shows one of the  
24 points in the E region, although in this case this  
25 error may be due, in fact, to the comparative meter.

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1 All home glucose monitoring systems have some error  
2 that can lead to inappropriate decisions. All.

3 Thus, the issue is not whether there is no  
4 risk, but, rather, what is the risk relative to  
5 current medical practice of just a few measurements  
6 per day? Moreover, what is the risk relative to the  
7 added benefits of the additional information provided  
8 by the biographer?

9 Clearly, evaluating performance by glucose  
10 range is crucial to the proper -- this proper  
11 assessment of risk and benefit. Thus, I will turn to  
12 an analysis of performance stratified by glucose  
13 range.

14 First, I would like to show the results  
15 stratified vertically by blood glucose as shown  
16 schematically on the left here. This is an analysis  
17 suggested by the FDA. Then, I would like to show you  
18 the results obtained when one stratifies horizontally  
19 based on the biographer glucose, shown schematically  
20 on the right.

21 In the home environment study, an analysis  
22 of the error grid distribution by blood glucose range  
23 shows that more than 90 percent of the data fall in  
24 the A plus B region, except in the low blood glucose  
25 range. In this range, 63 percent of the points are in

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1 the A plus B, and 36 are in the D region.

2 An analysis of the absolute error or  
3 absolute relative error by blood glucose range is also  
4 useful. The criteria used are shown here. The  
5 absolute value must be less than 20 milligrams per  
6 deciliter at blood glucose values below less than 80  
7 milligrams, or the absolute relative error must be 30  
8 percent at all other blood glucose values.

9 This shaded area on the left are the  
10 results that I showed you in the previous slide, while  
11 the absolute error results are shown in the right-most  
12 column. These results show that over most of the  
13 blood glucose ranges evaluated, 70 percent or more of  
14 the points satisfied the criteria.

15 Note, however, in the low glucose range,  
16 45 percent of the points satisfied the criteria.  
17 These results were obtained, as pointed out up above,  
18 using the One Touch as a comparative meter. Thus,  
19 performance reflects both error in the biographer and  
20 the One Touch meter.

21 To put error due to the comparative meter  
22 in perspective, let's look at what we call the  
23 laboratory method comparison study. In this data set,  
24 a One Touch was used as a calibrating meter, as you  
25 would expect in the home use, but the YSI was used for

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1 all comparative glucose values.

2           These results were obtained in a home  
3 simulated protocol, which allowed the subjects full  
4 freedom of activity between the times they were  
5 supposed to show up at the lab for a measurement. The  
6 results obtained in the home environment study, which  
7 I presented in the last several slides, are shown in  
8 this shaded area for comparison.

9           These results show that even at the low  
10 glucose values, the low glucose range, the number of  
11 points in the AB region increases from 63 to 81, and  
12 the values in the D region decrease from 36 to 19,  
13 simply by using the YSI as a comparative meter.

14           Similarly, the points within 20 milligrams  
15 per deciliter at blood glucose values below 80  
16 milligrams per deciliter increased from 45 percent to  
17 67 percent, simply using the YSI. Overall, the  
18 performance increased from 76 to 86 percent.

19           In every metric evaluated, at every blood  
20 glucose range studied, performance of the biographer  
21 was better when the YSI was used as the comparative,  
22 not calibrative device. These differences demonstrate  
23 the effect of having a more accurate meter, such as  
24 the YSI, when making comparative measurements.

25           Even with the more accurate comparative

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1 meter, the results continue to show less robust  
2 performance of the biographer at low glucose range.

3           What are the implications of those  
4 results? One question posed by the FDA to the panel  
5 is: Should real-time readings for low glucose values  
6 be replaced with an error code? To investigate the  
7 potential value of such a change, the stratified  
8 analysis must be repeated with stratification based on  
9 biographer glucose range, as shown schematically on  
10 the right.

11           This approach is necessary because during  
12 actual use the user does not object comparative blood  
13 glucose values. It's not possible to limit biographer  
14 use to occasion when blood glucose value is below 80  
15 milligrams per deciliter.

16           A possible approach would be to limit the  
17 readout to those occasions when the biographer glucose  
18 values are greater than 80 milligrams per deciliter.

19           I will now show you why such limitations  
20 are actually not beneficial.

21           When the same home environment study error  
22 grid is stratified by biographer glucose range, you  
23 see that more -- 91 percent -- 90 or more percent of  
24 the data are in the AB region, and 91 percent, in  
25 particular, in the range of 40 to 80 milligrams per

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1 deciliter. By contrast, only eight percent are found  
2 in the D region.

3 More importantly, these results show that  
4 the data are equally reliable across the entire  
5 biographer measurement range.

6 An analysis of the absolute difference or  
7 absolute relative difference shows -- also shows that  
8 over each biographer glucose range, 69 percent or more  
9 of the points satisfy the criteria. These are the  
10 data that I showed you a moment ago on error grid, and  
11 these are the difference values.

12 Once again, there is no dependence on  
13 glucose -- biographer glucose range. Moreover, the  
14 results of these analyses show even better performance  
15 when the YSI is used as the comparative meter. All of  
16 these values increased to greater than 80 percent if  
17 that YSI is used as a comparative meter.

18 Hence, when the error grid or absolute  
19 error distribution are evaluated by biographer glucose  
20 range, there is no evidence of poor performance at low  
21 values. Thus, there is no safety or effectiveness  
22 benefit to limiting biographer measurement range.

23 What, then, is the implication of the less  
24 robust biographer performance at low blood glucose  
25 range? Detection of low blood glucose is a major

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1 problem for many patients with diabetes. With current  
2 medical practice of just a few blood glucose tests per  
3 day, many low blood glucose events are not detected  
4 because no test is performed at the appropriate time.

5 The biographer performance at low blood  
6 glucose must be evaluated relative to the frequent  
7 absence of information with conventional testing.

8 Let us, therefore, turn to a specific  
9 analysis of the ability of the GlucoWatch Biographer  
10 to detect low blood glucose measurements.

11 The frequent and automatic measurements of  
12 glucose possible with the biographer provide the  
13 potential for an early warning of low glucose. Using  
14 current blood glucose measurement technology, it's  
15 difficult, in fact, if not impossible, for patients to  
16 predict low glucose events.

17 The GlucoWatch Biographer provides a  
18 method to alert the users to instances of low or  
19 rapidly declining glucose values. In addition, the  
20 user and health care team can control the low glucose  
21 setting used in the warning system. The adjustable  
22 low glucose alert determines the circumstances and  
23 frequency of alerts, as well as the number of what are  
24 called true positives and false positives.

25 Thus, a tradeoff occurs between the

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1 sensitivity and the frequency of alerts to which the  
2 user must respond.

3 It is common to evaluate diagnostic  
4 devices using what's called a receiver operator  
5 characteristic curve, or ROC curve. This provides a  
6 measure of the ability of a diagnostic test to  
7 properly detect an event which actually occurs, called  
8 sensitivity or true positive fraction, relative to  
9 false detection in the absence of an event, called the  
10 false positive fraction.

11 For the purpose of evaluating the low  
12 glucose alert, hypoglycemic events were defined as  
13 those instances where the One Touch meter showed  
14 glucose values that were less than or equal to 70  
15 milligrams per deciliter. Note that this ignores any  
16 error associated with the One Touch meter and assigns  
17 truth to that value.

18 In the home environment study, there were  
19 160 hypoglycemic events where corresponding biographer  
20 data were available. An ROC curve was constructed  
21 from those data, and it's shown in this slide.

22 These results show that, for example,  
23 setting the alert level at 90 milligrams per deciliter  
24 -- shown here and that's this point -- or about 20  
25 milligrams per deciliter above the hypoglycemic

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1 threshold, 62 percent of hypoglycemic events are  
2 detected. In contrast, only six percent of the time  
3 did the biographer detect an event where glucose  
4 actually exceeded 70 milligrams per deciliter.

5 If the alert is increased to 100, shown  
6 here and on the table, 75 percent of the hypoglycemic  
7 events were correctly identified. As would be  
8 expected, this also leads to an increase in the false  
9 positives to about ten percent.

10 Well, you can see the ROC curve is then  
11 constructed by taking all of these values -- 90, 100,  
12 110, and so on -- and this is the ROC curve. The  
13 overall results showed that increased sensitivity can  
14 be obtained with decreased specificity by simply  
15 changing the alert level.

16 In addition, as shown down here, these  
17 results show an area under the curve of 0.91,  
18 characteristic of a test with high diagnostic utility.

19 It's essential to note here that these results were  
20 obtained with all data, all paired values from the  
21 home environment study. All poor tracking events,  
22 regardless of how they were defined, are included in  
23 this analysis. And yet the results show the ability  
24 to accurately detect hypoglycemic events.

25 A comparison of the results obtained with

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1 finger stick blood glucose is really quite  
2 instructive. An analysis of the blood glucose data  
3 from the home environment study -- these are shown  
4 here -- shows that if you make two measurements per  
5 day you would detect 14 percent of all hypoglycemic  
6 events. If you increase that to four measurements per  
7 day, you would detect 39 percent of all hypoglycemic  
8 events.

9 By contrast, the biographer, with an alert  
10 setting at 90, non-invasively detects 62 percent of  
11 hypoglycemic events with only six percent false  
12 positives. Of course, increasing that value, the  
13 alert value, it leads to the detection of a greater  
14 number of low glucose events.

15 These results clearly demonstrate that the  
16 biographer can detect a far greater number of low  
17 glucose events than conventional blood measurements  
18 taken even as frequently as four times per day.

19 Finally, while time doesn't allow a  
20 discussion, I'd like to point out that similar results  
21 were obtained for hyperglycemic alert at high glucose  
22 results.

23 Now, let me summarize these effectiveness  
24 results. There are accepted metrics for paired value  
25 estimates of performance suitable for conventional

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1 blood glucose meters. Using these metrics, the  
2 biographer demonstrates comparable bias with somewhat  
3 higher data scatter relative to the home glucose  
4 meters.

5 However, as I've described, these methods  
6 underestimate the biographer performance and don't  
7 describe tracking.

8 Stratification of the results by glucose  
9 range provides an estimate of performance at low  
10 glucose. When stratified by biographer glucose  
11 values, the results show that the performance is  
12 equivalent across all glucose ranges evaluated.

13 Perhaps the most important assessment of  
14 the ability is the ability to detect trends and  
15 patterns, and this comes from an analysis of the low  
16 glucose alert. These results -- and I repeat -- which  
17 include all data show that the biographer can detect  
18 low glucose events with substantially greater  
19 effectiveness than the standard practice of just a few  
20 blood measurements per day.

21 Thus, the tracking capabilities, and  
22 particularly the low glucose alert provided by the  
23 biographer, far exceed what can be achieved with  
24 standard blood glucose monitoring alone.

25 We submit that the benefits of the

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1 GlucoWatch Biographer far exceed any risks.

2           Let me briefly summarize the safety  
3 studies. There were no serious adverse health  
4 consequences that resulted from the use of the  
5 biographer in any study. These results involved over  
6 25,000 hours of use. Most patients experienced mild  
7 to moderate skin irritation which resolved within a  
8 few days after use. Only two percent had strong --  
9 what's called strong or intense erythema. There were  
10 no -- repeat no -- serious or severe skin reactions.

11           A few subjects exhibited small what are  
12 called friction blisters, but in contact sensitization  
13 studies no contact sensitization was observed.

14           In conclusion, the biographer is accurate  
15 in both benchtop and clinical studies. It may produce  
16 mild to moderate irritation, but this irritation is  
17 self-limiting and resolves within a few days. The  
18 frequent, automatic, and accurate readings allow the  
19 device to detect trends in glucose levels.

20           As a result, it can provide a warning for  
21 hypo and hyperglycemia. The physician and patient can  
22 determine the sensitivity and specificity of that  
23 warning.

24           I'd like to end where I began. The  
25 GlucoWatch Biographer is different from standard blood

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1 glucose meters. The most relevant comparison of the  
2 biographer is to the absence of frequent glucose  
3 values. Measures which reflect the value of detecting  
4 glucose trends, such as the low glucose alert,  
5 demonstrate that the benefits of the GlucoWatch  
6 Biographer far outweigh the risks of requiring  
7 patients to continue to rely upon standard blood  
8 glucose monitoring alone.

9 I would now like to introduce Dr. Edelman  
10 who will describe his clinical perspective.

11 Thank you.

12 DR. EDELMAN: Hello, my name is Steve  
13 Edelman. I'm a diabetes specialist at the University  
14 of California at San Diego and the Veteran Affairs  
15 Medical Center. I am a paid consultant for Cygnus. I  
16 have received no stock or stock options from the  
17 company, and I have purchased a small amount of stock  
18 on my own personal account.

19 I am also here as a person living with  
20 diabetes for 30 years, and I'm also here to represent  
21 many of the patients whom I take care of. Today what  
22 I'd like to do is go over some of the clinical  
23 perspectives of the GlucoWatch to discuss how this  
24 device could be used in the real world.

25 I don't need to tell members of this panel

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1 or members in the audience that diabetes is a major  
2 health care problem. There really is a diabetes  
3 epidemic going on not only in the United States, but  
4 also around the world.

5 It's been proven, quite convincingly, that  
6 intensive management has proven to reduce the classic  
7 complications of diabetes -- the eye, the kidney and  
8 nerve disease. And one of the most famous studies,  
9 which I'll discuss, is the Diabetes Control and  
10 Complications Trial performed in Type 1 diabetics and  
11 the Kumanoto and the United Kingdom Prospective  
12 Diabetes Study in Type 2 diabetics.

13 And I want to say up front that  
14 hypoglycemia often limits the degree of glucose  
15 control that one can achieve with intensive therapy  
16 using the tools that we have today.

17 The next four slides are from the Diabetes  
18 Control and Complications Trial. I'll refer to it as  
19 the DCCT. And why am I spending so much time on this  
20 study is because this study really set the standard of  
21 care for diabetes in the United States and around the  
22 world.

23 It was an NIH funded study that lasted  
24 nine years, cost \$160 million dollars, and was  
25 probably one of the most well performed study in the

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1 history of diabetes. This slide on the left-hand  
2 panel shows the degree of control in the two groups.

3 The poorly controlled group that had a  
4 glycohemoglobin of 9 percent for approximately nine  
5 years, and that equates to an average daily blood  
6 sugar of about 230 mg/dL. Then the group that had  
7 intensive management that maintained an average  
8 glycohemoglobin of approximately 7 percent for the  
9 nine year duration with an average daily blood sugar  
10 pre and post meal, seven times a day, of 155 mg/dL.

11 Now what I'd like to point out is that the  
12 upper limit of normal is 6 percent down here. And  
13 despite the intense efforts of the research group, the  
14 clinical nurses, use of insulin pumps, multiple daily  
15 injections, home glucose monitors, they still could  
16 not achieve normal glycemia.

17 This is just one data slide showing the  
18 incidence of retinopathy over the nine year study.  
19 And as you can plainly see -- and strikingly see, I  
20 should say -- in the patients who had intensive  
21 glyceemic control and a glycohemoglobin of 7 percent,  
22 they experienced a 76 percent reduction in the  
23 incidence of diabetic eye disease.

24 This data was also shown for kidney  
25 disease and nerve disease, and it was also shown in

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1 the studies with Type 2 diabetes. I also want to  
2 point out a comment that one of my colleagues made at  
3 a medical lecture that even the patients who had  
4 glycohemoglobin of 7 percent after nine years, over 10  
5 percent of those individuals had eye disease.

6 And if you think about it, hopefully  
7 people with diabetes are living longer and longer and,  
8 if you take someone who's maybe 20 years old with a  
9 lifelong of diabetes, this rate, even at a  
10 glycohemoglobin of 7 percent, will result in a  
11 significant amount of retinopathy.

12 This is a slide showing the correlation  
13 between retinopathy, which is the best objective  
14 complication to measure -- you could measure it  
15 objectively -- in relation to the degree of glycemic  
16 control in the Diabetes Control and Complications  
17 Trial.

18 Remember that even though the average was  
19 seven to nine, patients were at all different levels.

20 And you can see that the risk of retinopathy along  
21 the right-hand arrow at an A1C of 9 percent, here is  
22 the 76 percent reduction to the patients with an  
23 average of 7 percent, and the rate really starts to  
24 drop significantly once patients reach into the normal  
25 range, which is the upper limit of six or below.

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1           And as I mentioned earlier, due to the  
2 sake of time, I'm not going to go over the UKDS study  
3 and the Kumanoto study in Type 2 diabetics that  
4 actually showed this almost very similar analogy. And  
5 the bottom line is, the duration and severity of  
6 hyperglycemia is the strongest determinant of the  
7 microvascular complications of diabetes, and it may  
8 also relate to the microvascular complications.

9           So this slide demonstrates the limiting  
10 factor in achieving intensive glycemic control in the  
11 DCCT study and out with clinical practice. It shows  
12 the rates of severe hypoglycemia defined as requiring  
13 assistance, passing out, requiring paramedics or help  
14 from others.

15           You can see the risk here with the poorly  
16 controlled group of 9 percent. And it goes up 300  
17 percent, a threefold increase, in the group that  
18 achieved intensive glycemic control and was the basic,  
19 main limiting factor in this clinical trial.

20           And you can see the rate -- what happens  
21 when you get to the upper limit of normal, and it gets  
22 even higher in the low normal range. So basically  
23 hypoglycemia has really limited us from achieving near  
24 normal or normal glycemic control in clinical trials  
25 with the help of a huge staff and out in the real

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1 world.

2 Now, this slide shows a composite of  
3 several studies done documenting the level of diabetes  
4 care around the world. You can see that there's quite  
5 -- putting together over 20,000 patients, Type 1 and  
6 Type 2 diabetes, in the U.S. and abroad.

7 And on these first two studies, you can  
8 see the relatively small amount of patients getting  
9 their glycohemoglobin less than 8 percent, which is  
10 the action suggested cut off point put forth by the  
11 American Diabetes Association.

12 And in these bottom three studies, you can  
13 see that a major amount of patients had  
14 glycohemoglobins over 9.5 percent, which represents  
15 worst control than the poorly controlled group in the  
16 Diabetes Complication and Control Trial.

17 And it's really very important to listen  
18 to this one statement that the advances in diabetes  
19 research, and treatment, and oral agents, and new  
20 insulins have far out paced the level of diabetes care  
21 that we see in the community.

22 So what are the barriers to intensive  
23 control? The first one is the non-physiologic  
24 pharmacokinetics of subcutaneous insulin. Insulin  
25 normally is delivered from the pancreas right into the

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1 blood stream.

2           And obviously, this is not a problem that  
3 the GlucoWatch can improve; but, with the advancements  
4 of a fast acting insulin analogs like Lispro, that has  
5 reduced this barrier. But with information from a  
6 device such as the GlucoWatch that can give us  
7 frequently monitored numbers, then we could use these  
8 insulins much more effectively and, I should say, more  
9 safely, too.

10           The need for frequent blood glucose  
11 testing -- when you look at statistics done that the  
12 average patient with diabetes in America tests less  
13 than two times a day, and when you look at the  
14 sophistication of a normally functioning pancreas that  
15 measures glucose on a second to second basis, that  
16 could measure the rate of change of glucose, and then  
17 you compare that to patients who test two times a day  
18 or four times a day or seven times a day, you can see  
19 why diabetes therapy today is very archaic, and that  
20 it's one big explanation why it's so difficult to get  
21 our patients under control.

22           Hypoglycemia is a major concern, and I'll  
23 expand upon that later. And the fear of hypoglycemia  
24 -- because, as a practicing diabetes specialist, once  
25 a patient passes out in public or driving a car, or

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1 while taking care of his or her child, it takes a  
2 tremendous amount of effort to get that individual to  
3 build up enough courage to try to achieve intensive  
4 glycemic control once again.

5 Well, how can we reduce the barriers using  
6 the GlucoWatch? First of all, the GlucoWatch can  
7 provide previously unavailable information on both the  
8 acute trends, which helps with the day to day  
9 management of diabetes, and the overall patterns in  
10 glucose levels, which will help us adjust the long  
11 term treatments and plans.

12 Along with the standard testing, this will  
13 enable better decisions by patients primarily, and  
14 secondarily by professionals who take care of these  
15 patients. And it will reduce the risk of  
16 hypoglycemia. And I can't underscore that word  
17 enough.

18 It will help identify opportunities for  
19 improving overall glucose control; specifically  
20 identify postprandial and incidental hyperglycemia,  
21 which is usually not picked up on current testing  
22 schedules; and investigate the causes of nocturnal or  
23 fasting hyperglycemia and hypoglycemia.

24 So how could we use this clinical  
25 practice? And I think that if we had a room full of

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1 people with diabetes, and we probably do, and a group  
2 full of practicing diabetes specialists, you can come  
3 up with maybe ten of these slides.

4 I'm just going to go over a few. First of  
5 all, I think that we'll have patients who will use  
6 this device routinely. These will be patients on  
7 intensive insulin regimens, insulin pumps, multiple  
8 daily injections who do not have easily controlled  
9 diabetes.

10 People who really bounce around despite  
11 following all the rules and regulations set forth by  
12 them by their care givers, they still cannot maintain  
13 fairly even blood sugars.

14 And for patients with hypoglycemic  
15 unawareness, just for this indication alone, it will  
16 be a life saving device for so many people who have to  
17 go out in the world and work and drive vehicles and do  
18 not detect their low blood sugars.

19 For periodic use, patients -- to confirm  
20 the status of their current therapy. Just like in  
21 clinical practice, we have patients maybe two days a  
22 week test their blood sugar seven to nine times a day  
23 because obviously the diabetes regimen changes over  
24 times, different seasons, other periods of medical  
25 conditions and we'd like to confirm their current

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1 therapy.

2 And it will be used to determine glucose  
3 patterns while sleeping and other problem time periods  
4 that that individual may be experiencing. Some  
5 patients will use this device only in certain  
6 circumstances -- when the normal routine is disrupted,  
7 *ie.* changes in work shifts and traveling.

8 Most people don't realize that we tell our  
9 patients -- I tell myself try to do the same thing  
10 every day, eat the same amount of food, take the  
11 insulin at the same exact time.

12 But when you have different work shifts,  
13 maybe the graveyard shift two days a week, on weekends  
14 you're not even working, it's very difficult to follow  
15 these guidelines, which is one reason why blood sugars  
16 are all over the place.

17 Changes in insulin regimen, *ie.* initiating  
18 insulin pump therapy. And hopefully, after getting an  
19 insulin pump you may not need it as much. Adding new  
20 oral medications or adjusting doses in individuals  
21 with Type 2 diabetes, especially those prone to  
22 hypoglycemic unawareness.

23 Determine problems in patients with higher  
24 than expected glycosylated hemoglobin values. When  
25 you compare that to the home glucose monitoring data

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1 -- because if you think about it, we test our blood  
2 sugars before meals, and that's probably the lowest  
3 time of the day.

4 And many times, the glycosylated  
5 hemoglobin is much higher than you'd expect, and this  
6 will really help solve that issue. And I personally  
7 believe it will be a huge educational tool. Because  
8 now patients will see the effects of different dietary  
9 choices and activity levels on their blood sugars.

10 And so this -- it will also become a  
11 behavior modification tool because we will learn to  
12 adjust our daily routine, activities and meals to  
13 control our blood sugars non-pharmacologically, even  
14 without using insulin or extra pills.

15 Now, this slide -- I'm going to go over an  
16 example of how you could respond to a high blood  
17 sugar. This is a typical sliding scale where we use  
18 short acting insulin analog and we determine the dose  
19 of insulin -- these are just an example -- according  
20 to the pre-meal blood sugar.

21 And of course, that doesn't take into  
22 account what the blood sugars were over the previous  
23 hour, what anticipated exercise, what size of meal  
24 you're going to eat. And what I have a lot of my  
25 patients do is they give themselves a little extra

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1 Humalog one to two hours after eating if they're over  
2 200.

3 This way they're not hyperglycemic for  
4 hours and hours until their next meal. And of course,  
5 this amount of insulin is determined not to cause them  
6 to get low, hopefully, and a small amount at bedtime  
7 if their blood sugar's over 250.

8 Now, I think that it would be very  
9 important that if we had information after eating, if  
10 the alarm went off, I would say to my patients confirm  
11 with your regular glucose meter. If it's high, take  
12 that extra dose of insulin that has been previously  
13 determined to counteract that level of blood sugar.

14 Now, I think what is really kind of  
15 exciting in the future, not now, is that when we have  
16 frequently monitored numbers over the previous, let's  
17 say, hour before a meal, we might be able to use the  
18 rate of change of the glucose up to that meal to  
19 determine the actual amount of insulin: if it's going  
20 up, if it's going down, or if it has been even.

21 And that's basically called trend  
22 analysis. And I think devices such as the GlucoWatch  
23 and others in development will open up this whole  
24 area.

25 Now this is an example on the other end of

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1 the spectrum, just two very good examples of how you  
2 use this device for low blood sugars. These two data  
3 analyses were taken from the Home Environment Study.  
4 In both cases, the low alert was set at 100.

5 Taking the worse case scenario, you'd be  
6 able to pick up most of the low blood sugars that  
7 actually occur below 70. And in this first case,  
8 let's just take this point here where I'm pointing.  
9 This patient gets a low glucose alarm, scrolls up the  
10 watch and says, "Gee, I've been dropping like crazy  
11 over the past hour. I better take some glucose now."

12 The worst case scenario is you've taken a  
13 little glucose and you may not be as low as you think  
14 with a false positive, but certainly I think being  
15 very prudent and avoiding a crashing low blood sugar.

16 Now, in the situation on the right, it's  
17 quite different. If you look at this point 12 hours  
18 after putting the GlucoWatch on, this patient would  
19 get a low glucose alarm.

20 They'd look at the blood sugars over the  
21 previous hour and they'd say, "Gee, my blood sugars  
22 have been very stable. They're hovering right around  
23 100 and I'm about to have dinner, so I'm not going to  
24 take any glucose. I'm going to wait until dinner.  
25 I'm going to use my own glucose meter to confirm the

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1 dose that I'm going to take to determine how much  
2 insulin I'm taking."

3 So what about the potential concerns with  
4 the GlucoWatch Biographer? Dr. Jovanovic will be  
5 talking about these in more detail. I'm just going to  
6 mention them now briefly. One is over treatment by  
7 patients unfamiliar with this much information.

8 First of all, any patient now can go out  
9 without a prescription, buy a glucose meter, test ten  
10 times a day and make the wrong decisions. You know,  
11 this is an education concern and it is a problem now.

12 There has not been enough education directly to the  
13 public regarding diabetes, and this may institute or  
14 initiate that.

15 The device will be a prescription device  
16 and it will come with extensive education. And I  
17 think that will put one layer of a safety net so  
18 patients who use this device can use it appropriately.

19 The possibility of erroneous glucose  
20 results -- you've heard from Russell Potts that the  
21 results looking at the E region of the Clark Error  
22 Grid Analysis occurred rarely. And basically, when  
23 you compare this device to a laboratory method, it's  
24 just as accurate as the meters that we're using now.

25 I think warnings never to base an insulin

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1 dose on the GlucoWatch reading, test and confirm with  
2 your home glucose monitor, and conservative settings  
3 in the low glucose level, especially for people with  
4 hyperglycemic unawareness. And I think the worst case  
5 scenario here, if you set your alarm at 110, is that  
6 you get a few false positives and you weren't as low  
7 as you thought.

8 But certainly you're going to be able to  
9 help many people who cannot detect their low blood  
10 sugars. And temporary skin irritation. You'll hear  
11 more from Lois, but it's self limited. It goes away  
12 in a few days. And I say, just thinking of it in  
13 common sense terms, if the person using this device  
14 doesn't like the skin irritation, then they don't have  
15 to use the device. They can go back to their usual  
16 methods.

17 So, in summary, self monitoring has  
18 advanced diabetes care starting in the 1980s, but we  
19 really have reached a "therapeutic wall" limiting  
20 tight control. And I think if you speak to any person  
21 with diabetes or any practicing diabetologist, they  
22 will agree with that statement.

23 The GlucoWatch Biographer provides  
24 additional information about acute glucose trends and  
25 long term overall patterns. The potential benefits

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1 for improved glycemic control and reducing the risk of  
2 hypoglycemia, in my opinion, far outweigh the risk of  
3 the device, and this device represents an important  
4 step forward to achieving the promise of the Diabetes  
5 Control Complications Trial.

6 Thank you very much.

7 (Applause.)

8 DR. JOVANOVIC: Dr. Nipper, ladies and  
9 gentleman, I'm Lois Jovanovic. I'm Director and Chief  
10 Scientific Officer of the Sansum Medical Research  
11 Institute in Santa Barbara. I'm also a Clinical  
12 Professor of Medicine at the University of Southern  
13 California.

14 As a person with diabetes, as well as an  
15 endocrinologist, I have championed and focused my  
16 career towards trying to make a difference to all  
17 people with diabetes. Our research institute has been  
18 a site for the GlucoWatch clinical trials.

19 I have not received any personal funding  
20 from Cygnus, nor do I own any stock. However, the  
21 research institute has been reimbursed and given  
22 grants for research for time I've invested either  
23 doing clinical trials or being an advisor to Cygnus.

24 In our home simulated studies, we were  
25 asked to recruit patients into the research institute

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1 for 14 hours during the day. We were asked to let the  
2 patients have free access to food and insulin, hoping  
3 that their blood sugars would swing spontaneously  
4 between 40 and 400.

5 Therefore, we advertised in our community  
6 for patients who are naive to intensive blood glucose  
7 monitoring or intensive care programs. Each day we  
8 tested about ten patients. They were wearing the  
9 Biographer and simultaneously had their blood glucose  
10 measured by the laboratory standard every 20 minutes.

11 Both the patients and the researchers knew  
12 the laboratory glucose results. The Biographer was  
13 blinded to us. Five of the patients in this  
14 particular day were my own personal patients who were  
15 savvy about self blood glucose monitoring and  
16 intensive diabetes control.

17 Five of the patients were naive to any  
18 programs of intensive monitoring. The graph you see  
19 in front of you is from a patient who was naive. She  
20 told me that her physician had labeled her as a  
21 "brittle" diabetic, which meant it was impossible to  
22 control her blood sugars and her sugars would swing  
23 from very high to very low, and that was the reason  
24 she had diabetes out of control.

25 We put her in the setting of ten patients.

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1 Remember, five of whom were savvy and knew about  
2 intensive care management. When she came into our  
3 research institute and after her biographer was  
4 calibrated, you can see documentation that her blood  
5 sugars were very high.

6 But with free access to food and insulin  
7 and having frequent knowledge of her blood sugars, she  
8 was able not only to normalize her blood glucose  
9 safely, but to sustain it in the normal range with  
10 remarkable stability.

11 It was the opportunity to have access to  
12 frequently measured blood sugars in the process of  
13 having support from people who would know what to do  
14 with the glucose data. She then was able to normalize  
15 her blood glucose level.

16 This slide has previously been shown to  
17 you by Dr. Pitzer. He showed to you two time points  
18 where the blood sugars were incredibly normal, a pre-  
19 lunch and pre-dinner blood sugar of 80 and 121  
20 respectively.

21 Now, a clinician would look at this  
22 glucose diary and say to the patient that she or he is  
23 doing very well. And therefore, the patient would not  
24 have to come back for several months and to continue  
25 to do everything exactly as the patient was doing

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1 without change in medication or therapy.

2 Dr. Pitzer then showed you what the  
3 GlucoWatch Biographer would have shown us had we had  
4 the opportunity to know the glucose patterns in  
5 between the pre-lunch and pre-dinner numbers. You can  
6 see the long periods of time the patient is in  
7 sustained hyperglycemic levels.

8 With this new information, physicians  
9 would not have concluded that the patient was doing  
10 well and could have counseled them on ways to improve  
11 their glucose control.

12 While certainly some degree of accuracy in  
13 the test method is important, what is more important  
14 for achieving good glucose control is the access to  
15 frequent glucose information.

16 Almost two decades ago, when self blood  
17 glucose monitoring was being developed, we were a part  
18 of the pilot programs to use these tools and  
19 techniques in insulin dependent Type 1 diabetic women  
20 who were pregnant. We were using machines with  
21 accuracy such that values were absolutely random when  
22 the blood sugar was less than 75.

23 In addition, these early machines could  
24 not accurately measure a blood sugar greater than 150  
25 mg/dL. With these machines, using blood sugar

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1 monitoring around the clock eight to ten times a day,  
2 we were able to bring the blood sugars into the normal  
3 range and published how normalization of blood glucose  
4 using self blood glucose monitoring could achieve a  
5 normal outcome of pregnancy.

6 We then applied these tools and techniques  
7 to non-pregnant persons. We were able also to show  
8 that self blood glucose monitoring around the clock  
9 could achieve normalization of blood glucose even when  
10 the machines could not accurately blood sugars less  
11 than 70 or greater than 250 mg/dL.

12 In summary, with access to frequent  
13 glucose data even when using monitors much less  
14 accurate than is possible with the GlucoWatch, we have  
15 shown that glucose control is enhanced.

16 Dr. Edelman said that one of the potential  
17 concerns might be over treatment by patients  
18 unfamiliar with this much information. Actually,  
19 there's no data that shows that more information is  
20 harmful. Instead, data is starting to emerge that  
21 continuous access to glucose sensing may actually be  
22 safer in the unfamiliar setting than less data.

23 Today, many patients are perhaps  
24 blissfully unaware of what really is going on with  
25 their blood sugar levels. For many of these patients,

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1 the access to additional information on trends and  
2 patterns will be the motivation they need to learn  
3 what to do to improve their glucose control.

4 Since this device will only be used under  
5 physician supervision, this is surely safer than our  
6 current medical practices.

7 Another potential concern previously  
8 mentioned was the possibility of erroneous glucose  
9 results. Recalling the slide earlier by Dr. Potts,  
10 who pointed out that the error was 37 mg/dL for this  
11 one paired point looped on this slide, while an error  
12 of almost 40 mg/dL may seem high to some, the key  
13 message is the biographer and comparative values were  
14 exactly the same clinically.

15 Both numbers were too high. What is of a  
16 primary importance when evaluating the value of a  
17 glucose measurement is the clinical interpretation of  
18 the result. While admittedly the Clark Error Grid  
19 Analysis has been controversial and does have its  
20 limitations, its strength is that it clearly  
21 emphasizes the clinical relevance of glucose results.

22 Recall that the results of the error grid  
23 analysis for the Home Environment Study showed that 94  
24 percent of the paired points were in the clinically  
25 acceptable A and B regions, while only three out of

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1 nearly 3,000 paired points were found in the E region.

2           Despite the concern about errors that were  
3 observed in some individual data points and with some  
4 biographers in some of the studies, the error grid  
5 analysis shows that the overwhelming majority of data  
6 points produced by the biographer in this and other  
7 clinical studies would have provided clinically  
8 acceptable information to subjects and physicians.

9           A final concern was the temporary skin  
10 irritation that many experienced following the use of  
11 the biographer. In our clinical trials, we were  
12 seeing mild irritation in almost every patient at the  
13 moment we took the watches off.

14           This very mild irritation shown on the  
15 left-hand portion of the slide disappeared in 24  
16 hours. It was only the moderate irritation that took  
17 about 48 hours to disappear.

18           Each and every time I asked the patient  
19 how did it feel and what is your opinion about the  
20 discomfort of this irritation, and each and every  
21 time, and I quote, "This is nothing. It's absolutely  
22 nothing. I am desperate for watch. If all it takes  
23 is this mild skin change for a day or so, please give  
24 me a watch." End of quote.

25           And in fact, when I tried to prescribe a

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1 cream to minimize the irritation, none of the patients  
2 wanted the cream. They all said I was making a fuss  
3 over nothing.

4 Finally, I'd like to emphasize the  
5 difference and importance of both patterns and trends.

6 For many patients with diabetes, a retrospective  
7 analysis of longer term glucose patterns over time  
8 would be useful to the patient and the health care  
9 team as they look for ways to adjust and optimize  
10 their glucose control.

11 However, for other patients, or in some  
12 situations, as illustrated by these series of five  
13 days from one patient worth of data in the Home  
14 Environment Study, long term patterns are difficult to  
15 discern due to the day to day variability that is  
16 present.

17 In this case, however, the acute trend  
18 information could be helpful if you just look  
19 specifically on days two, three and five when the  
20 subject current was extremely hyperglycemic in the  
21 afternoon. With current, infrequent testing, these  
22 with end day trends may have gone easily undiscovered,  
23 resulting in missed opportunities for better glucose  
24 control.

25 In summary, it is vitally important that

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1 patients have this frequent information available to  
2 use as directed by their health care team. With the  
3 information provided by the biographer, patients can  
4 see the impact of their diet, medication and activity  
5 choices.

6 The benefits of having additional  
7 information from the GlucoWatch Biographer far exceed  
8 any risk. And thus, in conclusion, having this device  
9 will certainly make me a better physician. But more  
10 importantly, having this device available will mean  
11 patients can take better care of themselves.

12 Thank you.

13 CHAIRMAN NIPPER: Thank you.

14 Are there any concluding remarks from the  
15 sponsor at this time? Okay, the agenda calls for a  
16 question and answer period. Since we are somewhat  
17 over time and I'm sure many of us need a break, I will  
18 call a 15 minute break at this point.

19 We'll reconvene at ten minutes before  
20 noon, and we'll go directly into the FDA presentation  
21 at that time. Would the panel hold questions until we  
22 finish those two presentations?

23 Thank you. We'll adjourn briefly for  
24 about 15 minutes.

25 (Whereupon, the foregoing matter went off

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1 the record at 11:35 a.m. and went back on  
2 the record at 11:56 p.m.)

3 CHAIRMAN NIPPER: Thank you. The audience  
4 will come to order, please.

5 Our next presentations are from the Food  
6 and Drug Administration. The presenter will be  
7 Patricia Bernhardt.

8 Ms. Bernhardt, are you ready?

9 MS. BERNHARDT: I'm ready.

10 CHAIRMAN NIPPER: The floor is yours.

11 MS. BERNHARDT: Good morning, ladies and  
12 gentlemen. My name is Patricia Bernhardt. I'm a  
13 reviewer in the Division of Clinical Laboratory  
14 Devices and I'm the lead reviewer of the PMA being  
15 discussed today.

16 I would first like to acknowledge the  
17 review team for this PMA. The team was comprised of  
18 individuals from several offices in CDRH, as well as  
19 from several divisions within some of those offices.  
20 This helped to provide a broad range of expertise  
21 spanning many disciplines for the review of this  
22 device.

23 From the Office of Device Evaluation, in  
24 addition to myself, was Arlene Pinkos, Dr. Jean  
25 Fourcroy, Dr. Max Robinowitz from the Division of

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1 Clinical Laboratory Devices, and Hung Trinh from the  
2 Division of Dental, Infection Control and General  
3 Hospital Devices.

4 From the Office of Surveillance and  
5 Biometrics, Dr. Kristin Meier from the Division of  
6 Biostatistics. From the Office of Health and Industry  
7 Programs was Ms. Mary Lou Pijar, Ron Kaye, and Dr.  
8 Jack McCracken from the Division of User Programs and  
9 Systems Analysis.

10 And from the Office of Science and  
11 Technology, Dr. Victor Krauthamer from the Division of  
12 Physical Science and Dr. Keith Wear from the Division  
13 of Electronics and computer science.

14 Since the introduction of the first home  
15 test systems for glucose measurement, this technology  
16 has been a cornerstone in modern diabetic management  
17 and has provided patients and physicians with one of  
18 the most powerful and significant tools for improving  
19 outcomes in this important disease.

20 The merits of tight control with the use  
21 of home measurement systems were unequivocally  
22 demonstrated in the studies recorded in the Diabetes  
23 Control and Complications Trial. Results of this  
24 study have been extrapolated to management of patients  
25 with Type 2 as well as Type 1 diabetes, and have

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1 served as important grounding for both the diagnostic  
2 and therapeutic approaches and objectives being  
3 applied to dealing with this disease process today.

4 The introduction of safe and effective,  
5 minimally invasive or non-invasive techniques for  
6 monitoring glucose at home or at the bedside would  
7 have obvious profound potential impact for diabetic  
8 medical care.

9 This technology offers potential  
10 improvements in the quality of life, enhanced control  
11 through increased frequency of testing or access for  
12 testing in a broader range of patients, and the  
13 potential to develop new insights into both the  
14 treatment and biology of this complicated disease  
15 process.

16 It is widely known that many groups are  
17 working on various types of devices in this area of  
18 new technology, and the agency is committed to  
19 interacting with sponsors at any and all stages of  
20 development to help bring these important advances to  
21 market.

22 In addition, FDA is interested in working  
23 with sponsors on new tools to complement, supplement  
24 or eventually replace existing testing methodologies  
25 in the pursuit of better ways to manage and deal with

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1 diabetes.

2 We are here today to consider a device  
3 which uses reverse iontophoresis to generate a  
4 transdermal fluid and then provides glucose  
5 measurements on this matrix. The intended use is  
6 stated by the sponsor as follows:

7 "The GlucoWatch Biographer is a glucose  
8 monitoring device intended for detecting trends and  
9 tracking patterns in glucose levels in adults (age 18  
10 and older) with diabetes. This device is intended for  
11 use by patients at home and in health care facilities.

12 "The GlucoWatch Biographer is intended as  
13 an adjunctive device to supplement, not replace,  
14 information obtained from standard home glucose  
15 monitoring devices.

16 "The Biographer is indicated for use in  
17 the detection and assessment of episodes of  
18 hyperglycemia and hypoglycemia facilitating both acute  
19 and long term therapy adjustments which may minimize  
20 these excursions. Interpretation of biographer  
21 results should be based on the trends and patterns  
22 seen with several sequential readings over time."

23 Based on review of the data and  
24 information in the PMA application and on discussions  
25 with the sponsor, it is FDA's understanding that the

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1 device is for prescription home use; the device  
2 provides supplemental information that is not a  
3 replacement for blood glucose results obtained from  
4 standard home glucose monitoring devices;

5           Although real-time results are provided to  
6 the patient, insulin changes should not be made based  
7 solely on the biographer results; approximately 25  
8 percent of values differ from comparative glucose  
9 results by greater than 30 percent in an unpredictable  
10 pattern;

11           Inter-individual variation is high and  
12 unpredictable; mild to moderate skin irritation occurs  
13 in many patients; skipped readings and unexpected shut  
14 offs may occur due to excessive perspiration, jarring  
15 or dislodgement of the device from the skin;

16           A built in alarm will sound when there is  
17 a skipped reading or an unexpected shut off; and the  
18 alarm will also function as a low glucose alert when  
19 set at predetermined levels which should be 20 to 30  
20 mg/dL above the desired alarm level to prevent some  
21 hypoglycemic events from being missed.

22           In assessing this device, FDA is aware  
23 that there is a clear trade off in its use. The  
24 benefits of the device are the availability of a large  
25 number of readings either during the day or at night

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1 with minimal inconvenience and discomfort.

2 The limitation is that these readings are  
3 different from those which have been the tradition  
4 base for the management of diabetes. The biological  
5 benefits or drawbacks of glucose measurements in this  
6 new matrix are obviously incompletely characterized  
7 and not fully known.

8 These differences in performance between  
9 the GlucoWatch Biographer measurements and more  
10 traditional measurements have been demonstrated in the  
11 numerous clinical and nonclinical studies conducted by  
12 the sponsor.

13 The nonclinical studies have included  
14 linearity, precision, interferences, biocompatibility,  
15 EMI testing, electrical safety, software validation  
16 and verification, and numerous other assessments.

17 A total of ten clinical studies were  
18 conducted, which generated nearly 19,000 paired data  
19 points from over 1,400 device applications over a  
20 total of 25,000 hours of use.

21 These ten studies included four studies  
22 which were designed to determine the performance of  
23 the device in a variety of use situations from  
24 clinical settings to actual home use with a series of  
25 different calibrating and comparative blood glucose

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1 monitoring devices.

2 Another four studies were designed to  
3 investigate specific features or aspects of device  
4 performance. And there were two additional studies  
5 designed to evaluate skin irritation and sensitivity.

6 Out of these ten clinical studies, the  
7 Home Environment Study most closely reflected the real  
8 life use of the device. This study enrolled 129  
9 subjects at six clinical sites across the United  
10 States.

11 The sponsor also conducted several  
12 additional evaluations of device performance in  
13 African-Americans, in individuals with varying body  
14 mass index, Draize skin assessments, and alarm  
15 sensitivity.

16 Dr. Meier will now discuss several of  
17 these studies, followed by Dr. Fourcroy, who will  
18 discuss the skin irritation and sensitivity  
19 assessments.

20 DR. MEIER: Thank you, Pat.

21 Before I begin, I'd like to acknowledge  
22 the FDA review team for all of their help with this  
23 presentation. And in particular, Arlene Pinkos for  
24 putting together the examples.

25 May I have the next slide, please?

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1           I had planned to discuss the following  
2 topics; however, since the sponsor has already covered  
3 some of these, in the interest of time, I will omit a  
4 few of the slides that the panel members have on their  
5 handout.

6           I'm going to just say a sentence about the  
7 Home Environment Study and move directly to a  
8 description of the data, and with examples elapsed  
9 time plots, some of which you've already seen. I will  
10 discuss some of the primary results from the Home  
11 Environment Study, including both a missing data  
12 summary and a comparative analysis.

13           I will also discuss some other results  
14 from the Home Environment Study. Finally, time  
15 permitting, I will mention some of the precision  
16 results.

17           Following a successful calibration of the  
18 GlucoWatch, the GlucoWatch attempts a reading every 20  
19 minutes in the Home Environment Study. A finger stick  
20 result is taken every 60 minutes. A comparison data  
21 set is obtained from these results by pairing the  
22 GlucoWatch and the finger stick results when the  
23 finger stick occurs ten to 20 minutes before the  
24 GlucoWatch reading.

25           I'll be saying a little bit more about

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1 this data set later. Actually, if you'll hold on one  
2 second. Next I'm going to show you several time  
3 elapse plots, several which you've seen earlier. What  
4 we tried to do here is pick some plots that  
5 characterize the varying degrees of the GlucoWatch's  
6 ability to track finger stick results.

7 What I hope will become evident is that  
8 it's virtually impossible to develop just a few  
9 statistical summaries that adequately capture all of  
10 the different phenomena that you're going to see. So  
11 keeping that in mind, we'll move to the first plot and  
12 note that all these plots are from the Home  
13 Environment Study and represent one day's worth of  
14 data.

15 Here's a plot where there was fairly good  
16 tracking between the GlucoWatch and the finger stick.

17 The open circles here are the finger stick results.  
18 And then the solid dots are the GlucoWatch readings  
19 connected by the line.

20 Again, you can see there was fairly good  
21 tracking here. There is some additional information  
22 on these plots that I'm not going to focus on, but the  
23 sponsor did collect information on activity levels.  
24 And, in addition, the calibration point is also shown  
25 on this slide.

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1           There's an additional piece of information  
2 on this plot and that is down here. Necessarily, to  
3 have comparative results, we need to have paired data.

4           And it's important to stress that even though we have  
5 a lot of data on this plot, unfortunately we only had  
6 two paired points for this.

7           So we are basically not using a lot of the  
8 data here in our comparative analysis. Throwing out  
9 so much data is a limitation of all the analyses  
10 presented, but I want to stress this is not a  
11 criticism of what the sponsor did; instead, it is just  
12 the reality of the difficulties in trying to do a home  
13 use type study.

14           So again, it's important to keep in mind  
15 that in all of the subsequent analyses and summaries  
16 you see, we are discarding sometimes a lot of the  
17 data.

18           Next slide.

19           Here's another example where the  
20 GlucoWatch went down and up as the finger stick  
21 results did. And here we had more paired points from  
22 this data. We had eight paired points there. There  
23 were many examples with similar patterns.

24           Now I'd like to show you some of the other  
25 kinds of patterns that occurred. Here is an example

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1 of when the GlucoWatch is higher than the finger stick  
2 in portions. In this case, in the beginning and  
3 ending period. Whereas, in the beginning, it's still  
4 higher, but not quite as far apart.

5 Next slide.

6 Here is sort of an opposite example where  
7 the agreement in the ends is fairly close, but in the  
8 middle the performance -- or the agreement, I should  
9 say, is not as close. Here's a case where, across the  
10 board, the GlucoWatch results are higher than the  
11 finger stick results.

12 And there are similar examples when the  
13 GlucoWatch is, across the board, lower. What's  
14 interesting to note is that as -- looking at some of  
15 these plots, it's not clear that we can associate  
16 these kind of differences with an individual.

17 You might get a different performance on  
18 one day than you do from the next, and that's  
19 something that we'll discuss a little later on. Now  
20 here's probably an example of what we might call a  
21 "not so good" plot, and this actually exhibits three  
22 separate phenomena.

23 The first thing you see is that the  
24 GlucoWatch is consistently quite a bit lower than the  
25 finger stick results. This also shows the GlucoWatch

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1 skipping results. These regions where you don't see a  
2 lot of dots in between means that there are results  
3 that aren't being reported out; whereas, here's a  
4 region where there were readings every 20 minutes.

5 This skipping could be due to a variety of  
6 reasons. Could depend on activity level. It could be  
7 due to bumping, perspiration or the temperature at the  
8 watch site being too high or too low. The last thing  
9 you see on here is an example of an early termination.

10 Again, for various reasons, the watch may  
11 shut off and you'd no longer get any readings. And  
12 sometimes it might shut off as early as four hours,  
13 sometimes the very last hour. It just depends.

14 In this final example, you see again where  
15 agreement is fairly good across the range except right  
16 in one small area. What we don't know is what's  
17 causing this. Is this an aberrant finger stick  
18 result, or is this a failure of the GlucoWatch  
19 methodology to pick up a peak?

20 We don't know from the kind of data that  
21 we have here and I'm not sure it would be easy to even  
22 design a study to figure out the answer to that kind  
23 of question.

24 Next I'll describe how much data was used  
25 in the comparative analyses that I'll describe. There

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1 were 129 individuals enrolled, but 111 were used in  
2 the comparative analysis. Again, there is several  
3 reasons for this. One big reason is that you needed  
4 at least one paired point to include the subject.

5 That doesn't mean they had -- they might  
6 have had plenty of biographer readings; but again, for  
7 comparative analysis, we need to be sure that they  
8 match up with the finger stick results. This group,  
9 by the way, throughout I may refer to as the "efficacy  
10 population."

11 Now each individual wore the GlucoWatch  
12 for up to five days. Of the possible days, there were  
13 420 days that were actually used in the comparative  
14 analysis. In terms of the data points, there were  
15 multiple points taken per day per person. And of  
16 these 65 percent, we used 65 percent of the points in  
17 the comparative analysis.

18 I hope what you're seeing is this is a  
19 fairly complicated data set, and this is just one of  
20 the many data sets that were sent in with the  
21 submission. There's going to be three different ways  
22 that I'm going to describe results.

23 I'm going to describe them on a per  
24 individual basis, on a per day basis, and on a  
25 prepared point basis. Next I'm going to actually

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1 describe the -- first a missing data summary and then  
2 a comparative analysis on the available data. I'll  
3 begin with the missing data summary.

4 As we said earlier, the GlucoWatch failed  
5 to give a reading for several reasons. Here's a few  
6 of them. On 4 percent of the days, the GlucoWatch  
7 failed to calibrate. They did not get a successful  
8 calibration at all and there were no readings on those  
9 days.

10 This converts -- or is analogous to 16  
11 percent of the individuals in this study failed to  
12 calibrate on at least one day of the five days.  
13 Another reason for missing data is that the GlucoWatch  
14 shut off early. This occurred on 27 percent of the  
15 days.

16 Eleven percent of the days it occurred in  
17 the first four hours, another 11 percent in the second  
18 four hours, and 6 percent of the time in the final  
19 four hours of wear. This corresponds to 66 percent of  
20 the individuals who experienced a watch shut off at  
21 least once during their five day wear period.

22 There were 21 percent of the gluco results  
23 that were actually skipped. All days had at least one  
24 skipped results. That is, no one ever obtained all  
25 possible results.

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1           In summary, out of the 36 possible results  
2 per day, including the calibration point -- I probably  
3 shouldn't have included that here -- but including  
4 that point, there were on average 26 readings per day  
5 with a median of 28 readings per day.

6           Some additional statistics: 12 percent of  
7 the days had at most four readings, or 1/9th of the  
8 results possible; 20 percent had at most nine results;  
9 28 percent had at most 18; 45 had at most 27 results.

10          The other thing, as you saw from the plots, that the  
11 statistics don't capture is that these missing points  
12 did not occur randomly throughout; they usually  
13 occurred in clumps.

14          This next slide you already saw from the  
15 sponsor I just want to briefly mention. This shows a  
16 scatter of all the paired points between the  
17 GlucoWatch readings here versus the finger stick  
18 readings here.

19          The sponsor overlaid a regression line and  
20 appropriately used a Deming Regression. Sometimes  
21 people want to use Lee's Squared Regression and that  
22 is not appropriate because there's variability in this  
23 one -- excuse me, in the finger stick reading. So the  
24 sponsor did appropriately do a Deming Regression here.

25          Below we have a difference plot. This

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1 shows the difference between the GlucoWatch and finger  
2 stick readings versus the finger stick readings. What  
3 you see from this plot is that in the low finger stick  
4 reading area, the GlucoWatch tends to be higher.

5 And in the upper finger stick reading  
6 area, the GlucoWatch tend to be lower. This could be  
7 an artifact of the error in the finger stick result.  
8 But the point is, in all of our comparative analyses,  
9 the agreement's going to differ depending on where you  
10 are.

11 The bottom line means, therefore, that you  
12 need to stratify your results because there's -- the  
13 agreement isn't consistent across the board. And  
14 here's a table that just captures the same findings  
15 numerically.

16 Another plot you also saw is the same  
17 scatter points, same scatter plot, only this time  
18 we've overlaid an error grid on top. This grid, as  
19 was mentioned, was proposed by Clark and colleagues to  
20 assess the clinical significance of differences  
21 between a new glucose monitor and a reference method.

22 Again, the A and B regions here -- A is in  
23 here, B is here -- are regions that are considered  
24 good and acceptable, whereas these other regions here  
25 are ones that could adversely affect the patient.

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1 Typically, results are presented in a table that you  
2 see at the bottom of that graph, which, again, you  
3 already saw some of these results earlier.

4 Let me take this opportunity to point out  
5 some of the statistical concerns with presenting the  
6 results this way alone, and that is that the  
7 distribution of these percentages are highly dependant  
8 on the distribution of results.

9 If you tend to have a lot of patients in  
10 your study with a narrow range of glucose values,  
11 you're going to necessarily have low percentages in  
12 the C, D and E area. For this reason, we had asked  
13 and the sponsor did stratify all of the error grid  
14 results by finger stick glucose range.

15 And I think that you really need to look  
16 at the stratified results rather than these overall  
17 summary tables.

18 For this data, FDA focused on two types of  
19 measurements of agreement. The first type is based on  
20 differences and relative differences between the  
21 GlucoWatch and finger stick. These are more  
22 statistical numerical measures, if you will.

23 The error grid analysis is more of a  
24 measure of clinical agreement. The first measure we  
25 looked at is the percent of GlucoWatch results that

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1 were within 20 percent of the finger stick or within  
2 plus or minus 20 mg of the finger stick depending on  
3 whether you were in the hypoglycemic range or above  
4 that range.

5 A similar definition here, only expanding  
6 the definition in the greater than 80 range to be plus  
7 or minus 30 percent. As I said, the second measure we  
8 looked at is the percent of points in the A region or  
9 the A plus B region. The A region is very similar to  
10 this definition up here.

11 In fact, it's identical except for this  
12 little difference here. It points within 20 percent  
13 of the finger stick in the hypoglycemic range whenever  
14 the GlucoWatch is also in that hypoglycemic range.  
15 The A plus B region is a little more complicated, and  
16 the next plot is a graphical display of what these  
17 regions are.

18 This innermost region is the within 20  
19 percent or 20 mg criteria. These bold lines here are  
20 the within 30 percent or 20 mg in this low region  
21 here. And you can see I've overlaid the A plus B  
22 region here. These are definitely not the same.

23 And the A plus B region together allows  
24 for a lot greater differences than the statistical  
25 criteria here. The catch here is that a point here is

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1 considered numerically close, but clinically could be  
2 quite bad.

3 Of course, you could just be off by a few  
4 points and jump in or out of this A plus B region  
5 here. Here's an area where points might be  
6 numerically far, but clinically would not cause any  
7 kind of problem.

8 Here's some of the actual results using  
9 these measures. The key thing to note from this busy  
10 slide here is that when we used the criteria within 20  
11 percent or 20 mg, overall 61 percent of all the paired  
12 points, almost 3,000 total, fell in this region.

13 The other thing you see here is that these  
14 percentages are not constant over the glucose range.  
15 In the hypoglycemic range, usually the results are  
16 less. Here are the stratified error grid analysis  
17 results.

18 Again, you've already seen some of these  
19 results before. Overall, 94 percent of all the paired  
20 results were in the A plus B region. What is also --  
21 and you also see that again, in the lower glucose  
22 ranges as defined by the finger stick, you get lower  
23 percentages.

24 The A region -- when you look at the A and  
25 B region separately, you see that 60 percent

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1 were in the A region. This corresponds to the 61  
2 percent that you saw on the previously slide for one  
3 of the other measures, and the B region was 34  
4 percent.

5 Now one question is how do these results  
6 compare on a per individual basis? We know about all  
7 these points lumped together in one joint analysis.  
8 Can we condense this down to information on a per  
9 individual basis?

10 We had used very similar -- as the sponsor  
11 had done, come up with some example definitions of  
12 what you might consider a good tracker. These  
13 definitions -- you could come up with all kinds of  
14 definitions here. These are just two that we picked  
15 out.

16 And what you'll see actually is that the  
17 answer really depends on the definition here. If we  
18 define a good tracker to be individuals such that 80  
19 percent of all their paired results are within 30  
20 percent of each other, or 20 mg in the low glucose  
21 range, that's one definition you might look at.

22 Another definition could be the percent of  
23 individuals such that 90 percent of their paired  
24 points fall in the A plus B region. The reason I  
25 chose a 90 here versus an 80 is that the A plus B

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1 region is a much wider region, so I figured I'd be  
2 more strict on the percentage of points that needed to  
3 be in that region.

4 The bottom line here though is that you  
5 see if we use definition one, we see that 44 percent  
6 of the individuals are good trackers. Seventy-eight  
7 percent of the individuals are good trackers using  
8 definition two. And again, in the hypoglycemic range  
9 here, you see that the tracking ability regardless of  
10 the definition you use is less.

11 So the next question is could we predict  
12 who would be a good tracker? And the sponsor did a  
13 lot of types of analyses to try and look at that.  
14 What this led us to do first, however, is to look at  
15 good tracker days.

16 A good tracker day is -- again, I'm just  
17 adopting this definition one here. Eighty percent of  
18 the days paired results are within 30 percent of each  
19 other or within 20 mg. There were 58 percent of the  
20 days were considered good tracker days versus the 44  
21 percent on a per individual basis.

22 Next slide.

23 What we found when we used that  
24 definition, however, is that the performance was not  
25 necessarily consistent from day to day. In other

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1 words, on one day you might be a good tracker; on  
2 another day, you might not be a good tracker; and we  
3 weren't able to tease out anything that could predict  
4 this.

5 Here's a table where, if you just restrict  
6 to those individuals that had five days worth of data  
7 with paired results, there were 43 individuals. You  
8 see that two of the individuals had no good tracker  
9 days. On the other hand, five individuals had five  
10 good tracker days. Most, however, of the subjects, 74  
11 percent, had two to four good tracker days out of five  
12 possible.

13 Changing tunes a little bit here, we were  
14 also interested in whether agreement was consistent  
15 over the entire day of wear period. This is again a  
16 fairly busy slide here, but what you see the bold  
17 lines represent error grid results.

18 They are the percent of points in the A  
19 plus B region. The unbolded lines represent the  
20 percent of points that were within 20 percent or 20  
21 mg. The difference between solid versus dashed line  
22 is whether we looked at the entire glucose range or  
23 the hypoglycemic range as defined by the finger stick  
24 result.

25 What we see here, at least in three of

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1 these four plots, is that there is a decrease in the  
2 percentages over time. Actually, in all four cases  
3 here, the decrease was statistically significant. The  
4 question is, is there something else that can explain  
5 this?

6 And of course, the other question is, is  
7 this -- if there really is decrease here, is that  
8 clinically important?

9 The sponsor has already provided some  
10 performance statistics on the biographer alert  
11 function. What I would like to note about these  
12 estimates -- and in fact, some of this generalizes  
13 here -- is first, as we've been saying all along, the  
14 finger stick is not a perfect standard, so I've  
15 actually put the "sensitivity/specificity" terms in  
16 quotes here.

17 The second point -- and again, this is  
18 true of all these measures here -- is that they don't  
19 account for the missing data. For example, the  
20 percent of time that the device fails to give a result  
21 due to a skip or early shut off.

22 If skipping and shut off are related to  
23 these hypo or hyperglycemic events, we're basically  
24 not using that data to estimate the performance. So I  
25 don't have a simple way to adjust these estimates, but

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1 I think that we need to maybe think hard about how  
2 that affects these sensitivity/specificity estimates  
3 provided.

4 Finally, I'd like to just briefly mention  
5 some results from the precision study. This was just  
6 actually one precision study. Precision was looked at  
7 in several studies. This was the home use precision  
8 study. And the key thing here is that the way  
9 precision had to be estimated here is from differences  
10 of simultaneous readings from two different watches  
11 worn at different skin sites.

12 You can't take a duplicate or a split --  
13 the traditional split sample kind of reading here. So  
14 really this precision includes extra sources of  
15 variation. In this study, there were 21 subjects over  
16 two days, 42 biographer days, and 52 percent of the  
17 possible points were included in the analysis.

18 Some of the results include the  
19 variability between the pairs increases as a function  
20 of glucose range. In other words, the device appears  
21 more precise in the lower glucose ranges and less  
22 precise in the higher glucose ranges.

23 If you compute coefficients of variations  
24 or CVs for each individual, all of them were less than  
25 25 percent. If you're -- one way to summarize all of

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1 these individual results is to note what proportion of  
2 the individuals had CVs less than 10 percent  
3 or less than 15 percent, say.

4 Fifty-two percent of all the individuals  
5 had CVs less than 10 percent. And 86 percent of all  
6 individuals had CVs less than 15 percent. Again, what  
7 you see here is that as the glucose level increases  
8 here, fewer and fewer individuals meet that 10 percent  
9 criteria. So, in other words, it's less precise.

10 This concludes my statistical  
11 presentation. The next speaker is Dr. Jean Fourcroy,  
12 who will discuss skin irritation and sensitivity  
13 assessment.

14 DR. FOURCROY: Good afternoon, ladies and  
15 gentlemen, distinguished panel members.

16 My name is Jean Fourcroy, a medical  
17 officer in the Division of Clinical Laboratory  
18 Devices, and I've been asked to speak briefly  
19 regarding the safety of GlucoWatch, particularly the  
20 skin changes associated with this device.

21 Skin is clearly the largest and most  
22 interesting organ of the body and offers new  
23 possibility for the diagnostic world. We have learned  
24 much in the last decades regarding the permeability of  
25 the skin from occupational hazards and drug delivery

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1 studies.

2 The issues we are concerned with in these  
3 safety studies are erythema, irritation, edema and  
4 other skin changes. Erythema is compressed skin which  
5 impedes cutaneous blood flow to some degree and  
6 vessels dilate in response to the build up of  
7 metabolic waste.

8 Skin irritation can be produced by both  
9 mechanical friction and substances permeating the  
10 skin. The early work of John Draize while at FDA  
11 established the standards for the prediction and  
12 measurement of human dermal changes as well as  
13 systemic toxicity from topical applications.

14 His early work developed the Draize scores  
15 which have been modified for the measurement of  
16 changes in human skin -- for example, irritation and  
17 erythema. In most cases, erythema is scaled on a zero  
18 to four. No visible reaction to two; four, intense  
19 erythema, flaring beyond the site edge or necrosis.

20 Edema is also scored on a similar scale of  
21 zero to four with four having intense edema higher  
22 than one millimeter. The standardization of cutaneous  
23 measurements are accepted tools for measuring skin  
24 irritation and are the ones used in these studies.

25 The most important element regarding the

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1 skin changes are possible changes in the diagnostic  
2 efficacy of this product. Specifically, do the  
3 changes with skin irrigation, edema, vesicle or scar  
4 formation alter the diagnostic ability of the device?

5 The sponsor states that most subjects in  
6 the glucose watch studies experienced mild to moderate  
7 skin irritation at the extraction and adhesive sites  
8 after use of the device.

9 The proposed labeling includes a caution  
10 statement directing users not to apply the device to  
11 any site at which irritation remains from previous  
12 use, as well as recommendations for the management of  
13 the skin changes.

14 The objective of study PIR-23 was to  
15 evaluate the GlucoWatch Biographer's potential to  
16 cause irritation after a single 15 hour wear period.  
17 The protocol consisted of exposing the skin to a  
18 single 15 hour application of the active biographer  
19 delivering electric current.

20 Four active test systems were placed on  
21 the subjects, two on each forearm. Following removal  
22 of the active biographers, the skin sites were  
23 evaluated and scored on day -- 15 minutes post removal  
24 on days two, three, four, six and eight.

25 As you can see, there were a total of 103

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1 patients. There were only six African-Americans in  
2 this group from a total number. And of these, five of  
3 the African-Americans had diabetes.

4 There were no clinically meaningful  
5 differences in irritation rates between diabetic and  
6 non-diabetic subjects, according to the sponsor.  
7 However, there are a fair number of skin changes that  
8 clearly could affect the user and perhaps the  
9 extraction process.

10 No photographs were submitted. Objectives  
11 of study PIR-24 was to evaluate the active GlucoWatch  
12 Biographer for the induction of contact sensitization  
13 by repetitive application to the skin of human  
14 volunteers and to report any irritation observed.

15 They also used an adaptation of the Draize  
16 Patch Test. Active test systems were worn by each  
17 subject according to a randomization schedule. The  
18 application of the biographers consisted of an  
19 induction period with nine repetitive applications of  
20 the active test systems to alternating sites on the  
21 forearm for approximately three weeks.

22 A rest period following the induction  
23 period where the subjects did not receive any  
24 application of the active test systems for  
25 approximately two weeks, and a challenge application

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1 of the active test system to a naive site to test for  
2 reactions indicative of contact sensitization.

3 A hundred individuals wore a watch on nine  
4 occasions over a 21 day period for 14 hours. And two  
5 weeks later, a watch was applied for an eight hour  
6 period with all of the components of the active watch.

7 Note that this is a relatively short period of time.

8 Of these 87 who completed the study, ten  
9 African-Americans were in the study and six Native  
10 Americans to look for the contact sensitization or the  
11 iontophoretic electrodes glucose sensors and sweat  
12 sensors electrodes during the wearing periods.

13 The evaluations were made 48 and 72 hours.

14 Irritation was most prevalent in extraction area with  
15 the scores of one and two for erythema and edema.  
16 There were 17 occurrences in 13 subjects out of the 87  
17 who had a moderate blister at the site.

18 Fifty percent of all measured scores had a  
19 plus one erythema at the site with blank and active  
20 extraction. Fourteen percent of the scores were Type  
21 2 erythema. The data would suggest that there is a  
22 significant skin irritant effect by the system.

23 It is not clear if the skin irritation  
24 affects the glucose measurement in any way. And there  
25 was no documentation of the dermal changes by

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1 photography, nor was the performance of the biographer  
2 assessed in many of these studies.

3 In the last study, the Home Environment  
4 Study, it was done over a five day period, six sites,  
5 with a total of 129 diabetic patients enrolled. Each  
6 patient started at 7:00 a.m. They used a modified  
7 Draize scoring system on the last day of use of the  
8 system, day five in most cases.

9 And of these total of approximately 112  
10 patients with records, at least 52 to 60 percent had  
11 some mild erythema and/or edema. Forty-two percent  
12 had skin spots, spots with vesicles or spots with  
13 scar, eschars when evaluated on the last day.

14 And several of these patients were noted  
15 to have multiple spots such as 30 spots with vesicles  
16 or 35 spots with scab.

17 In summary, it's fair to say that anything  
18 on the skin will change the skin. We know there are  
19 race, gender and age changes in how the skin will  
20 respond. Much of the variability of using the skin as  
21 an electro osmotic extraction site will be overcome by  
22 the use of intra-individual calibration for 12 hours.

23 And though we do not know the effect of  
24 diurnal skin changes or efficacy over the device over  
25 this 12 to 15 hour period, the skin varies between

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1 race, gender and age, but individual calibration  
2 should reduce this variability.

3 There is unknown intra-individual  
4 variability across the 15 hours of use. And areas of  
5 abrasion, scars and intense erythema clearly should be  
6 avoided. It is not clear whether the performance of  
7 the device varies with skin changes, and there is no  
8 long term safety evaluation with this device and no  
9 pediatric studies.

10 Thank you.

11 CHAIRMAN NIPPER: Thank you very much.

12 Ms. Bernhardt.

13 MS. BERNHARDT: FDA is seeking panel input  
14 on how to evaluate and characterize performance of  
15 this device and in determining if additional  
16 information is necessary to establish the safety and  
17 effectiveness of the device for its stated intended  
18 use and also for suggestions on how to appropriately  
19 label it.

20 In light of this, FDA has the following  
21 questions. Question one: Do the data support the  
22 proposed intended use of GlucoWatch Biographer? If  
23 not, what adjustments and intended use or additional  
24 data to support intended use might be required?

25 Question two: What controls might be

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1 applied to this product to ensure safe and effective  
2 use? Some suggestions might be should the intended  
3 use be modified to recommend that GlucoWatch  
4 Biographer readings be used only to decide when extra  
5 finger stick testing is indicated?

6 Should real time readings for high and low  
7 GlucoWatch values be replaced by error codes? Should  
8 special educational efforts be put into place to  
9 ensure proper understanding of the use of the device  
10 and interpretation of the results?

11 A model for this might be the home use  
12 prothrombin time meters that were cleared with  
13 requirements for formal training of both physicians  
14 and patients along with proficiency testing to ensure  
15 that this training had been successful.

16 And are there appropriate labeling or use  
17 controls that might be appropriate for this device?

18 Question three: Study data suggests that  
19 mild to moderate skin irritation occurs in many  
20 patients, but it is not clear if the skin irritation  
21 affects the glucose measurement in any way. Should  
22 the performance of the device be assessed in  
23 additional studies of skin irritation and sensitivity  
24 as either a pre or post market condition of approval?

25 Question four: Should there be additional

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1 studies as either pre or post market conditions of  
2 approval on time and/or duration of wear, overnight  
3 wear, different patient populations, other endogenous  
4 or exogenous interferences, and any other potentially  
5 confounding items.

6 And question five: Since the device is  
7 known to occasionally skip readings and have  
8 unexpected shut offs, is the low glucose alert  
9 reliable enough to warn of hypoglycemic events,  
10 especially while sleeping?

11 I'd like to take this opportunity to thank  
12 the sponsor for their cooperation and assistance  
13 throughout each step of the review process. And thank  
14 you for your attention.

15 CHAIRMAN NIPPER: Thank you.

16 At this point, we are close to being on  
17 time if we skip the question and answer period for the  
18 FDA. If any of the panel has a highly focused and  
19 urgent question that they would like to pose to either  
20 the sponsor or the FDA, I would entertain it at this  
21 time.

22 Yes, Dr. Andrade.

23 DR. ANDRADE: I would like to --

24 CHAIRMAN NIPPER: Speak into the  
25 microphone a little closer, please.

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1 DR. ANDRADE: I'd like to ask if there's  
2 any mechanism by which the 4,000 capacity stored  
3 glucose readings can indeed be made permanent and  
4 transferred to the health care provider or to -- so  
5 forth.

6 And I presume that that's the case, but  
7 I'd just like to know one way or the other.

8 CHAIRMAN NIPPER: Identify yourself,  
9 please.

10 DR. PITZER: Yes, this is Dr. Pitzer from  
11 Cygnus.

12 CHAIRMAN NIPPER: Are you getting that on  
13 the microphone? Okay.

14 DR. PITZER: We indeed are in the process  
15 of developing such a capability to download the data.  
16 It's not part of the current application, but it is  
17 in development.

18 CHAIRMAN NIPPER: Thank you, Dr. Pitzer.

19 Dr. Everett.

20 DR. EVERETT: Was any of the data  
21 stratified based on the demographics, particularly the  
22 skin irritation data?

23 CHAIRMAN NIPPER: Is this directed at the  
24 sponsor?

25 DR. EVERETT: Yes.

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1 CHAIRMAN NIPPER: Please identify  
2 yourself.

3 DR. TAMADA: Tamada, Cygnus. The  
4 irritation data, in specific, has not been addressed  
5 to demographics. Some of the performance data has  
6 been addressed to demographics. That's something that  
7 could be done though.

8 CHAIRMAN NIPPER: Yes, Dr. Rosenbloom.

9 DR. ROSENBLOOM: Can the -- this is  
10 directed toward the sponsor. Can the rate of -- the  
11 alarm for the rate of drop of blood glucose be  
12 programmed, adjusted, as can the upper and lower  
13 limits?

14 DR. PITZER: Ken Pitzer again from Cygnus.  
15 The rate of decline alert is fixed at 35 percent. It  
16 looks back for the immediate preceding result and it  
17 will go back up to 60 minutes if there was a skip.  
18 The rate of decline that we selected was designed in  
19 order to enhance detection of really rapid decline, so  
20 we chose a lower level to be conservative, but it  
21 cannot be adjusted.

22 CHAIRMAN NIPPER: Yes, Dr. Manno. Make  
23 sure you get into the microphone, please.

24 DR. MANNO: Thank you. I have a couple of  
25 questions on the skin studies that were done starting

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1 with the precision studies, I think it was called,  
2 where you use the cadaver skin. Was there any type  
3 testing done, for example, before the testing began  
4 and after the testing ended to show any differences in  
5 the skin?

6 And was the skin all the -- shall we say  
7 the same age from death to time of use? And were the  
8 skin sites used all the same?

9 DR. POTTS: This is Dr. Potts from Cygnus.

10 The skin that we obtained was normally obtained from  
11 a skin bank, and so it was of a broad range of age  
12 demographics. As far as was the skin the same before  
13 and after, in each of these studies we made measures  
14 of what we call passive permeability; that is, not  
15 facilitated by iontophoresis or electro osmosis before  
16 and after.

17 And those measures were exactly the same  
18 decreased relative to the iontophoresis.

19 DR. MANNO: You had no EM studies?

20 DR. POTTS: No, we did not do EM studies  
21 on the cadaver skin.

22 DR. MANNO: While we're talking about the  
23 skin, I might as well ask another question. You  
24 mentioned shaving the site prior to use, and there's  
25 two different mentions in that stack of documents I

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1 had to read before I came.

2 One implies just to shave prior to  
3 application of the device. In another place it  
4 mentions a 12 or 24 hour wait. And then there's also,  
5 in the presentation today, use of the alcohol wipe  
6 prior to application of the device between the  
7 shaving.

8 At any rate, can you clarify this?  
9 There's also mention of use of electric shaver. I  
10 have done skin testing and I know that you get a lot  
11 of irritation depending upon how you shave. Can  
12 someone give me some advice on this -- clarification  
13 rather?

14 DR. PITZER: Yes, this is Ken Pitzer from  
15 Cygnus again. First of all, the need to shave is to  
16 ensure a good electrical connection between the device  
17 and the skin. Our experience is that you can shave  
18 either immediately before putting the device on;  
19 however, that may be associated with slightly  
20 increased irritation.

21 That's why we recommend that patients  
22 consider shaving the site 12 to 24 hours prior.  
23 Secondly, our experience has been that an electric  
24 razor has less disruption of the stratum corneum than  
25 a bladed razor, and once again is generally associated

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1 with less skin irritation after device use.

2 So the ideal and optimal method would be  
3 to use an electric shaver about 12 to 24 hours in  
4 advance, or select a site on your arm that doesn't  
5 have sufficient hair that it would interfere with the  
6 electrical connection.

7 DR. MANNO: Okay, are you recommending for  
8 blade shaving the use of dry shaving or with one of  
9 the shaving products?

10 DR. PITZER: To my knowledge, we have not  
11 considered a difference between the two, but we can  
12 look at it.

13 CHAIRMAN NIPPER: I think we'll let you  
14 look at that during lunch instead of --

15 (Laughter.)

16 Dr. Doumas, if you have an urgent  
17 question, go right ahead. But I hope we'll let that  
18 be the last one because I'm getting hungry.

19 DR. DOUMAS: I am, too.

20 I referred to the handout by Dr. Bernhardt  
21 about poor tracking. There were examples there where  
22 the glucose -- the difference is over 100, close to  
23 150 mg. I'm referring to page three and also page  
24 four in the diagrams.

25 Do you have any idea about what is this

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1 due to? Unless really we understand the nature of the  
2 problem, I don't think it can be corrected and I think  
3 it should be corrected, because what this patient is  
4 supposed to do, I mean when there is poor tracking?

5 Do you have any idea what is causing that?

6 DR. POTTS: This is Dr. Potts from Cygnus  
7 again.

8 I think it's important to keep in mind  
9 that in a number of those cases, as Dr. Meier has  
10 pointed out, it's difficult to distinguish which  
11 device is in error. Let's assume that the biographer  
12 is in error.

13 We believe that the indicated use suggests  
14 that if there is something unusual, you should verify  
15 that result with a home meter.

16 CHAIRMAN NIPPER: Thank you. We'll  
17 reassemble in an hour. And if the panel would  
18 approach the Chair, we'll discuss eating arrangements.

19 (Whereupon, the proceedings were  
20 recessed for lunch at 12:49 p.m.)

21

22

23

24

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A-F-T-E-R-N-O-O-N S-E-S-S-I-O-N

(1:53 p.m.)

CHAIRMAN NIPPER: The panel will come to order. The audience will take their seats, please. We're working against the clock and we'd like to give the sponsor and the FDA and the panel as much time as possible to --

(Whereupon, at this point in the meeting, one of the participants dislodged the taping cord, causing a gap in the recording.)

DR. RIFAI: Let me tell you what I'm thinking. It might be a better measure of the performance of the device if you look at just one device per patient, per individual patient, than looking at the total number of readings that were collected. And my question is, if you look at the subjects individually, how many of them -- what is the percentage in which a hypoglycemic response was totally missed by the biographer?

DR. PITZER: Let me see if I understand what you're asking. If we started with 111 subjects in the study, there were 160 paired points with a glucose below 70. So then we want to --

DR. RIFAI: What I'm trying to say is that

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1       although the device could have missed a few points and  
2       that would be reflected in the sensitivity; but in  
3       reality, if it beeps eventually, then it still  
4       achieved the purpose.

5                   DR. PITZER: I'm still not quite sure that  
6       I totally understand analytically how to respond. We  
7       looked systematically at the Home Environment Study  
8       and looked at each and every one of those 160 points  
9       and just looked at the entire day before we looked at  
10      the four readings, the biographer results that  
11      surround each one of these patients when the blood  
12      went below 70.

13                   We have looked at unpaired points where  
14      the blood glucose went below 70 to see what the  
15      biographer was doing around those, but that doesn't  
16      sound like it's quite what you're asking either. So  
17      this is the same chart that Dr. Potts just mentioned  
18      showing the relationship between selecting the alert  
19      level, for example, a level of 100 associated with a  
20      sensitivity of 75 percent.

21                   And if one wanted to get all the way up  
22      towards a 90-plus percent sensitivity, then you need  
23      to set the alert level in the 110 to 120 range.

24                   DR. RIFAI: I guess you need to have the  
25      pair or you will not be able to know for sure if it

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1 was really 70 or not.

2 DR. PITZER: Yes. That is the challenge.

3 If you'd go to slide six, Matt. Let me just speak  
4 briefly to this challenge of pairing. This is an  
5 accountability chart showing 160 points in that study  
6 that were paired points where the blood glucose was  
7 less than 70. There were actually a total of 247  
8 occasions when we have a One Touch reading below 70.

9 And this chart just shows you why  
10 different types of points would not be able to be  
11 paired with the GlucoWatch. For example, 26 of the  
12 blood glucose points below 70 occurred outside of this  
13 timing window that Dr. Potts and Dr. Meier described,  
14 where you need to be within 10 to 20 minutes of the  
15 GlucoWatch reading in order to be paired.

16 Thirteen of the low blood glucose readings  
17 actually occurred during the calibration, so we don't  
18 have a comparison to the biographer because we're  
19 going to set the biographer equal to that. Six  
20 occurred before the device was calibrated. Three  
21 occurred after a shut-off. Remember, the alarm will  
22 sound if the device shuts off. Eleven low blood sugar  
23 results occurred when the GlucoWatch skipped due to  
24 perspiration. And 28 low blood glucose results  
25 occurred when the device was skipping for some other

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1 reason.

2 If we go to the next slide, what we've  
3 done is gone back and again looked at the surrounding  
4 GlucoWatch readings to see whether this occasional low  
5 blood glucose would have been detected, which perhaps  
6 it's a little closer to what you were asking.

7 Looking first at those points that were  
8 just out of window, they were just slightly out of the  
9 timing window, if we look at the preceding and the  
10 following GlucoWatch results -- and for purposes of  
11 what I've shown here, assume that the low glucose  
12 alert level was set at 100 -- then 91 percent of those  
13 cases would have sounded the alarm. So even though  
14 it's an unpaired point, there's a high sensitivity at  
15 a low alert level of 100.

16 When we look at the perspiration results,  
17 the device has skipped due to perspiration, and we  
18 look at the preceding GlucoWatch reading and the  
19 following GlucoWatch reading, we see that 36 percent  
20 of them were associated with a glucose result from the  
21 GlucoWatch that was below 100.

22 However, remember that every time that  
23 there's a skip due to perspiration, the alarm will  
24 sound. Because we know that perspiration might be due  
25 to hypoglycemia, we make the same effort to notify the

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1 user, just as if we actually measured low blood  
2 glucose.

3 So if you consider a perspiration skip  
4 alarm as a positive alert, then sensitivity would be  
5 100 percent in this subcategory. And then, finally,  
6 readings that were skipped due to other data integrity  
7 checks. When we look at the preceding and the  
8 following GlucoWatch readings, 54 percent would have  
9 triggered the alarm if it was set at 100 mg/dL.

10 And that 54 percent is a little lower than  
11 what we see with the paired points, and that's  
12 because, as Dr. Meier mentioned, we tend on occasion  
13 to get a couple skipped points in a row. The user can  
14 configure the device to sound an alarm when there's  
15 any type of skip.

16 That's one of the user options. The alarm  
17 will always sound if there's a skip due to  
18 perspiration, and it's the user's choice whether they  
19 want the alarm to sound due to other skips. If you do  
20 a weight average of these categories and try to get a  
21 sense of overall sensitivity and unpaired results,  
22 it's right about 75 percent, which is the same as we  
23 saw in the paired points with the low glucose alert  
24 set at 100.

25 So our conclusion from this analysis has

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1       been that the sensitivity at unpaired points is not  
2       different than the sensitivity at the paired points.

3                   Is that helpful at all?

4                   DR. RIFAI:     Why did you ignore children  
5       and adolescents?

6                   DR. PITZER:        Could you repeat the  
7       question, please?

8                   DR. RIFAI:     Why was the device not studied  
9       in children or adolescents?

10                  DR. ACKERMAN:  Mr. Fermi.

11                  DR. FERMI:     Steve Fermi, Cygnus.

12                  Basically, we decided to concentrate our  
13       efforts to try to get the product to market as quickly  
14       as we could, and this was the population, of patients  
15       over 18, we decided to study first.  Certainly that  
16       study in that half of the population is one that would  
17       be high on our list if we get the product approved.

18                  DR. RIFAI:     Can you elaborate a little bit  
19       on the effect of smoking?  Because in most of your  
20       studies, you either -- if I recall -- didn't include  
21       smokers or, if they were smoking, asked them not to  
22       smoke throughout the study.

23                  DR. ACKERMAN:  Mr. Fermi, please.

24                  DR. FERMI:     Steve Fermi with Cygnus.

25                  Actually, there were only three of the

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1 studies where we specifically excluded people who  
2 smoke from participating. Most of the studies that  
3 were done in the Home Simulated or Home Environment  
4 Study allowed people to smoke during the course of the  
5 studies.

6 If you recall, we had a Home Simulated  
7 Study and a home use study particularly where they had  
8 five days of use, and there were no restrictions on  
9 activity. So although we didn't record for those  
10 people the times they were smoking and when they were  
11 not smoking, they were certainly included. Smokers  
12 are definitely part of this population.

13 CHAIRMAN NIPPER: Dr. Rosenbloom, go ahead  
14 and ask questions.

15 DR. ROSENBLOOM: One of our concerns in  
16 the deep south is humidity. No one has mentioned  
17 where the clinical studies were done -- by that I  
18 mean the geographical locations -- but I wondered  
19 whether there was any concentration of experience in  
20 the Mississippi Delta or Florida or places where the  
21 humidity 80 percent of the time is 80 percent or more?

22 Because this could be a problem both in terms of skin  
23 reactions and in terms of the perspiration failure.

24 DR. ACKERMAN: We had that concern as  
25 well.

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1           Mr. Fermi, again, would you comment on the  
2 locations of the clinical sites?

3           DR. FERMI:    Yes.    We did have a broad  
4 range of geographic locations for our clinical sites.

5       We actually had three sites in Florida:    one in  
6 Orlando, one in Ft. Lauderdale, and one in Miami.  We  
7 also had sites in Mesa, Arizona, and San Antonio,  
8 Texas, as well as throughout the rest of the country,  
9 a couple of sites in California, a site in Denver,  
10 Colorado, as well.

11           So I think we had a pretty broad  
12 geographic distribution.  There wasn't any attempt  
13 made to correlate data with average humidity.  When we  
14 looked site to site, we didn't notice any differences  
15 due to that.

16           CHAIRMAN NIPPER:    Other questions, Dr.  
17 Harrington-Falls?  Dr. Andrade.

18           DR. ANDRADE:    Just one.  This issue that  
19 the FDA presents about intra-individual variations,  
20 day to day and so forth.  Admittedly, I guess you  
21 don't have a lot of experience of that beyond what's  
22 in here.  But I guess the question is -- it's more of  
23 a curiosity question -- is there any particular  
24 hypothesis or set of hypotheses as to why some  
25 individuals are highly variable and others perhaps are

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1 not? You know, assuming this device is available,  
2 what sort of research studies can you foresee to get  
3 at some of those issues?

4 DR. ACKERMAN: Dr. Tamada, please.

5 DR. TAMADA: Okay. I think that I need  
6 just to clarify if you were discussing the question  
7 that Dr. Meier was discussing that subjects -- there  
8 was no difference. Subjects did not tend to show all  
9 good behavior or all bad behavior, that performance  
10 for a subject would be similar to that expected by the  
11 pool from all the subjects?

12 We did not, in other words, find that  
13 there were people who were consistently "good  
14 trackers" above that which would be expected by a  
15 random draw over the entire biographer-use population.

16 So we weren't finding a lot of subject effect.

17 It sounds like you're asking a different  
18 question.

19 DR. ANDRADE: Well, I guess -- let me just  
20 rephrase the question. And that is, if you find that  
21 people are very "bad trackers", what would be your  
22 hypothesis as to why they might be very "bad  
23 trackers"?

24 DR. TAMADA: Well, again, we believe that  
25 the tracking is on a per use basis, not on a per

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1 subject basis. We were able to identify a particular  
2 condition per use that was calibrated at very high  
3 blood glucose levels. Above 280 mg/dL was associated  
4 with poor tracking, and because of that, we restricted  
5 the use to below 280 mg/dL, and that's a per use type  
6 of criteria that we were using.

7 DR. DiGIOVANNA: Can I make a comment  
8 related to that?

9 CHAIRMAN NIPPER: Yes. Identify yourself.

10 DR. DiGIOVANNA: John DiGiovanna.

11 From a graph that Dr. Meier presented  
12 looking at performance by time of wear and from what I  
13 was able to extract with respect to that concept that  
14 there are people who are good trackers at some point  
15 and bad trackers at other points. Has there been some  
16 information derived to determine that the tracking --  
17 to exclude the concept of the bad tracking situation  
18 being related to the location of the application of  
19 the device?

20 And in particular, not necessarily the  
21 static location -- in other words, three centimeters  
22 from the wrist -- but that the individual wearing it  
23 on this particular day, if they had another monitor in  
24 another location, that one monitor might have been a  
25 good tracking monitor and the other monitor plus

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1 location might have not been so good.

2 DR. ACKERMAN: Dr. Tamada.

3 DR. TAMADA: There was a study --  
4 actually, three of the studies have two biographers  
5 applied on the same person at the same time. And the  
6 relationship between the two biographers was generally  
7 very good as far as the precision statistics.

8 There were certainly some distribution of  
9 some cases where one biographer might track better  
10 than the other, but I don't think I'm answering your  
11 -- what is the question specific to that?

12 DR. DiGIOVANNA: Yes. You're getting  
13 close to it. Is there a difference within the same  
14 individual with multiple biographers on different  
15 locations and, particularly, whether or not there's  
16 some information in that assessment within the same  
17 individual over time.

18 In other words, if you apply two  
19 biographers today and then we view that over a four-  
20 or six-week or x-period of time, do those two  
21 biographers consistently record the same for the  
22 different body locations?

23 DR. TAMADA: Yes. If you have two  
24 biographers at the same time going on the same day,  
25 the first thing is, they're going through the same

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1 activities and the same blood glucose excursions. You  
2 certainly find that those two biographers correlate  
3 better with each other in their own performance than a  
4 biographer on that person on one day and then on that  
5 person on the next day because they're undergoing  
6 different types of situations, different activities.

7 CHAIRMAN NIPPER: Any more questions?

8 DR. DIGIOVANNA: Yes. Since we didn't at  
9 lunch, is it possible to see and play with the device?

10 DR. ACKERMAN: Yes, it is. This will take  
11 a few minutes.

12 CHAIRMAN NIPPER: It depends on whether  
13 you have to shave. While we're waiting for the  
14 device, Mr. Reed, do you have comments or questions?

15 MR. REED: In the documentation that's  
16 provided, you have a list of medications that you  
17 tested against for reactions and problems. Most  
18 notably among that list was acetaminophen. I don't  
19 know if it's a "Beltway phenomenon," but most people I  
20 know have some form of headache every day.

21 (Laughter.)

22 How much problem is this going to be in  
23 getting your test results?

24 DR. ACKERMAN: Mr. Kennedy, if you could  
25 address that for him, please.

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1 DR. KENNEDY: We did do a separate study  
2 to assess, at least in a preliminary fashion, the  
3 effects of acetaminophen on the behavior of the  
4 biographer. Matt, could I have 3-42?

5 This study, which was conducted with only  
6 18 patients because we merely wanted to assess if  
7 there were any gross effects of acetaminophen on the  
8 comparisons between the biographer and the comparator  
9 meter. On Day One the entire group of 18 subjects in  
10 this study was assessed over a 12-hour period with the  
11 biographer with no acetaminophen administered.

12 This group was split into two different  
13 groups of nine subjects each for Day Number Two. The  
14 first group had acetaminophen administered 1.5 hours  
15 prior to the calibration so that its peak level would  
16 correspond to the time that the biographer was  
17 calibrated.

18 The second group of nine subjects, after  
19 about 5.5 hours of operation of the biographer, was  
20 also administered 1,000 mg of acetaminophen. The  
21 point of the study was to determine whether or not the  
22 effects of the acetaminophen could be seen in the  
23 comparison of Day Two to Day One.

24 Go to number three, Matt.

25 These are the results of the experiment.

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1 As you can see, the mean error, which would be the  
2 primary indicator of any differences in acetaminophen,  
3 on Day One for the entire group that had no  
4 acetaminophen was about 10.7 mg/dL.

5 The nine subjects on Day Number Two had a  
6 mean error of about 11.8, a difference of only about  
7 1.1 mg/dL between the biographer and the comparator  
8 meter. And, in fact, for those that received  
9 acetaminophen on Day Number Two, there was a mean  
10 error of 8.2. So it was actually lower by about 2.5  
11 mg/dL.

12 All of the other indicators were roughly  
13 equal. The mean absolute relative error of 20.4 for  
14 the 18 subjects, which partitioned into 16.3 or  
15 actually a lower mean absolute relative error on the  
16 days with the acetaminophen, and roughly equivalent  
17 percentages of points seen in the A plus B region.

18 We did a particular hypothesis test here  
19 in this study in an attempt to prove that that  
20 difference was less -- the effect of acetaminophen  
21 caused a difference of less than 10 mg/dL in the  
22 comparison between the biographer and the watch.

23 We could not prove that hypothesis, but  
24 additional analyses showed that the differences that  
25 you see here were pretty small. So we at least have

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1 preliminary indications that there's no effect of  
2 acetaminophen.

3 The decision as to what to put on the  
4 label about this is up to you and the agency.

5 MR. REED: Continuing with some of the  
6 drug interactions or potential ones, you had a list.  
7 Some of the things I recognize, some of the things I  
8 didn't. Couldn't find my drug guide to check them  
9 out. Many of us diabetics have a litany of  
10 complications that require certain medications, things  
11 like neuropathy, things like that.

12 There's also a fairly high incidence of  
13 things like thyroid and immune system problems with  
14 diabetics. Did you check those out as well?

15 DR. ACKERMAN: Yes. We evaluated a number  
16 of different drugs retrospectively and Dr. Potts can  
17 better address that problem.

18 DR. POTTS: Here's a list of the -- in the  
19 429 subjects, there were 253 different medications in  
20 the four clinical trials. These are the Accuracy,  
21 Home Simulated, Home Environment and the acetaminophen  
22 study.

23 These are the number of subject uses.  
24 Clearly, many subjects use multiple drugs, and so the  
25 total is greater than 429. We analyzed the results on

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1 five of the largest categories of these, and those are  
2 shown in slide four.

3 And here you see across the top we  
4 analyzed ACE inhibitors, statins, aspirins, diuretics,  
5 Vitamin C, and then these medications not taken during  
6 the study. And if you look across here, you can see  
7 that the results are identical across the board.

8 We did the same analysis with the other  
9 statistics and the results were the same, suggesting  
10 to us that there was no systematic effect of these  
11 drugs on this particular device.

12 DR. DiGIOVANNA: I assume those are oral?  
13 Because many of those preparations are -- many of  
14 those compounds are available in topical, over-the-  
15 counter preparations, certainly Vitamin C. Many  
16 people use Vitamin E on sore skin, particularly if  
17 they've been told to put some kind of cream on it,  
18 urea, a variety of those.

19 So this is -- am I correct?

20 DR. POTTS: These are oral drugs. This is  
21 Dr. Potts. Yes, these are oral drugs.

22 CHAIRMAN NIPPER: Okay. Other questions?

23 Mr. Reed.

24 MR. REED: One of the things that I guess  
25 disturbs me a little bit is the number of readings not

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1 available, whether it's from skip or whatever. Some  
2 statistics I read in some of the documentation: 3,233  
3 or 22 percent of the biographer readings were not  
4 available from 14,615 maximum possible biographer  
5 points.

6 It gives a number for "early shut-offs,  
7 skipped points by virtue of biographer's logic" -- I'm  
8 not sure I understand what that means --and "user  
9 error during calibration." I can pretty much figure  
10 that one out.

11 But what does "skipped points by virtue of  
12 biographer's logic" mean?

13 DR. ACKERMAN: This is for Dr. Tamada.

14 DR. TAMADA: Okay. As mentioned by Dr.  
15 Pitzer, we have various data integrity checks that try  
16 to examine each and every reading to determine -- to  
17 try to maximize the accuracy of that reading. And if  
18 something is found, such as the user was perspiring or  
19 a rapid change in temperature or other factors, that  
20 reading is removed to try to prevent that reading from  
21 being used by the user.

22 And so that is what the term "skipped by  
23 virtue of the biographer's logic" means. It was  
24 designed into the system. It is an intentional method  
25 to try to improve the reliability of the device.

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1 MR. REED: Okay. What would cause early  
2 shut-off?

3 DR. TAMADA: Early shut-off. Why don't we  
4 go to slide seven. Yes. Okay. The specific reasons  
5 for early shut-off. Right when the biographer is  
6 started up, we check to make sure that certain things  
7 have taken place; such as, there should be an  
8 AutoSensor in it, and so it will shut off if there's  
9 no AutoSensor in place.

10 We check the iontophoresis circuitry, the  
11 reference and biosensor electrode circuitry to make  
12 sure that they're operational. So that would be  
13 immediately at start up. During the monitoring  
14 period, there's a number of things that could cause it  
15 to shut off.

16 One is if the AutoSensor becomes  
17 completely disconnected. Second, if the device  
18 becomes disconnected from the user's skin. We monitor  
19 to make sure that there is a good electrical  
20 connection. Third, we make sure that the biosensor is  
21 connected.

22 So with every biosensor cycle, we check to  
23 make sure that the biosensor isn't shorted together or  
24 isn't disconnected. Probably the preponderance of the  
25 shut-offs are consecutive skips. So six skips of any

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1 type in a row will cause the biographer to shut off.

2 Excessive perspiration -- technically,  
3 it's 18 perspiration counts, which essentially means  
4 the user is perspiring for an extended period of time  
5 -- will cause a biographer to shut off. And, finally,  
6 at calibration, if there are six aborted calibrations,  
7 then the biographer will shut off.

8 MR. REED: Okay. And it does give you an  
9 alarm if it skips or shuts off?

10 DR. TAMADA: Yes. It gives an alarm if it  
11 shuts off. Now, the skip alarm is somewhat setable by  
12 the user. It always alerts for a perspiration alert,  
13 for a low blood glucose or out-of-range low, high  
14 blood glucose or out-of-range high.

15 But for some of the other skips, like skip  
16 date and skip temp, it's user setable. You can set it  
17 to "all", where it would notify, or "most" where it  
18 will notify for the critical ones: perspiration,  
19 shutting off, high and low glucose.

20 MR. REED: Okay. You also said in one  
21 place that "the study results demonstrated an  
22 important lag between BG measurements and the  
23 biographer readings. In addition, qualitative review  
24 of the tracking plots show that the lag varies  
25 depending on whether glucose levels are rising and

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1 falling."

2 Can you explain or elaborate on these two  
3 statements?

4 DR. ACKERMAN: Yes, sir. This also would  
5 be an issue that will be discussed by Dr. Tamada.

6 DR. TAMADA: Okay. I'm sorry. Could you  
7 repeat the first question? Elaborate on the lag time?

8 MR. REED: Yes, it says, "The study  
9 results demonstrate an important lag between BG  
10 measurements and the biographer readings. In  
11 addition, qualitative review of the tracking plots  
12 shows that the lag varies depending on whether glucose  
13 levels are rising and falling." Can you explain or  
14 elaborate?

15 DR. TAMADA: Okay. Why don't I start with  
16 the first question. Set 4, slide 4 explains a little  
17 bit more about where this lag time arises from. The  
18 components of the lag time from the blood measurement  
19 has two main components.

20 One we call the measurement lag, and the  
21 measurement lag is the amount of time it takes us to  
22 physically take the measurement. So this is at the  
23 midpoint between our two three-minute extraction  
24 periods here.

25 So we have this point here plus the last

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1 seven-minute biosensing period. So the biographer  
2 requires 13 and a half minutes to extract the sample  
3 and make the biosensor measurement. So this is a  
4 measurement lag and it's fixed for the biographer.

5 The second part would be the physiological  
6 lag of glucose going from the blood to the  
7 interstitial fluid. And from the literature, there's  
8 a variety of values, but they tend to average around  
9 five minutes between the blood and the interstitial  
10 fluid.

11 And so it's a combination of the  
12 physiological lag and the measurement lag that will  
13 contribute to the lag time, the effective lag that's  
14 seen in the biographer.

15 On the second question of the increasing  
16 and decreasing, that's a little more addressed to some  
17 of the fundamental literature on interstitial fluid to  
18 blood glucose. It's been found by, say, implantable  
19 sensors or microdialysis sensors in some cases.

20 It appears when the glucose is increasing,  
21 there's more of a lag than when it's decreasing. That  
22 is, the interstitial fluid actually can detect the  
23 decrease in glucose first, and that's believed to be  
24 because physiologically the glucose is consumed in the  
25 interstitial fluid.

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1                   And so it's thought that this might  
2 actually be a better indicator of what the person is  
3 going through physiologically than the blood because  
4 that's where the glucose is actually being used.  
5 That's based on literature of the interstitial fluid  
6 to blood equilibrium.

7                   MR. REED: Thank you.

8                   CHAIRMAN NIPPER: Thank you.

9                   Ms. Kruger, do you have questions for this  
10 sponsor?

11                  MS. KRUGER: A couple of questions.

12                  What are your plans for individuals with  
13 Type 2 diabetes that are on oral agents?

14                  DR. ACKERMAN: Dr. Pitzer.

15                  DR. PITZER: Can you clarify just a bit in  
16 terms of --

17                  MS. KRUGER: You haven't tested it in any  
18 individuals, except for Type 1 and Type 2 that are  
19 insulin using?

20                  DR. PITZER: Correct. All of our studies  
21 did involve patients on insulin primarily for the  
22 practicality of ensuring wider fluctuations in glucose  
23 levels during the study period so that we could  
24 hopefully get better data in terms of assessing the  
25 accuracy of the device.

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1           Again, Type 2 diabetics on oral therapy is  
2 a real obvious group that we're anxious to move  
3 forward into further studies, subsequent to the  
4 initial approval.

5           Did that answer the question?

6           MS. KRUGER:     I think Lois wants to  
7 comment.

8           CHAIRMAN NIPPER:   We had another comment  
9 from Dr. Jovanovic.

10          DR. JOVANOVIC:   In the concomitant drugs  
11 that our patients were taking, our Type 2s were 90  
12 percent of the time also taking oral agents.

13          MS. KRUGER:   That was my next question.  
14 Have you looked at the interference or potential  
15 interference with the multitude of oral agents that  
16 are on the market at this time?   And you're saying  
17 that you have, in fact, looked at that as well.

18          I've read labeling and books on education  
19 and what have you.   What do you foresee -- I've heard  
20 over and over again about intensive education.   How do  
21 you perceive that?   What are you planning?

22          DR. ACKERMAN:   Dr. Pitzer.

23          DR. PITZER:   Well, I think it will take  
24 the form of a lot of different actual activities, the  
25 first key step being the prescription nature of the

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1 device and the ability then of the health care team to  
2 help us individualize the training needs of each  
3 patient.

4 So that will be a key part of it. We've  
5 gone a little bit beyond the typical instructional  
6 materials that come with the home blood glucose meter.

7 You've probably seen our user's guide. It's thicker.

8 There are more issues, a videotape, and so on, that  
9 goes with it.

10 And, recently, we've had conversations  
11 with the FDA review team about this idea of doing  
12 something similar to the home prothrombin testing,  
13 where there is some specific mechanism to ensure that  
14 each patient understands the key safety information.

15 And we've agreed to do that, and we would  
16 expect to work out the particulars with the agency  
17 team as we go through the details of the labeling.

18 MS. KRUGER: So that's still up in the  
19 air?

20 DR. PITZER: Yes. The details still are  
21 yet to be finalized.

22 MS. KRUGER: My one concern is that, as we  
23 move forward on all of these devices, which obviously  
24 are incredible for our patients, is that the devices  
25 become more sophisticated than the provider's

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1 knowledge. Not the patient, but the provider's  
2 knowledge. I have more confidence in the patient's  
3 use of most of these devices than I do the provider's.

4 And as you move into the Type 2 market,  
5 you have only ten or 15 percent, at the most, of those  
6 patients being taken care of by specialists like  
7 myself.

8 So my concern would be not just to train  
9 on the actual mechanics of the device; but once they  
10 have this multitude of data, then most of them aren't  
11 going to know what the heck to do with that, and so,  
12 as you move it out onto the market, that that be part  
13 of the training package.

14 DR. ACKERMAN: Dr. Pitzer.

15 DR. PITZER: Yes. We absolutely agree  
16 that the educational programs need to be both for  
17 patients and for health care professionals.

18 MS. KRUGER: Thank you.

19 CHAIRMAN NIPPER: Thank you.

20 Dr. Habig.

21 DR. HABIG: Based on the statistics of the  
22 home use study where you're measuring finger-stick  
23 glucoses hourly, I think it was -- there's probably  
24 not much, but I wonder -- is there any data -- did you  
25 collect data from home use at night? Was some of

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1 these through the night?

2 DR. ACKERMAN: Yes, there was, and Dr.  
3 Potts will address that issue.

4 DR. POTTS: Number 30, please, Matt.

5 We did this evaluation in the Home  
6 Simulated Study because we wanted people -- in the  
7 laboratory at night. There's a certain dilemma here  
8 of doing overnight testing when people have to wake up  
9 and make measurements.

10 So let me go through the overnight  
11 nighttime wear in the Home Simulated Study. And in  
12 this study, the subjects wore the biographer overnight  
13 in a clinical site. One hundred and six subjects  
14 calibrated the biographer at bedtime.

15 If the hypo or hyper alert alarmed during  
16 the night, a blood glucose measurement was obtained.  
17 Now keep in mind you had to get these people up and  
18 make a measurement quickly in order to pair these  
19 values.

20 So data were paired, if the HemaCue value  
21 was obtained at a time that could be paired. And I'll  
22 just verbally go through the answer here. We found  
23 that the frequency of skips was virtually identical in  
24 day and night.

25 We found that we had 36 paired values.

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1 Keep in mind, you know, some of the limitation was  
2 getting people up and getting a value quickly enough.

3 We had 36 paired values from these 106  
4 subjects. The correlation coefficient for those  
5 values was .98. The mean relative error was 16.4.  
6 The MARE was 18.7. I'm citing the same numbers that I  
7 cited this morning. And we analyzed the number of  
8 skips. And in both cases, the skips were around 15  
9 percent.

10 So, Matt, if you'd go to number five in  
11 this series, please. There we go.

12 We found that the alert sound is adequate,  
13 the frequency of skips is the same, fewer data skips  
14 occurred at night, more sweat skips occurred during  
15 the night. Accuracy was comparable, day versus night.

16 DR. HABIG: Okay. Then a follow-on  
17 question, which is maybe really what I'm trying to get  
18 at. You didn't do a study, I suppose, where you  
19 purposefully woke people up every hour so that you  
20 could have data points?

21 You only allowed the alarm to wake them up  
22 if -- so you could -- you don't actually have data on  
23 whether there were hypoglycemic events that were  
24 missed?

25 DR. POTTS: No. That is correct. We did

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1 not.

2 DR. HABIG: I don't know who you'd get to  
3 volunteer for that kind of a study.

4 (Laughter.)

5 DR. POTTS: Would you care to volunteer?

6 (Laughter.)

7 DR. HABIG: There's another question, but  
8 I won't answer it.

9 DR. ACKERMAN: May I interrupt for just  
10 one second? Because one of the questions that the  
11 agency asked the panel to consider is whether the  
12 sponsor had addressed overnight use. And we certainly  
13 believe that we've done a significant amount of work  
14 and have shown equal performance, overnight as well as  
15 during the day.

16 DR. HABIG: Another question I have in a  
17 slightly different area. The users in the Home Use  
18 Study used One Touch Profile meters. Were those  
19 meters their subject's usual meter or was that, for  
20 some of them, a new device which you trained them on?

21 And the last part of this multiple point  
22 question is, how confident are you in the home -- in  
23 those finger-stick meter results? What sort of QC and  
24 things were done about that?

25 DR. ACKERMAN: Mr. Fermi, if you can

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1 discuss that portion of the protocol.

2 DR. FERMI: Yes. We looked for subjects  
3 who were familiar with using the One Touch meter. I  
4 think in a few instances we actually got subjects who  
5 we even trained on it. We primarily looked for One  
6 Touch users. But we provided the meters, so we took  
7 all the manufacturer recommended precautions  
8 beforehand to be sure they were in proper operation.

9 DR. HABIG: And if you don't mind while  
10 you're still there, those meters might have been brand  
11 new meters or they might have been the meter that that  
12 subject --

13 DR. FERMI: No. They were all brand new  
14 meters --

15 DR. HABIG: They were all brand new?

16 DR. FERMI: -- that we provided.

17 DR. HABIG: Thank you. Okay, understood.  
18 Thanks.

19 Just one further question that's kind of a  
20 mechanical thing. The press that you use to apply the  
21 --

22 DR. ACKERMAN: The pressure?

23 DR. HABIG: Thank you.

24 (Laughter.)

25 Is there -- I guess I'll preface it by a

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1 comment. In people with diabetes who use insulin  
2 injecting pens, the typical instruction is push the  
3 plunger and hold for five seconds. And it's amazing  
4 how five seconds go by when you say "one, two, three,  
5 four, five" compared to "one thousand one."

6 Do you plan to do some kind of education  
7 about the ten seconds? Because I presume ten seconds  
8 is required, compared to one or two or three seconds,  
9 which might not be sufficient length of time for  
10 adhesion.

11 DR. ACKERMAN: Dr. Pitzer.

12 DR. PITZER: Yes, let me answer. There's  
13 kind of two questions in there. First of all, we set  
14 the ten seconds to be longer than what is actually  
15 required. So we studied the effect of pressure for  
16 five seconds, ten seconds, and up to several minutes  
17 in bench-top type of studies and then set it at ten  
18 because it was well above the minimum required.

19 And it turns out there's no effect of  
20 holding it shut for too long. But I agree, the more  
21 likely thing is people might not count to ten as  
22 slowly as perhaps they should.

23 So that would certainly be one of the very  
24 specific things that would be part of the educational  
25 program to make sure that each user clearly

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1 understands the importance and how to use the press  
2 correctly.

3 DR. HABIG: Great.

4 CHAIRMAN NIPPER: Thank you, Dr. Habig.

5 Did you have something you wanted to say,  
6 Dr. Gutman? Then we're back to Dr. DiGiovanna.

7 DR. DiGIOVANNA: A number of the issues  
8 that I read about in all of the documentation related  
9 to this concept of skin irritation associated with  
10 application -- I have a number of questions to try to  
11 get a clearer idea as to exactly what is going on and  
12 what the potential implications are of that.

13 And it was helpful to see the device, but  
14 perhaps you can start by giving us some more  
15 information about exactly what contacts the skin.  
16 From what I can see, it appears that there is, in  
17 effect, an adhesive surrounding the gel or the  
18 electrodes.

19 And what of the electrode, the gel, and  
20 the adhesive does actually contact the skin? And if  
21 possible, what are they made of?

22 DR. ACKERMAN: We will probably not go  
23 into what they're made of for proprietary reasons, but  
24 we will talk about contact with the skin.

25 Dr. Tamada.

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1 DR. TAMADA: Slide number nine of 40-A.

2 Okay, specifically what contacts the skin.

3 This is kind of the bottom view that would contact  
4 the skin. So this is the imprint. Here is what we  
5 call the mask. And the mask has an adhesive, a  
6 typical transdermal adhesive, and this helps keep the  
7 watch in place and keep it from moving. So that  
8 adhesive contacts the skin.

9 The other part that contacts the skin is  
10 the extraction areas. The hydrogel is on the other  
11 side, so with these holes -- through these holes, the  
12 hydrogel contacts the skin.

13 And then the plastic on the outer part of  
14 the tray contacts the skin, and also the two sweat  
15 detectors contact the skin. The biosensor does not  
16 contact the skin. It's on the other side of the gel,  
17 so there's no contact between the biosensor and the  
18 skin.

19 DR. DiGIOVANNA: I think the reason that  
20 this is of interest to me is because of the issue of  
21 contact sensitization. I did go through the studies  
22 that were done with respect to the standard approach  
23 to assessing contact sensitization.

24 With this device, I think there's a subtle  
25 difference, and that is that there's a current applied

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1 and there's this iontophoresis process going on.  
2 While I'm not an expert on iontophoresis, we do use it  
3 in dermatology occasionally as -- with an apparatus  
4 for hyperhidrosis to prevent -- basically, what we  
5 think is happening is we're preventing sweat from  
6 coming out of the sweat glands.

7 So the issue here really is that the way  
8 you're using this device is to enhance the reverse of  
9 penetration, to be able to extract. And by increasing  
10 the transit across the skin, there's several things  
11 that may be happening, one of which may be an enhanced  
12 delivery of various components the same way that the  
13 glucose is coming out.

14 For example, if a component of this  
15 apparatus is nickel, that's a rather common  
16 sensitizing agent. And one would expect that if one  
17 wore nickel apparatus or jewelry or watches for many  
18 years, one may or may not become sensitized to them.

19 I'm not quite sure what would happen under  
20 the influence of constant or very frequent  
21 iontophoresis of nickel or, for example, the agents  
22 involved in the adhesive. While most people who  
23 infrequently use tape and bandages don't get allergic  
24 to it; if we go into a hospital population,  
25 individuals who use bandaids all the time very

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1 frequently become allergic to the adhesives without  
2 any enhancing issues going on.

3 So I don't know if it's a fair question to  
4 ask you how to address it, but how would one approach  
5 this considering the fact that the standard tests  
6 really don't look at this kind of special situation?

7 DR. ACKERMAN: One response would be we  
8 have the same concern, and that's why we did what we  
9 thought was a very robust contact sensitization study  
10 and over 100 subjects. I agree that that was  
11 relatively short term, but it was still the one that  
12 most individuals or most companies use to address  
13 contact sensitization.

14 We've also done six-week studies in an  
15 extended wear. It was in a smaller set of  
16 individuals. But at least to this date, we have not  
17 seen contact sensitization in our studies.

18 DR. DIGIOVANNA: Can I ask, approximately,  
19 of the studies that have been done where you have  
20 experience with individuals wearing this apparatus for  
21 periods of time, what is sort of the longest and most  
22 frequent exposure?

23 I get a sense, from what I read from the  
24 literature, that this would be an intermittent use.  
25 However, some of the discussion I heard today would

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1 strongly suggest to me that for certain populations  
2 this would be an apparatus that people would want to  
3 wear daily for an extended period of time.

4 DR. ACKERMAN: Dr. Garg.

5 DR. GARG: Thank you, Neil, for asking me  
6 to respond to the question of the extended wear study.

7 My name is Dr. Garg and my title is  
8 Professor of Medicine and Pediatrics at the University  
9 of Colorado Health Sciences Center, and I'm also the  
10 Director of the Adult Diabetes Program at the Barbara  
11 Davis Center for Diabetes in Denver.

12 The extended wear study, specifically you  
13 asked, was done in Denver, which included 15 adult  
14 patients using the GlucoWatch every day on the forearm  
15 for six weeks. All the patients were asked to put on  
16 the watch, one watch a day every day for six weeks.

17 In addition to that, all patients were  
18 asked to return back to the clinic every two weeks for  
19 an all-day accuracy study. During that accuracy study  
20 day, the patient's forearms were inspected by me.  
21 And, specifically, all the patients were asked  
22 regarding skin irritation.

23 On the clinical examination, all patients  
24 -- I could only see the skin irritation which was  
25 relevant to the previous two to three days of the skin

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1 applications. I could not visualize any of the skin  
2 irritation which was pertinent to the skin  
3 applications of more than 72 hours ago.

4 And then I asked all the patients whether  
5 the skin irritation was any reason to not use the  
6 product. Every one of the patients said it was not a  
7 big deal at all if it's going to give me all the bulk  
8 of information that I need.

9 Thank you.

10 DR. DiGIOVANNA: Is there some data from  
11 that experience that would suggest that -- that's  
12 approximately 40 daily applications -- that towards  
13 the end of that period of time, when I would assume  
14 the device would be repeatedly placed over areas that  
15 have previously seen the iontophoresis and the device,  
16 that the accuracy was suffering compared to the  
17 earlier experiences when the device had been placed on  
18 new skin, skin that hadn't seen it before?

19 DR. ACKERMAN: Well, we can address the  
20 accuracy. And that might also might be a way that we  
21 can address the irritation issue.

22 Dr. Pitzer.

23 DR. PITZER: This is Ken Pitzer. Let's  
24 start with slide 4 from set 32 just to complete the  
25 skin irritation question.

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1                   These are the quantitative results  
2 relevant to Dr. Garg's description. What's shown here  
3 is the four accuracy study days across the six-week  
4 period: the very first day, Day 15, Day 30 and Day  
5 43. And on the Y axis we have the average score, and  
6 this is a one-to-four score.

7                   And we show in the blue bars the erythema  
8 score. And then the striped bar is the edema. And as  
9 Dr. Garg mentioned, the irritation results were  
10 similar to what was seen in other studies and there  
11 was no apparent change throughout the six-week study.

12                   In regards to performance, if we can go to  
13 slide two from this set. This slide summarizes the  
14 accuracy or difference statistics, as we call them,  
15 from Day one, 15, 30 and 43. And these are the means  
16 of the per biographer values.

17                   Again, the key thing here is that there's  
18 no apparent change in the performance of the device  
19 over the 43-day study period on any of these measures.

20                   The note at the bottom, as Dr. Tamada mentioned, we  
21 have discovered that when patients calibrate with a  
22 very high blood glucose greater than 280, we have seen  
23 greater error.

24                   So in this particular analysis, because  
25 there was one subject that calibrated high on three

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1 days, this is a small enough study that, with that one  
2 subject's data, it is quite impactful. So this is the  
3 one slide where we have taken that person out of the  
4 data set because the device, as described in the PMA -  
5 - those calibrations wouldn't have been accepted, so  
6 the data would not have resulted.

7 But we did not see in this study any  
8 change in performance over the 43-day period.

9 DR. DiGIOVANNA: Has there been an  
10 assessment somewhere, which I wasn't able to extract  
11 from the information that I had gotten, of the  
12 performance of the device when it's been placed on  
13 very hairy skin, or skin that's been shaved, compared  
14 to non-hairy skin, except for the adhesion  
15 characteristics?

16 And I guess my sense here is to try to  
17 develop some kind of a concept as to where best  
18 movement of glucose is really occurring, whether or  
19 not there is some component of transit in the hair  
20 follicles and sweat glands, which is kind of what we  
21 would expect more so than directly through the  
22 epidermis and stratum corneum, and whether or not that  
23 may be a way of explaining some of the performance  
24 changes that occur over time.

25 DR. ACKERMAN: An interesting point.

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1           Mr. Fermi, would you talk about -- do you  
2 have any comments relative to the protocol and looking  
3 at different levels of hairiness in a site?

4           DR. FERMI: I think there may be other  
5 members who can talk about that sort of design  
6 characteristic, if you will, and where the hypothesis  
7 is that this is coming from. What I can tell you is  
8 that all of our studies sort of removed that issue  
9 from consideration.

10           We did ask everyone -- who did have hairy  
11 arms to shave, so we don't really have the capability,  
12 I think, to do the kind of analysis that you're  
13 suggesting.

14           DR. ACKERMAN: Dr. Potts.

15           DR. POTTS: There has been a wealth of  
16 literature, and continues to be a wealth of  
17 literature, on precisely where things go through the  
18 skin under the influence of an electric field. I  
19 don't have enough knowledge to say where that is, and  
20 I'd be surprised if anyone does.

21           Keep in mind, the use of a one point  
22 calibration is specifically because there are  
23 variation in skin permeability, and that that one  
24 point calibration offsets the vast majority of that  
25 variation.

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1 DR. DiGIOVANNA: I think the reason for me  
2 to try to get a little better understanding of that  
3 again relates to the issue of performance of the  
4 device specifically over time. And as with many  
5 things when we study them in a very controlled  
6 situation, we get some information we believe we  
7 understand and then, when they're widely used under  
8 other conditions, things happen we don't very well  
9 understand.

10 Dr. Meier showed a nice table of  
11 performance by time of wear, and this sort of  
12 highlights several of the concepts that I think I've  
13 been reading about in much of this literature. One of  
14 the concerns that I have with respect to that is that  
15 there are several things that go on when one wears and  
16 removes this device.

17 One is a matter of redness and edema. The  
18 other is a matter of some small vesicular regions  
19 which may be related to hair follicles or sweat  
20 glands. And another physical mechanical change that's  
21 occurring in at least some individuals is an abrasion,  
22 a shaving that occurs in another way.

23 I think when conceptually one would apply  
24 this to intact skin, one could measure what would  
25 happen over time and the skin would likely remain

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1 relatively intact.

2 I would think that with repeated  
3 applications from the size of the device and at least  
4 in the population that would be interested in using  
5 this on a very frequent basis, there is a limitation  
6 on the number of places that you could put it without  
7 reapplying it to the same place.

8 And my real concern is that the mechanical  
9 issue of shaving, small breaks in the skin, and the  
10 healing of that over, for example, the 12 to 14 hours  
11 that would occur in application time or whatever  
12 changes occurred during chronic iontophoresis with  
13 respect to the skin -- we know that in the axillae we  
14 use it as a treatment to block the sweat glands.

15 So we know that we would expect changes  
16 over time. How this relates to the performance of  
17 that application on that skin over the duration of  
18 time -- for example, if someone were to put it on at  
19 night and at three in the morning would -- you would  
20 want a particular assessment, would that be the same  
21 in skin where this has been applied for three months  
22 and now you're applying it -- it's on a place where  
23 it's seen many times before versus not.

24 DR. ACKERMAN: Dr. Tamada.

25 DR. TAMADA: It seems like there's many

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1 questions in that, and I'm not sure I'm going to be  
2 addressing --

3 DR. DiGIOVANNA: I apologize for not being  
4 a little more clear about that.

5 DR. TAMADA: In terms of the  
6 reapplication, the actual extraction area, which is  
7 where the primary irritation occurs, they're actually  
8 one centimeter squared. So it is possible for the  
9 user to rotate sites.

10 And we see full recovery in 100 percent of  
11 the subjects generally by a week, and the absolute  
12 worst case in two weeks. And so with the size of the  
13 actual iontophoresis extraction area, that should be  
14 sufficient so the users don't put it on an old site in  
15 terms of just the surface area involved.

16 Clearly there's also an education issue in  
17 terms of people not applying to sites which already  
18 have irritation.

19 It seemed like there were other questions  
20 like changes during the 12 hour wear or --

21 DR. DiGIOVANNA: I think my -- one of the  
22 concerns was that during the performance time there  
23 are certain skin changes, for example, related to  
24 shaving that would occur and whether or not those  
25 would be expected to affect performance.

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1           For example, if you're instructing the  
2           wearer to shave immediately before applying the  
3           apparatus -- you know, most men who will shave with a  
4           blade will notice that occasionally they'll get skin  
5           irregularities or leave them with nicks and cuts that  
6           they can see and bleed, but there are probably many,  
7           many more that they can't see and bleed that are not  
8           of much consequence to them, but clearly can affect  
9           the skin barrier for a period of time in a variable  
10          way.

11           So that one hour post shaving and ten  
12          hours post shaving, there's a different effect on the  
13          barrier. And I don't see that as something that is a  
14          major issue unless one controls for that and knows  
15          whether or not that has an effect on the performance.

16           DR. TAMADA: Okay, we haven't addressed  
17          the shaving issue in particular. To clarify, most  
18          studies, just for standardization, it's requested that  
19          the site is shaved 24 hours in advance. This is to  
20          assess irritation.

21           It's a very specific protocol that we  
22          would use in animals and in humans so that the  
23          irritation doesn't have an artifact of the shaving  
24          itself. I'd say maybe Dr. Pitzer could talk about the  
25          user instructions for shaving.

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1           But, at any rate, in the Home Environment  
2 Study, of course people would have been doing variable  
3 things in shaving, using it according to the user  
4 instructions. I'm not sure I can --

5           DR. DiGIOVANNA: I think that's my point.

6           I think that you would expect -- the way I read at  
7 least the labeling, you would expect a wide variety of  
8 procedures to be used, and I think that that very well  
9 may or may not, but I can't extract from the data,  
10 affect the performance over a period of the subsequent  
11 ten to 15 hours.

12           I don't know, but -- and I think the last  
13 issue that I had really was with respect to -- again,  
14 I think the labeling where it suggests that the wearer  
15 apply a cream afterwards for areas that may be  
16 irritated, but it's rather nonspecific as to what they  
17 would apply.

18           If you go into any cosmetic or drugstore  
19 today, you'll find many thousands of additives,  
20 including things like urea and Vitamin C and Vitamin  
21 E, many of which may or may not affect the  
22 performance. And I don't think you want to test for  
23 all of those, but you may want to not be quite so  
24 general in what you recommend someone apply.

25           DR. ACKERMAN: Dr. Pitzer.

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1 DR. PITZER: Yes, I think the key point  
2 from the labeling perspective that we tried to do is  
3 to focus on not putting on any type of cream before  
4 use of the device at a site; but, during the recovery  
5 process for a given site, it may be of some palliative  
6 use.

7 So the focus there is trying to be on use  
8 of those type of things after as opposed to before so  
9 that we hopefully would not have any performance  
10 implications.

11 DR. DiGIOVANNA: One last question. Has  
12 there been any thought of using this on other body  
13 areas -- for example, using it on the ankle at night  
14 or places you might not necessarily want to read it  
15 all the time, but would give an increased area of sort  
16 of unused skin?

17 DR. ACKERMAN: Dr. Pitzer.

18 DR. PITZER: Again, that's an area of  
19 interest and perhaps future investigation, but not  
20 subject to the application at hand or the studies that  
21 we've done so far.

22 CHAIRMAN NIPPER: Thank you.

23 Dr. Janosky.

24 DR. JANOSKY: Yes, I'm trying to get  
25 around -- trying to understand some of the error in

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1 the system. Started this day with laryngitis, so  
2 hopefully we can sort of get through this. And I'm  
3 actually looking at the handout from Dr. Meier, and I  
4 was -- a request to the sponsor to address some of the  
5 issues that Dr. Meier had raised.

6 If I look at error within the system, you  
7 have two devices and it's only one device that is of  
8 concern for you, and that's your device. But your  
9 device is also measuring with error. And the device  
10 that you're comparing that against is measuring with  
11 error also.

12 So this leaves you in a quandary and to  
13 try to tease apart any nonagreement that you find and  
14 what is it due to. So that's the issue that I'm  
15 trying to get at, is tell me how much of that error is  
16 from your device and how much of that error is from  
17 the glucometer?

18 And to answer that question, clearly any  
19 other data that you might have available to help me  
20 understand that would also then -- it looks like slide  
21 ten and 11 from Dr. Meier. If you would also take a  
22 look at those to answer that question.

23 DR. ACKERMAN: We don't have copies of  
24 that, unfortunately.

25 DR. JANOSKY: You don't have a copy of it?

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1 DR. ACKERMAN: No, we do not.

2 DR. JANOSKY: Is Dr. Meier still here?

3 CHAIRMAN NIPPER: Give us a second and  
4 we'll put it up.

5 DR. JANOSKY: Okay, so just to go through  
6 it again, the short version of the question is trying  
7 to determine what percentage of error in the system is  
8 due to your device?

9 CHAIRMAN NIPPER: We'll need to kill that  
10 projector a little bit. There we go. Yes, just put a  
11 cap on it. That's fine. Thank you.

12 DR. POTTS: So -- this is Dr. Potts.

13 CHAIRMAN NIPPER: Is that the one you had  
14 in mind?

15 DR. JANOSKY: Yes, it is.

16 DR. POTTS: These are the data that both  
17 Dr. Meier has shown and we've shown in our  
18 presentation of the correlation between the biographer  
19 value and the comparative blood glucose value, in this  
20 case obtained with a One Touch Profile meter.

21 I'd like to, if possible, take that off  
22 and put one of our slides on, if I could.

23 And I would like, Matt, 19-2, please.

24 This speaks specifically -- thank you.

25 This speaks specifically to the sources of error. To

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1 our mind, there are four apparent -- there is apparent  
2 error due to four sources. Clearly, as you have said,  
3 the error in the device itself and the error in the  
4 calibrating meter.

5 And these are clearly relevant to the  
6 performance in the hands of the user. There are also  
7 these errors on the comparative meter and sample  
8 source and timing, which, while important to  
9 explaining how the device works and how people should  
10 use it, do not -- are not relevant to use in the real  
11 world.

12 And in fact, we believe that these lead to  
13 an underestimate of the performance of the biographer.

14 Now, it's very difficult, I dare say impossible, to  
15 parse out specifically all of these sources of error.

16 But let me talk to the comparative meter and, if I  
17 could, Matt, have slide four in this same series.

18 Four. Thank you.

19 This is a specific test that, in fact, the  
20 FDA suggested that we do to get at this question. And  
21 -- oh, yes, I'm sorry, speaking into the microphone.  
22 This is what's called the lab method comparison study.

23 It's a home simulated study where people were free to  
24 roam about except in those times when they had to  
25 report to the laboratory to take measurements.

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1                   They were literally free to go wherever  
2 they wished. We measured both cases using the One  
3 Touch as a calibrating meter, but we then compared the  
4 data either using the One Touch as the comparative  
5 meter or the YSI as a comparative meter.

6                   And you can see that the mean absolute  
7 relative error diminishes substantially where the only  
8 difference is the use of this YSI device. The same is  
9 true for all other metrics of scatter.

10                  DR. JANOSKY: Okay, so that's addressing  
11 that the error in the device that is not your  
12 device --

13                  DR. POTTS: That's addressing specifically  
14 the error of the comparative meter.

15                  DR. JANOSKY: Right.

16                  DR. POTTS: The calibrated meter is the  
17 same and the biographer.

18                  DR. JANOSKY: So you're roughly -- I think  
19 that's 17 and 21?

20                  DR. POTTS: Yes.

21                  DR. JANOSKY: Right. So it's 18, 19  
22 percent error within the other device?

23                  DR. POTTS: There are lots of other  
24 sources of error.

25                  DR. JANOSKY: Right.

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1 DR. POTTS: I mean, the timing issues  
2 and --

3 DR. JANOSKY: Right, but that's the first  
4 part.

5 DR. POTTS: And those I'd be welcome to  
6 suggestions as to how you exactly parse those numbers  
7 out. It's very, very convoluted.

8 DR. JANOSKY: Okay. I'm going to still  
9 have slide ten put up there in a second, --

10 MR. POTTS: Okay.

11 DR. JANOSKY: -- but not yet, not yet.

12 MR. POTTS: Okay.

13 DR. JANOSKY: Dr. Meier also presented to  
14 us precision study. I think it was her slide 24 and  
15 then it was concluded on her slide 25. And my  
16 understanding of the precision study, that that was a  
17 study that, for any one patient, they were wearing two  
18 of your devices and then you were looking for  
19 agreement between those two devices.

20 Now, based on -- we don't have any numbers  
21 presented in what she showed us today. Do you have  
22 numbers?

23 MR. POTTS: Yes.

24 DR. JANOSKY: Because she has statements  
25 here that lets me think that there's a fair deal of

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1 error within the agreement for your two devices.

2 MR. POTTS: Matt, could I have 6-2,  
3 please?

4 Oh, wait, do you want to show her data  
5 first? I'm sorry, have I preempted this?

6 DR. JANOSKY: It's her --

7 MR. POTTS: Yes.

8 DR. JANOSKY: -- slide 25. So again,  
9 we're still trying to get around the error within your  
10 device.

11 MR. POTTS: Yes.

12 DR. JANOSKY: That's the issue that I'm  
13 dealing with. Yes, that's it. From what I understand  
14 you presented to us here is actually very similar to  
15 the results that you showed for slide ten, that there  
16 does seem to be a variability given actual blood  
17 value.

18 So that there's probably more error in the  
19 system along different ranges. Is that the conclusion  
20 that you're presenting to us for the number one?  
21 Within your precision results, your very first  
22 conclusion is variability between pairs increases as a  
23 function of glucose range.

24 DR. ACKERMAN: Okay, this slide up there  
25 now is not a precision slide. The second slide is a

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1 precision slide.

2 DR. JANOSKY: Okay, so that first  
3 statement that you have up there, that's the statement  
4 that says that there is heterogeneity in terms of  
5 error across glucose values. Is that --

6 DR. ACKERMAN: Yes.

7 MR. POTTS: Yes.

8 DR. JANOSKY: Okay, so this is -- that's  
9 looking at it -- that's looking at patients that have  
10 two devices placed simultaneous readings --

11 MR. POTTS: Right.

12 DR. JANOSKY: -- right some variability?

13 MR. POTTS: Right.

14 DR. JANOSKY: Okay. Now if you then back  
15 to slide ten that she presented to us, slide ten is  
16 look -- not that same study. That's not the precision  
17 study. But that was what you were calling your  
18 pivotal study.

19 MR. POTTS: Yes.

20 DR. JANOSKY: Your pivotal clinical study.  
21 And even though you're looking at it quite  
22 differently, you come to a very similar conclusion in  
23 that there's heterogeneity of error given the blood  
24 glucose value if you place slide ten up there again.

25 DR. ACKERMAN: We agree.

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1 MR. POTTS: Yes.

2 DR. JANOSKY: Oh, you're agreeing?

3 DR. ACKERMAN: We agree. I mean, that was  
4 a major part of Dr. Potts' presentation.

5 DR. JANOSKY: Okay. So given those pieces  
6 of information, could you then go back and address the  
7 percentage of error that you're finding and what  
8 percentage is for your device?

9 DR. ACKERMAN: Dr. Potts.

10 DR. JANOSKY: All of those pieces of  
11 information that you just presented to me.

12 DR. ACKERMAN: Dr. Potts, maybe if you  
13 showed the precision data --

14 MR. POTTS: Yes.

15 DR. ACKERMAN: -- that we've generated and  
16 then try to contrast that with the error in the  
17 accuracy study that would help us.

18 MR. POTTS: If I could, please, have slide  
19 6-2. And I guess we have to turn the overhead  
20 projector on. First of all, I just want to point out  
21 that the differences in precision as measured by the  
22 biographer relative to conventional blood meters, this  
23 requires two different devices which also need to be  
24 synchronized quite closely.

25 So you actually have two samples at two

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1 different times which you try to synchronize. If I  
2 could see the next slide, please. These are three  
3 different studies, a laboratory environment and the  
4 accuracy study, a home simulated environment, and the  
5 home use, as in the home environment study.

6 And we've shown here the precision as a  
7 percent CV as a function of biographer range. As  
8 presented as a percent CV, these values all say that  
9 the coefficient of variation is 10 percent or  
10 thereabouts across the blood glucose ranges.

11 Furthermore, if you look at the next  
12 slide, which goes back to these values that we're more  
13 accustomed to looking at of mean absolute error --  
14 mean absolute relative error, you find that under  
15 these conditions where two biographers are compared  
16 head to head in synchronized mode, you find that the  
17 mean absolute relative error is somewhere in the range  
18 of 10 to 15 percent.

19 The mean -- I would try to put this in  
20 context of what you find with home use devices. And  
21 the mean absolute relative error for home use devices  
22 is in that same region. So I think you can get at  
23 this. The difficulty is this is a precision study,  
24 not an accuracy study.

25 DR. JANOSKY: Right, exactly.

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1 MR. POTTS: And there's some inherent  
2 intellectual risks in trying to go down that path.

3 DR. JANOSKY: So if we just sort of  
4 summarize what we know so far, you have about 10  
5 percent error within --

6 MR. POTTS: Yes.

7 DR. JANOSKY: -- the device when you  
8 compare it to a similar device?

9 MR. POTTS: Yes.

10 DR. JANOSKY: You have about 15 percent  
11 error in the other device, correct?

12 MR. POTTS: We're talking orders of  
13 magnitude here, yes.

14 DR. JANOSKY: So then what do you conclude  
15 for the peer error within your device?

16 MR. POTTS: Well, I'm still not sure that  
17 you can get at that number because there are other  
18 sources of error such as the dynamics and the timing  
19 issues that I'm at a loss to figure out how you  
20 absolutely de-convolute that information.

21 CHAIRMAN NIPPER: Thank you, Dr. Janosky.

22 We are -- in my main function as time  
23 keeper, we're headed toward about a 3:30 to 3:45  
24 break. Maybe our questioning could -- the rest of the  
25 panel could -- I don't want to truncate discussion at

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1 all, but let's aim toward that in the next few minutes  
2 wrapping up the questions with the sponsor.

3 Dr. Everett, fire away. Don't feel  
4 inhibited by my thinking about time, but I thought I'd  
5 just let you know what was on my -- I don't know what  
6 kind of mean absolute relative error I've got in my  
7 time keeping, but let's try to keep on track here.

8 DR. EVERETT: My question deals again  
9 around how well the machine, the instrument itself,  
10 actually functions. That is, how does the precision  
11 and accuracy change as you move from the bench to the  
12 individual? That is, from the in vitro to the in vivo  
13 type of environment.

14 Not to just look at it the way you've been  
15 explaining, but whether the actual ability of the  
16 machine performance drops off as you move from a pure  
17 environment of glucose solution to one that you pull  
18 out of an individual.

19 How does the machine's ability to function  
20 vary as you move again from the bench to the  
21 individual?

22 DR. ACKERMAN: Dr. Potts.

23 MR. POTTS: I want to make sure, Dr.  
24 Everett, that I understand your question. You're  
25 asking how does the performance change from the

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1 laboratory experiments that I presented --

2 DR. EVERETT: Right.

3 MR. POTTS: -- early on to in reality, in  
4 real time?

5 DR. EVERETT: Yes, exactly.

6 MR. POTTS: I think the major difference  
7 is in terms of what I would call "ambient" conditions,  
8 ambient noise. Those experiments that I showed with  
9 linearity at the very beginning were designed to show  
10 how well the detection system can work if you control  
11 the ambient conditions.

12 We clearly cannot do that in real use  
13 environment. This is similar to the studies that you  
14 will see for many, many diagnostics where you find  
15 that there are laboratory studies demonstrating the  
16 inherent ability to make a measurement, which are  
17 always compromised as you go into field studies.

18 For example, changes in temperature,  
19 perspiration, people, banging the watch, things like  
20 that, impact, the quality of the data.

21 DR. EVERETT: Do you place a number on  
22 precision and accuracy?

23 MR. POTTS: It is -- I cannot. I honestly  
24 cannot give that number out. It's not possible to de-  
25 convolute all of that because you can't do a

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1 controlled experience in human use where you only vary  
2 temperature or you only vary perspiration or you only  
3 vary activity.

4 And that would be the only way to really  
5 get at these and properly, quantitatively analyze  
6 these sources of error.

7 DR. EVERETT: In the laboratory.

8 MR. POTTS: In the laboratory, you can do  
9 that. And if you cycle temperature, you can see  
10 changes in the measurement. And if you particularly  
11 rapidly recycle temperature, you can get changes in  
12 measurement.

13 DR. EVERETT: In the laboratory, can you  
14 put a number on precision and accuracy there?

15 MR. POTTS: The precision in the  
16 laboratory --

17 DR. ACKERMAN: Dr. Kersten.

18 MR. POTTS: Brian did those experiments,  
19 so he should answer that question.

20 DR. KERSTEN: My name is Dr. Brian Kersten  
21 and I'm Director of Analytical Sciences and Quality  
22 Assurance at Cygnus. We did these precision type  
23 studies using aqueous glucose solutions. The  
24 equivalent glucose concentrations were at 40 and 100  
25 and 400 mg/dL.

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1           The temperature that we controlled it at  
2           was between 20 and 25 degrees.     We used three  
3           AutoSensors.     We measured per 12 hour day per  
4           concentration for a total of ten days.   So we studied  
5           about 90 AutoSensors relative to the precision study  
6           in which we generated 2,160 total measurements of  
7           glucose per concentration.

8           From this data, we did the statistical  
9           analysis.   And as you can see, overall concentrations  
10          the percent CVs were equal to or less than 7 percent.

11          So on the bench top, we have very good precision.

12           DR.   EVERETT:       And you picked this  
13          temperature of what again?

14           DR.   KERSTEN:     It was between 20 and 25  
15          degrees.

16           DR.   EVERETT:     And why did you decide to  
17          pick that particular temperature?

18           DR.   KERSTEN:     That was our standard  
19          laboratory bench top testing environment.   So we  
20          wanted to be consistent in what we did.

21           DR.   EVERETT:     Did you do it at, let's say,  
22          normal physiologic temperature of the human body?

23           DR.   KERSTEN:     The in vitro -- Dr. Potts  
24          can comment.

25           MR.   POTTS:     We ran the in vitro skin flex

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1 experiments that I described to you at 32°C, which we  
2 believe simulates body temperature certainly. We've  
3 also done a precision measurement in that, and it  
4 follows over the same glucose concentration range, we  
5 get the same sort of values that Dr. Kersten just  
6 talked about in the order of 5 percent coefficient of  
7 variation over a long period of measurement at 32°.

8 DR. EVERETT: And then when you mention  
9 the concentration that you used -- I think it's 40,  
10 100 and 400 -- are those the actual concentrations you  
11 used?

12 MR. POTTS: Doctor, there are two  
13 measurements here. One is the bench top measurement  
14 and one's the in vitro measurement. And the 40, 100  
15 and 400 are what Dr. Kersten did.

16 DR. EVERETT: Set the bench, is that  
17 correct?

18 MR. POTTS: Pardon?

19 DR. EVERETT: So 40, 100 and 400 --

20 DR. KERSTEN: Could I see the slide back?  
21 Those were equivalent concentrations as we do it on  
22 the bench top. If I could have the slide.

23 DR. EVERETT: I guess in the interest of  
24 time, what I'm really getting at is how close can two  
25 numbers be before the machine can't tell the

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1 difference? Can it tell the difference between a 150  
2 mg/dL sample and a 160 mg/dL sample? Or must it be 40  
3 and 100, about 60 units apart?

4 MR. POTTS: Yes, it's difficult to answer  
5 that question unless you define in vitro or in vivo.

6 DR. EVERETT: Well, let's just take one at  
7 a time. It won't take a lot of time.

8 (Laughter.)

9 In the laboratory, the machine can  
10 distinguish between two concentrations. My question  
11 is, at what point can the machine no longer  
12 distinguish the difference?

13 MR. POTTS: Well, if you look at these  
14 data here, you would say that it --

15 DR. EVERETT: It's a little far for me to  
16 see, to be honest with you.

17 MR. POTTS: Okay.

18 DR. EVERETT: I wouldn't want to tell the  
19 world, but --

20 MR. POTTS: The data shown right here  
21 suggests that at 100 the standard deviation -- thank  
22 you, Matt -- that the standard deviation is 5 mg/dL at  
23 100 in this bench top experiment.

24 DR. EVERETT: And now in the individual,  
25 when we get to the human being, --

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1 MR. POTTS: Right.

2 DR. EVERETT: -- at one point they have  
3 150. At another point they may have 170 mg/dL. Can  
4 the machine tell the difference?

5 MR. POTTS: Go ahead, Janet.

6 DR. TAMADA: Well, the coefficient of  
7 variation for the human studies depending on the blood  
8 glucose range and the study ranged from four in a home  
9 simulated type of situation to around ten. Thirteen  
10 was the highest in a home use situation at high blood  
11 glucose levels.

12 So we're talking four to 13 versus that  
13 range was four to seven percent. So in vivo, I guess  
14 they would be saying there's somewhat less precision,  
15 but the coefficient of variation information --

16 DR. EVERETT: So you're saying when the  
17 numbers get less than 13 units apart, that is in  
18 mg/dL, the instrument can't tell the difference?

19 DR. TAMADA: In the high blood glucose  
20 range there at greater than 240 mg/dL, the percent  
21 change of 12.9 is a coefficient of variation between  
22 two biographers worn at the same time and a home use  
23 situation.

24 Home simulated and laboratory studies  
25 showed tighter numbers in that blood glucose range.

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1 DR. ACKERMAN: Dr. Pitzer.

2 DR. EVERETT: I'm not sure what the answer  
3 to the question really is that you just explained.

4 DR. PITZER: Your question, I believe, is  
5 if you had a value at 150, what would be the  
6 variation?

7 DR. EVERETT: Yes.

8 DR. PITZER: These results suggest that in  
9 the home use, the average coefficient of variation  
10 over that range would be about 10 percent. So at 150,  
11 you would have about 15 mg/dL variation.

12 DR. DOUMAS: No, no, no, 15 times two,  
13 right?

14 DR. PITZER: Plus or minus 15.

15 DR. DOUMAS: Two coefficients of  
16 variation, so it will be plus or minus 30.

17 DR. PITZER: Okay, yes.

18 DR. EVERETT: And as he mentioned, my  
19 question is do you think that's comfortable for a  
20 clinician to see a number where we have that kind of  
21 variation?

22 DR. EDELMAN: I think the question is,  
23 with the coefficient of variation, is that acceptable  
24 in a real world -- when you're prescribing insulin and  
25 sliding scales. And I think we actually did analysis

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1 where we actually designed sliding scales like the  
2 kind I showed and looked at how many times that this  
3 coefficient of variation would lead to a wrong insulin  
4 dose, either higher or lower.

5 And if you talk to most diabetologists,  
6 the ones on the panel, out in the audience, a  
7 difference of 10 to 15 mg/dL is a very small  
8 difference and we're actually pretty happy with that  
9 with our home glucose meters.

10 DR. EVERETT: This is twice that.

11 DR. EDELMAN: Well, you're going around a  
12 mean, so it's not -- like if the blood sugars 150,  
13 it's either going to be somewhere between 135 and 165.

14 And in that range, you're not making major different  
15 therapeutic doses. Now, maybe in the very low ranges  
16 it takes on much greater importance.

17 But if someone's blood sugar is, for  
18 example, you know, over 250, then it takes on less  
19 importance. But I think that we've been dealing with  
20 this degree of coefficient of variation in the real  
21 world now with the current glucose meters.

22 And it is a concern because there's no  
23 meter out there on the market now that's very  
24 accurate, and so we always have patients confirm or  
25 measure twice or check the visual strip on the back.

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1 But the difference of coefficient of variation of 10  
2 to 15 mg/dL is -- I'm quite satisfied with that as a  
3 clinician, and I feel very comfortable prescribing  
4 insulin doses based on the numbers.

5 DR. JOVANOVIC: It's actually why I  
6 quoted some very old data from our institute dating  
7 almost two decades ago when all we had available were  
8 machines that could tell us too low, just right, or  
9 too high. And with frequent blood sugar monitoring,  
10 it's possible, even with that kind of large glucose  
11 bracketing, to be able to target glucoses and achieve  
12 normalization of blood glucose.

13 As the machines were starting to give us  
14 the tools and techniques to have glucose bracketing so  
15 we could create sliding scales a little more  
16 accurately, we still made clinical decisions based on  
17 large glucose ranges because we realized that the  
18 accuracy of home blood glucose monitoring may not be  
19 perfect.

20 Therefore, clinically usually physicians  
21 will suggest that changes in behavior or insulin are  
22 based on blood sugars less than 70. So anything less  
23 than 70 you would do the exact same behavior on; 70 to  
24 about 140 would be about the same behavior; 140 to  
25 perhaps 240 would be the same behavior; and greater

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1 than 240 or 250 would be an alternative behavior.

2 And that's because we realize that the  
3 accuracy may be questionable. But even given those  
4 large glucose bracket ranges, we're able to achieve  
5 normal glucose control. So yes, the glucose  
6 variations we're seeing with the Biographer are  
7 sufficient to allow the clinician and the patient to  
8 achieve better glucose control.

9 DR. EVERETT: Okay, I only have a couple  
10 of other questions in the interest of times. One is  
11 the interference acceptances. That is, in a lot of  
12 diabetics, they generally end up on quite a few  
13 antihypertensive drugs, and then most will end up with  
14 cholesterol problems.

15 Both of these interfere with the ability  
16 of things to move across that membrane barrier that  
17 you will depend on in order for this instrument to  
18 work properly. My question is, have you looked at  
19 calcium channel blockers, cholesterol, and the ace  
20 inhibitors?

21 These are the three things in most all  
22 diabetics that create a problem with fluids moving  
23 across that membrane barrier.

24 DR. ACKERMAN: Dr. Potts.

25 MR. POTTS: 51-4, please, Matt.

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1                   This is Dr. Potts.    These are the data  
2                   that I showed a moment ago.

3                   Excuse me, Matt, could I have -- yes,  
4                   that's the right one.

5                   These are the data that I showed earlier  
6                   with respect to a large number of concomitant  
7                   medications taken by the people.    The 429 subjects  
8                   took 253 medications.        We divided those into ace  
9                   inhibitors, statins, aspirins, diuretics, Vitamin C,  
10                  and then those that did not take such medications.

11                  When we did the analysis, we saw no  
12                  difference between those who took these medications  
13                  and other groups of medications or those who did not  
14                  take medications.

15                  DR. EVERETT:    Okay, then my last question  
16                  is the stratification of the demographic data.    In  
17                  many studies, minorities represent a very small group.

18                  And then what you do with them gets swallowed up in  
19                  what the majority of the population results are.

20                  So did you stratify the data based on  
21                  race, or age, or sex and look at the -- how well the  
22                  instrument performed in those three different groups?

23                  DR. ACKERMAN:   Mr. Kennedy.

24                  DR. KENNEDY:    We did indeed stratify the  
25                  data by all of those things.    The two that did come

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1 out of the various analyses as having a significant --  
2 statistically significant difference was race and body  
3 mass index related to weight as opposed to the height  
4 component of body mass index.

5 We did a variety of analyses, including  
6 mixed model analyses of variants and a variety of  
7 other things to demonstrate this and to assess the  
8 clinical and statistical significance of the magnitude  
9 of the differences that we did see.

10 Matt, could I have 49-3?

11 These were the results of the estimation  
12 of bias from the Deming Regression Line between the  
13 African-Americans and the other -- all the other  
14 people combined. What we observed and what was found  
15 to be statistically significant was the bias at these  
16 various levels.

17 As you can see, what happens is that the  
18 bias is actually smaller in African-Americans at 50  
19 and 80 in the hypoglycemic range; about the same at  
20 100; and somewhat larger, but in the opposite  
21 direction, at 150 and 200 mg/dL.

22 Can I have number four in that series,  
23 Matt?

24 If you look at the percentage of subjects  
25 with 80 percent of their points in the A plus B

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1 regions of the error grid -- and again, we have  
2 selected those that maximize this difference to  
3 illustrate it as opposed to minimize it -- you'll see  
4 that there is a slight difference in terms of the  
5 percentages in the hypoglycemic range representing  
6 something similar to the table that we just saw with  
7 the smaller bias in the African-Americans than with  
8 the other races.

9 And we had 56 percent of the subjects as  
10 opposed to 42 percent of the other races, so the  
11 performance was slightly better in the hypoglycemic  
12 range.

13 DR. EVERETT: In which group?

14 DR. KENNEDY: In the African-Americans.  
15 So the performance was better in the African-Americans  
16 in the hypoglycemic range and slightly worse in the  
17 hyperglycemic range.

18 Why the difference? We examined the data  
19 a variety of ways to try to determine what might be  
20 the source of this difference.

21 And can I have number six, Matt?

22 Some of the things that suggested itself,  
23 but in the analysis of the data could not be proven to  
24 be the actual causes, is 70 percent of the African-  
25 Americans are Type 2 diabetics in this study as

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1       opposed to 33 percent for the other groups combined.

2               The median body mass index for the  
3 African-Americans in this study was 29.9 versus a  
4 slightly different 27.4. We examined the glucose  
5 range to see if there was a difference in the  
6 distribution of glucose values observed in the  
7 African-Americans versus the other groups to possibly  
8 explain why this race difference showed up.

9               Not really. Twenty-six of the points of  
10 the African-Americans were greater than 240 versus  
11 only 17 percent of the others, but it was inadequate  
12 difference that you see here to explain it.

13              We looked at the glucose levels of  
14 calibration for the two race groups and there were no  
15 differences there.

16              Can I have number seven?

17              I am forced to conclude that we were  
18 unable to determine, at least from the data in this  
19 study, why there were differences in the performance  
20 of the Biographer in terms of race. And we also saw  
21 the similar thing for body mass index.

22              The device works slightly better in  
23 heavier people than lighter people. However, the  
24 magnitude of the differences we saw were, we believe,  
25 quite small. And while we can't explain it, it's

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1 right there.

2 I don't know how more to explain it. The  
3 observed differences were slightly different  
4 performance, as I say, in the low glucose range.  
5 There were fewer differences, smaller differences,  
6 between the Biographer and the comparative meters in  
7 the low glucose range, were slightly worse in the  
8 higher range.

9 We were unable to find an apparent reason  
10 for this.

11 MR. EVERETT: Okay, thanks.

12 CHAIRMAN NIPPER: Dr. Manno, do you have  
13 further questions?

14 DR. MANNO: Yes, could I follow up on this  
15 --

16 CHAIRMAN NIPPER: Try the microphone.  
17 There you go.

18 DR. MANNO: Could I follow up with the  
19 gentleman who was just up here?

20 DR. ACKERMAN: Mr. Kennedy.

21 CHAIRMAN NIPPER: Mr. Kennedy, right.

22 DR. MANNO: Am I right in assuming from  
23 what you showed up there by dividing the groups into  
24 African-American and "other" is that you did not have  
25 enough of any one single race to give you a large

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1 enough sampling to compare them individually --

2 DR. KENNEDY: That's correct for the  
3 groups other than the African-American group. We had  
4 a small number of Native Americans and Asians and  
5 Latinos in the cohort. And we examined whether they  
6 were "poolable" with the Caucasians for the purposes  
7 of this analysis and they were.

8 DR. MANNO: Okay. Did you happen to have  
9 any demographic data on socioeconomic background of  
10 your subjects, as well as educational level?

11 DR. KENNEDY: I don't know.

12 DR. ACKERMAN: Mr. Fermi.

13 DR. KENNEDY: Steve would know that.

14 DR. MANNO: And did that -- if you did  
15 have, did that make any difference as to the outcome?

16 DR. FERMI: Steve Fermi. We don't have  
17 that data to be able to answer that question.

18 DR. MANNO: Okay. I have --

19 DR. ACKERMAN: Excuse me.

20 DR. MANNO: Sure.

21 DR. ACKERMAN: Dr. Pitzer.

22 DR. MANNO: Sorry.

23 DR. PITZER: Yes, let me just make one  
24 comment. Not in the clinical program, but in our  
25 human factors program, we did have several studies

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1 where we specifically recruited subjects with  
2 different levels of education and different age  
3 levels.

4 And when we were doing things like  
5 assessing the understandability of the instructional  
6 materials and the ability to physically operate the  
7 device, we had those types of subgroups analyzed and  
8 did not see significant differences, at least in  
9 understanding the instructions and operating  
10 physically the device.

11 DR. MANNO: Okay, that's what I was  
12 getting at. In that pile of material that I looked at  
13 before I came, I'll go back to that, there was a  
14 question that was addressed to you. And I'm going to  
15 have to give you the notation on the page. It was  
16 question 35 and the date on the page was 9/22/99.

17 And it was page 0-0044 and it had  
18 reference to QC check. And as I interpreted the  
19 comments there, that if you got a -- some sort of  
20 reading that was a non-reading, if you will, in terms  
21 of a numerical reading, that the user was to do a QC  
22 check and you referred to it as "functional  
23 performance."

24 Could you kind of describe what the person  
25 would have to go through with that at that point? I

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1 didn't quite understand what was going on there.

2 DR. ACKERMAN: Yes, Mr. Kersten. Dr.  
3 Kersten.

4 DR. KERSTEN: Yes, the purpose of the QC  
5 test is to check the performance of the AutoSensor.  
6 And to perform the QC check, what the user must do is  
7 they first apply the gel to the sensor with the  
8 AutoPress, after which they -- after they apply the  
9 gel, they start the test and this is followed by a 20  
10 minute conditioning period.

11 After the 20 minutes of conditioning, the  
12 watch will beep and alarm the user to apply the  
13 glucose solution. To apply the glucose solution, they  
14 need to first attach this test well to the laminate,  
15 which will stick to the adhesive and apply the glucose  
16 solution through the hole in this well.

17 So the test well serves two purposes.  
18 One, it will contain the glucose solution on top of  
19 the gel, and it will also make sure that you get an  
20 even spread over both of the gel discs. After this is  
21 applied, you then put a label over the hole to prevent  
22 spillage.

23 After the glucose solution is then  
24 completely added, this is followed by a 30 minute data  
25 collection period in which the glucose will react with

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1 the enzyme glucose oxidase and then, at the end of the  
2 test, which is approximately 50 minutes, produce a  
3 result.

4 So what you're testing here is basically  
5 is the enzyme alive and is the sensor capable of  
6 detecting the hydrogen peroxide that's detected. So  
7 when you get that reading, you're eliminating whether  
8 it's due to the AutoSensor or not.

9 DR. MANNO: Okay, now does that glucose  
10 solution and that test well come as part of the  
11 package that you --

12 DR. KERSTEN: It's a QC kit that is sold  
13 separately from the GlucoWatch Biographer. So it's a  
14 separate package and Dr. Pitzer could comment more on  
15 how we --

16 DR. MANNO: I didn't see any reference to  
17 that, and I might have missed it, in the labeling  
18 material that I read.

19 DR. PITZER: Yes, this is Ken Pitzer.

20 The proposed labeling recommends that the  
21 patient perform a QC test under several different  
22 circumstances. The first would be if the patient  
23 suspects that the AutoSensors may have been stored at  
24 extreme temperatures.

25 Second, a condition would be if while

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1 using a particular box of AutoSensors they experience  
2 a large number of skips or inability to calibrate the  
3 device. I think those are -- I'd have to look back at  
4 the user's guide to see, but those are both  
5 indications that perhaps that particular box of  
6 AutoSensors -- that the glucose oxidase in the gel  
7 discs has degraded, which would primarily happen due  
8 to prolonged exposure to high temperatures.

9 And then the instructions say before you  
10 use any more AutoSensors from that box, do a QC test  
11 with one of the AutoSensors from that box to determine  
12 whether that's a source of the problem.

13 DR. MANNO: Thank you.

14 And you do a one point cal on the  
15 instrument. At least this is my impression.

16 DR. ACKERMAN: That's correct.

17 DR. MANNO: I'm assuming that's at around  
18 the mid range area there, 240?

19 DR. ACKERMAN: Actually, there are no  
20 limitations on that except that it must be below 280.  
21 So anywhere below 280 would be acceptable.

22 DR. MANNO: Okay, what I'm getting at is  
23 that you, in your materials, say that it's usable for  
24 quantitation between 40 and 400. You also say that it  
25 tests out to 500. But if you're doing a mid line cal,

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1 aren't you kind of stretching it a little bit in terms  
2 of any readings above your cal point?

3 And also the fact that in your data  
4 presentation in your packet, you had some values that  
5 are read above the 400 level. And usually in  
6 quantitative laboratory work, one does not go beyond  
7 the limits of their standardization, let's say.

8 DR. ACKERMAN: Actually, the device is  
9 intended to read between 40 and 400, we did not do any  
10 analysis of points above 400 mg/dL. So --

11 DR. MANNO: Excuse me, go ahead.

12 DR. ACKERMAN: Okay. I'm not sure what  
13 data set you have found something greater than 400.

14 DR. MANNO: I don't know. I had a --  
15 (Laughter.)

16 DR. ACKERMAN: So do we.

17 DR. MANNO: But I just noticed that 442 in  
18 there. And it might have just been something that  
19 slipped in there, but -- okay.

20 DR. ACKERMAN: We're unaware of that.

21 DR. MANNO: Thank you.

22 That's all I have.

23 CHAIRMAN NIPPER: Thank you, Dr. Manno.

24 Dr. Doumas, you've been very patient.

25 DR. DOUMAS: Thank you. There are still a

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1 couple of questions left, Mr. Chairman.

2 I'm referring to the gram augment plot on  
3 page 13.051. It's been reproduced in a micrograph by  
4 Dr. Meier in slide ten. There are differences there  
5 between the biographer minus the comparative method  
6 against the average of the two values of 50, 100 mg/dL  
7 or above, which really are not quite uncommon.

8 Although I sympathize with the problems  
9 that you're having comparing values because you cannot  
10 take the sample that the glucose watch or the sensor  
11 gets out and analyzes, I would like to know do you  
12 intend to pursue this issue trying to minimize those  
13 differences?

14 Because, I mean, you have to agree with me  
15 that sometimes it could be very misleading to the  
16 person who is using really this instrument.

17 DR. ACKERMAN: I guess the best thing I  
18 can say is that we will be continually working to  
19 improve performance for many different of the  
20 characteristics, and that obviously would be one.

21 DR. DOUMAS: The second question is on  
22 page 13.055. First Table 632. First of all, I'd like  
23 to know the definition of "per biographer Deming  
24 Regression statistics." What exactly is meant by  
25 that? I've read it and read it and I've been unable

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1 to understand it.

2 DR. ACKERMAN: Mr. Kennedy.

3 DR. KENNEDY: Per biographer Deming  
4 Regression means that the points within a given  
5 biographer use were involved in the calculation of the  
6 Deming line. So each Deming -- the Deming line is  
7 calculated for each biographer individually.

8 DR. DOUMAS: What data are you using to do  
9 that thing?

10 DR. KENNEDY: The data that you -- the  
11 paired points that were collected during the course of  
12 a day, anywhere from three to 26 or 27 points within a  
13 day.

14 DR. DOUMAS: Then there is a problem with  
15 Table 632. For example, on site four, you have a mean  
16 of slope, a mean of 1.13 and a standard deviation of  
17 two. That means the slope is zero. Even one standard  
18 deviation goes to zero.

19 DR. KENNEDY: I'd have to see what you're  
20 referring to.

21 DR. DOUMAS: And also there are intercepts  
22 which are in hundreds or in thousands.

23 DR. ACKERMAN: If you give us just one  
24 moment, we'll see if we can project the slide.

25 DR. DOUMAS: Fine.

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1 DR. KENNEDY: I believe that the data you  
2 see in that table is taken over many, many different  
3 Biographer uses, 420 or so of them.

4 DR. ACKERMAN: Would you repeat again the  
5 page number?

6 DR. PITZER: 13055.

7 CHAIRMAN NIPPER: Would it be better if we  
8 want on to another question and then came back to  
9 this?

10 DR. DOUMAS: I have one more short  
11 question while you find the slide. You're talking  
12 about an unsuccessful calibration. What is meant by  
13 this? How a calibration could be unsuccessful when  
14 you take the value from a glucometer and you dial it  
15 into the other --

16 DR. ACKERMAN: Okay, before -- we do have  
17 the slide, so let's go to the first slide, the first  
18 question, and then we'll go to the second.

19 DR. DOUMAS: I cannot see from here, so I  
20 will read from my table here.

21 DR. ACKERMAN: Okay.

22 DR. DOUMAS: If you look at site four, it  
23 says slope mean value 1.13, standard deviation of the  
24 slope 2.00. That means the slope is zero. It's  
25 indistinguishable from zero.

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1 DR. KENNEDY: No, that's not a single  
2 slope. That's the mean of many different slopes.  
3 What it's saying is that each individual Biographer  
4 has its own Deming slope computed with anywhere from  
5 three to 26 points involved.

6 There's a great deal of variability on the  
7 per Biographer point.

8 DR. DOUMAS: All right, I've got it.

9 DR. ACKERMAN: Okay.

10 (Laughter.)

11 DR. DOUMAS: When you get 40 pounds of  
12 documents -- (laughter) -- no matter how many notes  
13 you keep while you review them, you have to miss some  
14 points. Okay.

15 DR. KENNEDY: I understand. It took us a  
16 year to produce these. It seemed reasonable to expect  
17 you to absorb it in a few days.

18 (Laughter.)

19 DR. DOUMAS: Yes, because the sensitivity  
20 varies from -- yes, the response of -- the last  
21 question is --

22 DR. PITZER: I'm just going to answer the  
23 aborted calibration question. Was that your last --

24 DR. DOUMAS: You said the -- you're  
25 talking about unsuccessful calibration. What is meant

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1 by this? Because you are introducing a value that you  
2 find by the glucometer. You dial it in.

3 DR. PITZER: Yes, the way the calibration  
4 process works is the five minute window opens up in  
5 advance of a GlucoWatch reading because we have this  
6 lag time between the GlucoWatch and the blood. So we  
7 time the calibration window to be in advance of the  
8 GlucoWatch reading, take a blood sample, enter it into  
9 the device, and then we have to wait for that  
10 GlucoWatch reading to be completed.

11 An aborted or an unsuccessful calibration  
12 occurs when the data integrity checks see a problem in  
13 that GlucoWatch reading. And unfortunately, we don't  
14 know that until the end of the GlucoWatch reading 15  
15 minutes later.

16 DR. DOUMAS: Okay.

17 Mr. Chairman, one more quick question.

18 Why does it take a three hour period to  
19 warm up? What is being warmed up in that case, the  
20 electronics?

21 DR. ACKERMAN: Dr. Tamada, please.

22 DR. TAMADA: Okay, the warm up period was  
23 determined by a set of development studies and three  
24 hours was taken as a very conservative amount where  
25 all the subjects would be warmed up. It actually

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1 should be less than that.

2 The actual -- what's going on during the  
3 warm up period is several things. One is, of course,  
4 the Biographer checks to make sure it's connected,  
5 attached to the person, the biosensors all work. The  
6 second is sensor conditioning. That is to bring the  
7 sensor into its equilibrium for the sensing process.

8 And the third is what we call skin  
9 conditioning. That's the application of the current  
10 across the skin causes a slow change in the resistance  
11 over time, and this change stabilizes in the case of  
12 the Biographer in usually about a two hour period.  
13 And three hours is very conservative in which all the  
14 subjects that we saw had stabilized.

15 DR. DOUMAS: Thank you.

16 CHAIRMAN NIPPER: I'd like to ask one  
17 question that pertains to Basil's question.

18 Dr. Clement, if you'd forgive me.

19 I wonder if you've thought of putting a --  
20 adding one more feature to the calibration, and that  
21 is since there's a fairly narrow window after warm up  
22 for you to do the calibration, I know that I'd have to  
23 set a timer or ask a significant other to kick me when  
24 it was time to calibrate.

25 Have you thought about just having -- once

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1 you apply it and start a timer on the watch itself so  
2 that when it comes time -- becomes time to calibrate,  
3 you give us a pre-beep and then -- maybe you've  
4 already done that and I missed it in the ten tons of  
5 paper.

6 DR. ACKERMAN: Dr. Pitzer, would you  
7 comment on that idea?

8 DR. PITZER: Yes, let me clarify a bit on  
9 that process. Put the device on, start it up, go  
10 about your daily routine. Two hours and 55 minutes  
11 later, the alarm will sound. Ah, okay. And that --

12 (Laughter.)

13 CHAIRMAN NIPPER: I thought I read the  
14 labeling and I didn't see that.

15 DR. PITZER: Well, I even tried to say it  
16 today, but I've been saying a lot of things.

17 CHAIRMAN NIPPER: Yes, it's in there?

18 DR. PITZER: From the time that alarm  
19 sounds, you have five minutes to get your meter out,  
20 do the test and enter the result into the watch. If  
21 you're driving your car or otherwise want to do it  
22 later, just hit a button. The alarm will shut off and  
23 20 minutes later the window will open up again so you  
24 can do it when it's convenient for you.

25 CHAIRMAN NIPPER: Does the meter do a

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1 count down?

2 DR. PITZER: Yes.

3 CHAIRMAN NIPPER: Elapsed time in reverse?

4 DR. PITZER: Yes, if you just press the  
5 down button during the warm up period, you can see how  
6 --

7 CHAIRMAN NIPPER: I won't take anymore  
8 time with that. You've covered it.

9 Dr. Clement, I'm sorry I interrupted you.

10 DR. CLEMENT: Oh, sure. Did you want to  
11 take a break?

12 CHAIRMAN NIPPER: No, we're stoic here.  
13 We're going to do it. Go ahead, Dr. Clement. Unless  
14 you're going to take an hour or something.

15 DR. CLEMENT: No, no.

16 CHAIRMAN NIPPER: Okay then.

17 DR. CLEMENT: First I'd like to  
18 congratulate the sponsors. This is quite a device,  
19 huge undertaking. And it's been incredible how  
20 forthcoming you are on all the data. Good, bad,  
21 whatever, it's great. It's the only way you can do  
22 it.

23 Have one very good question on the skin  
24 issues. You mentioned on one of the slides about  
25 eschars. We know that a lot of folks with diabetes

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1 can develop brown spots, discoloration of the skin  
2 when they have minor trauma to the skin.

3 Do you have any data regarding permanent  
4 markings, discoloration on the skin that may last  
5 longer than the 15 day window that you did your  
6 analysis?

7 DR. ACKERMAN: Maybe Dr. Garg, who ran our  
8 six week study, can comment on that.

9 DR. GARG: Dr. Garg from Denver.

10 When we did the six week study at our  
11 site, all of these patients who took part in the study  
12 were my patients. When I reexamined them for the  
13 subsequent visits, which are usually two to three  
14 months apart, you could not even make out that these  
15 patients had worn the GlucoWatch a month or two later.

16 DR. CLEMENT: This question is more about  
17 accuracy and all these other things. On the issue on  
18 sensitivity and trying to enhance the sensitivity  
19 using some of your decision-based information on using  
20 prior data, can you show that one slide where you show  
21 the difference in enhancing sensitivity by adding the  
22 previous sample and some of your other data?

23 DR. ACKERMAN: Dr. Pitzer.

24 DR. CLEMENT: I was very confused.  
25 Primarily, what does it mean when it says adding

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1 previous result, which obviously makes a lot of sense?

2 How was the plus 15 or the future result added? I  
3 know this is retrospective data.

4 DR. PITZER: Yes, let me try to explain a  
5 little better. The top bar would be looking at the  
6 paired glucose result. And ideally, our Biographer  
7 reading in the study would have been exactly 15  
8 minutes after the blood glucose reading.

9 So when we look at sensitivity and I say  
10 here plus 15 minutes, that means we're comparing the  
11 Biographer reading to the blood glucose result 15  
12 minutes earlier, or the Biographer result 15 minutes  
13 prior.

14 When we add the previous result, I'm  
15 talking about adding the -- I'm talking about adding  
16 the previous Biographer reading. So that was 20  
17 minutes earlier since the Biographer gives a reading  
18 every 20 minutes. And so now we're looking at the  
19 combination of the Biographer readings that were  
20 between five minutes before and 15 minutes after the  
21 blood glucose was documented to be less than or equal  
22 to 70 mg/dL.

23 So we're just adding as we go down the  
24 step here. And then the third bar we're adding the  
25 next Biographer result. So the one after the paired

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1 result. So now we're looking further out in time and  
2 we would now be up to 35 minutes from when the blood  
3 glucose was less than 70.

4 DR. CLEMENT: Okay, that's makes sense.  
5 One issue, from a clinical standpoint, for example, at  
6 nighttime, if you're trying to detect hypoglycemia,  
7 you don't have the privilege of knowing what the  
8 future blood sugar is. This machine cannot predict  
9 the future.

10 So it would be a great device if we could,  
11 but we can't do that. So I guess to enhance the  
12 sensitivity of the device, I guess the second bars  
13 would be sort of the maximal sensitivity because  
14 you're trying to identify --

15 DR. PITZER: Right.

16 DR. CLEMENT: -- an event at that point in  
17 time.

18 DR. PITZER: Right, that would be the most  
19 relevant. We'd ideally like to catch it at the paired  
20 result or, even better perhaps, 20 minutes before.  
21 And certainly that is the issue behind directing  
22 patients to set the low glucose alert level 20 to 30  
23 mg/dL higher than the point that they want to make  
24 sure it's detected.

25 DR. CLEMENT: The last question had to do

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1 I guess on your slides -- actually your slide 34 on  
2 the Biographer blood glucose range you're discussing  
3 how to raise the data either vertically or  
4 horizontally, and that was leading up to it.

5 And were you comparing the data to the One  
6 Touch Profile?

7 DR. ACKERMAN: Dr. Potts.

8 MR. POTTS: I'm not sure of your question.  
9 I understand which slide.

10 DR. CLEMENT: Right. Well, Dr. Meier's  
11 talked about in her presentation, that particularly  
12 when you look at the data vertically in terms of when  
13 you slide the data -- there it is, okay. Particularly  
14 looking at the lower end, 40 to 80, trying to  
15 determine the performance how good is this device on  
16 detecting a hypoglycemic event at that point in time,  
17 40 to 80 is pretty close.

18 I mean, we talked at 70 as sort of being  
19 the critical factor. Based on the One Touch Profile  
20 data, you know, we talked a lot about the sources of  
21 error and so forth, which can be corrected upwards a  
22 little bit.

23 The data we have, however, here, which is  
24 on the home use study, was that there was only 45  
25 percent chance of being within what's called the

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1 certified range or agreed upon range that we use.  
2 Using a calculation on the following slide from that,  
3 that showed that well if we had to compare it to the  
4 YSI data, that this number would potentially be  
5 better, correct?

6 How did you come to that calculation? How  
7 did you come up with that information?

8 DR. TAMADA: Okay, could I start -- is  
9 this the main presentation? Could you go back a few  
10 slides -- I don't know exactly which one -- to the  
11 stratified error grids? Just click back.

12 DR. ACKERMAN: This is Dr. Tamada.

13 DR. TAMADA: Click back 32, 31.

14 Okay, well I'll start by explaining the  
15 analysis a little while the slide is coming up.  
16 There's two analyses and they both address the  
17 question of low blood glucose, and they're both very  
18 important analyses, but one is addressing the question  
19 of low blood glucose, what happens when the person is  
20 low.

21 And the other one is addressing the  
22 question of low Biographer glucose, what happens if  
23 the person looks at the Biographer and sees the  
24 measurement is low.

25 The analysis on the low blood glucose was

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1 suggested, I believe by Dr. Meier, and it's a very  
2 nice analysis. It does two things. As Dr. Meier  
3 mentioned, it helps prevent the bias in the subject  
4 blood glucose population and it also separates the  
5 range into some clinically important intervals such as  
6 looking at the question when a person here is actually  
7 -- when a person here -- okay, this is a blood  
8 glucose, a comparative meter.

9 So here is where the person actually --  
10 between 40 and 80, they have a low blood glucose and  
11 what does the meter reading. And here on this axis  
12 the reading -- the meter is reading a certain range,  
13 how accurate is the blood glucose.

14 So there's an important issue brought up.

15 Can you put forward -- we're looking at the data that  
16 has a lot of numbers. Hard to read. Go forward one.

17 Okay, forward two more. No, that one. Okay.

18 This is the data slide I think you're  
19 referring to. Okay, so when we look at it by blood  
20 glucose range -- now this is when the user could  
21 potentially be hypoglycemic -- we see the results from  
22 a home environment study for in the low blood glucose  
23 range. Forty-five percent of the points have lower  
24 error.

25 When we do the study with the YSI as a

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1 comparative meter -- and this was also done in a home  
2 simulated environment. It wasn't done with sedentary  
3 subjects. The subjects were encouraged to move about.

4 We actually reduced the finger prick frequency to  
5 encourage the subjects to move about.

6 And so here we think we have an estimate  
7 of the analytical -- part of the error that might be  
8 from the analytical method and not related to the  
9 Biographer. So we see an improvement in that low  
10 glucose range.

11 But you can see it's still lower, so  
12 there's still a question in this low blood glucose  
13 range. Now one of the suggestions is to limit the  
14 Biographer reading range. And so, to investigate  
15 that, we have to stratify in the other direction.

16 Because if we're stratifying by blood  
17 glucose range, we're saying okay, the user has to have  
18 a finger prick value and they see it's 79, and then  
19 they know they can ignore the Biographer value. But  
20 that's not really what can happen.

21 The Biographer value will read in a  
22 certain level and they have to decide if they can look  
23 at it. So that's stratifying in the other direction.

24 So can we go to that next -- okay, so  
25 we're stratifying in this direction across -- now for

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1 the Biographer reading range in the next slide. And  
2 so we see -- oh, can you go to the next one? This is  
3 a little hard to -- okay, if we look at, say, the  
4 percent D region, that's when the blood glucose is --  
5 that's when the person's blood glucose is actually  
6 low, but the Biographer or whatever device it was  
7 didn't detect it.

8 We see the percentage of D points is  
9 actually low if the Biographer is reading in that  
10 blood glucose range. And this is sort of intuitive  
11 because if the Biographer's actually reading in the  
12 low blood glucose range, that means that it measured  
13 there.

14 The problem is not when the Biographer is  
15 reading low. There it's notifying the person that  
16 they are low. And so also we see if we stratify in  
17 the percent within, we see similar performance across  
18 the Biographer glucose range.

19 And so we feel that blinding the display  
20 is not something that will address the issue of  
21 accuracy in the low blood glucose range, but there  
22 still is an issue of accuracy in the blood glucose  
23 range. That's not to minimize that that is an issue,  
24 but that's an issue of the hypoglycemic alert, how  
25 well can we detect when a person's blood glucose is

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1 low versus how well can conventional meters and  
2 testing do.

3 DR. CLEMENT: Have you done any linearity  
4 studies with the blood glucose in that range -- in  
5 that low range to see if the data is actually linear  
6 based on either YSI or any other type of machine?

7 DR. TAMADA: We haven't done linearity.  
8 It starts to get difficult when you have a very small  
9 measurement range to do things like correlation and  
10 linearity. When your delta X variable distance gets  
11 very small, it becomes a difficult analysis.

12 DR. CLEMENT: Okay, thank you.

13 CHAIRMAN NIPPER: Thank you. Let's take  
14 about a 15 minute break, please, and then we'll  
15 reconvene at ten after 4:00 by my watch. I still have  
16 a couple of questions, so would you -- sponsor please  
17 come back to the table?

18 (Whereupon, the foregoing matter went off  
19 the record at 3:58 p.m. and went back on  
20 the record at 4:14 p.m.)

21 CHAIRMAN NIPPER: Okay, folks, we're in  
22 the home stretch. Let's take our seats, please. I  
23 did have a couple of questions of my own for the  
24 sponsor and, if you'll forgive me while you're still  
25 taking your seats, I'll go ahead and ask.

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1 I'm Henry Nipper and I appreciate your --  
2 just for the record. I sweat a lot, so, if I become  
3 diabetic, how will I know whether to tell my doctor I  
4 don't want to fool with your product or not? How  
5 sweaty is sweaty? How do you figure out when it's  
6 time to cut bait with this device because a person  
7 sweats too much?

8 DR. ACKERMAN: Dr. Tamada.

9 DR. TAMADA: The Biographer will notify  
10 the user when they're sweating. And I think it would  
11 be up to the user if it's happening all the time to  
12 decide if it's just too much for them or what they  
13 want to do with their behavior.

14 But the notification is automatic.

15 CHAIRMAN NIPPER: I don't know what your  
16 cut off for the Biographer telling me I'm sweating is.

17 DR. TAMADA: Oh, okay. In terms of --

18 CHAIRMAN NIPPER: In other words, I've got  
19 -- I don't have to mop right now, but, you know, I'm a  
20 little moist up here.

21 (Laughter.)

22 Does that mean that I'm going to -- well,  
23 I know, but I'm being physically appropriate for  
24 public demonstration.

25 (Laughter.)

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1                   So I just would like to know a little bit  
2 about how you figured a cut off, whether it's based on  
3 salt, water, whatever, you know?

4                   DR. ACKERMAN: Yes, we do know.

5                   Dr. Tamada.

6                   DR. TAMADA: Well, as far as how the user  
7 knows it, you know, people's perception of sweat is  
8 somewhat subjective. But when you ask the user --  
9 when it goes off, people generally know they're  
10 sweating for sure. It's not maybe I'm sweating.  
11 They're sweating for sure, but it's a little less than  
12 profuse sweating.

13                   I mean, that's about the best I can  
14 describe it.

15                   CHAIRMAN NIPPER: Not broadcast news  
16 quality?

17                   DR. TAMADA: No, no.

18                   CHAIRMAN NIPPER: Okay.

19                   DR. TAMADA: Okay, in terms of determining  
20 --

21                   CHAIRMAN NIPPER: But like in a tennis  
22 match, you'd take the thing off, right?

23                   DR. TAMADA: That would probably not be  
24 the best place to use it.

25                   CHAIRMAN NIPPER: Or jogging or something

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1 like that where you'd be expected to perspire freely.

2 DR. TAMADA: If you were, yes, perspiring  
3 for an extended period of time.

4 CHAIRMAN NIPPER: But if you're just  
5 working in a panel meeting, you could probably do it,  
6 right?

7 (Laughter.)

8 DR. ACKERMAN: It depends on if you're the  
9 sponsor or the panel.

10 (Laughter.)

11 CHAIRMAN NIPPER: Okay. I had another  
12 question that I'd like to focus the group a little bit  
13 to think about. We've spent a lot of time today on  
14 hypoglycemic episodes. And I was struck by the  
15 endocrinologist, the diabetologist discussion of the  
16 fact that we really can make some hay here with  
17 hyperglycemia and control.

18 I marked a section in Volume 3 of the  
19 packet that dealt with -- the tab dealt with -- well,  
20 I thought I had it right. Pattern management. Did I  
21 do it right? Yes, I did. And I got over into dosing  
22 of insulin and information from Dr. Edelman and Dr.  
23 Garg about how they would use the data to help with  
24 insulin dosing.

25 And I know that we're not supposed to dose

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1 -- do extra doses or doses of insulin without a second  
2 measurement, but I think that looking down the road  
3 one could say all right, could we make a difference in  
4 better glucose control prompted by the watch.

5 So I found a Table 422E, as an example,  
6 summary of benefits and risks with Dr. Edelman's  
7 algorithm. And Dr. Garg has one also. And I'd like  
8 to ask them to tell us a little bit about in  
9 particular how they're -- we're detecting  
10 hyperglycemia better with this device.

11 DR. EDELMAN: I have the handout that  
12 you're referring to, the overhead. First I'd like to  
13 just give you the quick background. When I was first  
14 asked to review documents for Cygnus and -- and this  
15 is only part of the sliding scale that I gave them  
16 typically seen, and I just want to point out for many  
17 of you non-diabetes specialists that this was for an  
18 insulin insensitive subject, an insulin requiring  
19 person with Type 2 diabetes.

20 They're taking 45 units of a basal insulin  
21 and at least ten units of regular or a fast acting  
22 analog three times a day, which is a minimum of 75  
23 units. The average person who doesn't have diabetes  
24 uses about 35 to 40, and that's typically what a  
25 person with Type 1 or juvenile onset diabetes uses.

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1           And that's pertinent because -- and then  
2 if a patient is high, let's say over 200 mg after  
3 eating, I usually instruct patients to take a little  
4 extra fast acting insulin depending on how high their  
5 blood sugar is.

6           And the graph that the Chairman was  
7 referring to is here on the summary of results. And  
8 we wanted to see at the time how does the data from  
9 the GlucoWatch compare to the readings that you would  
10 take in clinical practice.

11           And we compared to really is what we  
12 consider now patients who are testing a lot before  
13 each meal and at bedtime compared to the Biographer  
14 where you would get numbers throughout the day. And I  
15 just want to start off down here, which is the percent  
16 of incidental dose decision points with undetected  
17 hyperglycemia.

18           What this says is how many times after a  
19 meal or at bedtime when you're high you're going to  
20 pick it up. You're going to miss it with a four times  
21 a day regimen 45 percent of the time. And you're only  
22 going to miss an incidental hyperglycemia 9 percent  
23 of the time with the GlucoWatch Biographer.

24           And remember, this was analysis not  
25 assuming that you're going to have to confirm each

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1 measure that you get with a regular home glucose  
2 monitoring device. And up here we thought well,  
3 what's the worst case scenario?

4 A percent of planned insulin decision  
5 points with insulin dose that would be greater than 20  
6 percent of what you would choose if you had a regular  
7 glucose meter. And most -- 87 percent of the time the  
8 numbers were -- the decision to choose a certain  
9 insulin dose was the same with the Biographer as it  
10 was with the home glucose monitor.

11 But remember, in this scenario, in the  
12 real life and with the indicated use of this device,  
13 any time the alarm goes off, and just to put it in the  
14 real sense, let's say you're at Thanksgiving dinner,  
15 for example, and about an hour and a half after eating  
16 the alarm goes off. You're 210.

17 And I would basically -- personally, what  
18 I would tell my patients to go to the part of the  
19 sliding scale that I showed you earlier when you're  
20 above 200, take three or four or five, whatever, how  
21 sensitive you are to a certain insulin, take a little  
22 extra insulin analog and then wait at least another  
23 hour, hour and a half before you would possibly think  
24 about giving yourself an extra dose.

25 So I think the fact that the watch will

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1 help patients be alerted to when they go above a  
2 certain range, and then with the education process,  
3 you tell patients what to do with that number. And in  
4 my experience, there is no problem doing that.

5 And for most diabetes specialists, when  
6 you give a patient an insulin algorithm and someone  
7 who's really savvy and likes to test because they want  
8 to stay in the normal range, it's not a huge  
9 educational problem.

10 But this device will help pick up periods  
11 where previously were just not available or not usual  
12 testing periods.

13 CHAIRMAN NIPPER: So, Dr. Edelman, do I  
14 understand that line, the third line down under risks,  
15 that when you have a patient with undetected  
16 hyperglycemia, the current QID scheme testing two,  
17 four times a day is going to miss about half of those  
18 episodes; and with the GlucoWatch, you're going to  
19 miss only about 10 percent of them.

20 Did I read that right? Did I understand  
21 you right?

22 DR. EDELMAN: That's exactly right. And  
23 remember, the QID regimen, this really says that if  
24 you took 100 percent of the -- if someone gets  
25 hyperglycemic 100 times in this particular analysis,

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1 half of that time it's going to be pre-meal blood  
2 sugars.

3 The other half is going to be post meal  
4 blood sugars, really just highlighting the fact that  
5 people with diabetes get high after eating quite  
6 commonly and it's missed with the typical four times a  
7 day testing.

8 Exactly. And 9 percent of the time,  
9 because the Biographer may not have reached the 200  
10 point because compared to a paired sample from the --  
11 from a regular glucose monitor, you're missing a  
12 potential hyperglycemic period 9 percent of the time.

13 That's right.

14 CHAIRMAN NIPPER: Well, do you have any  
15 way to guesstimate or project what kind of effect this  
16 kind of control -- improved control will have on  
17 hemoglobin A1C? In other words, you made a very good  
18 point today that we're not even close to the upper  
19 limit of the reference range.

20 Do you see this as an advance to get to  
21 that upper limit in patients?

22 DR. EDELMAN: Well, that's primarily why  
23 I'm here today. And I do believe quite strongly that,  
24 you know, the fluctuations that we commonly see in  
25 people with diabetes, this oscillation certainly won't

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1 be what the normal, non-diabetic individual does.

2 But I do believe you'll take an  
3 oscillation like this and you'll be able to dampen  
4 them quite significantly not only in the hyperglycemic  
5 side, but also on the hypoglycemic side.

6 And I do think that we will be able to get  
7 much better glucose control with a device that tells  
8 patients when they're too high much more frequently in  
9 compared to not having the data before. And it's hard  
10 to put an actual number on it.

11 I would imagine that some patients who are  
12 extremely high can drop their A1C several points. If  
13 you take someone testing four times a day with a  
14 glycohemoglobin of 7 percent, I do believe that you  
15 might get much closer to that normal range than you  
16 could previously with current testing, unless that  
17 person's just testing maybe 12, 14 times a day.

18 So I do think it will make a significant  
19 impact on the way we manage person with diabetes,  
20 especially people on multiple injection regimens,  
21 insulin requiring Type 2s or Type 1 diabetics.

22 CHAIRMAN NIPPER: Thank you.

23 Dr. Garg, you had a scheme in that same  
24 packet for insulin insensitive studies. Did your data  
25 show the similar things?

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1 DR. GARG: Exactly.

2 CHAIRMAN NIPPER: We need a mic.

3 DR. GARG: Thank you, Dr. Nipper.

4 My data was also identical. And again, I  
5 was asked by the sponsor to give a scale which was  
6 retrospectively analyzed as to how the blood sugars  
7 and the insulin dosage would be made. And this was  
8 the scale that I gave based on an insulin insensitive  
9 subject.

10 And I would also refer to another table  
11 that I'm going to show which is based on an insulin  
12 sensitive Type 1 diabetes patient. And when you look  
13 at the similar data that Steve showed a few minutes  
14 ago -- the next slide. No, the next one.

15 I'm sorry. Insensitive. Is this the one?

16 That was the algorithm that I had used,  
17 which was much narrower range, as you can see, based  
18 on the blood glucose values whether they're less than  
19 100, 100 to 170, 171 to 240, or if they're more than  
20 241.

21 That's the range that I usually use in  
22 patients. Please note that most of these patients  
23 were using an NPH as a basal insulin, which is about  
24 55 units per day. And also it included insulin -- the  
25 incidental dosages that patients were advised based on

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1 the similar numbers.

2 The incidental dosages that patients would  
3 take were based on the level of hyperglycemia at each  
4 of the numbers. And when you look at what we find in  
5 analysis, we find since the doses are -- pretty much  
6 run into each other, and you can see that 23 percent  
7 of the times that would be missed if the patient was  
8 checking four times a day versus only 6 percent of the  
9 times.

10 So the data is identical to what Dr.  
11 Edelman says. And I can also show, if you wish to  
12 see, the data on the Type 1 diabetes subjects.

13 CHAIRMAN NIPPER: Quickly.

14 DR. GARG: There again, the algorithm was  
15 based on the blood sugar values.

16 CHAIRMAN NIPPER: Can you slide it up just  
17 a hair? There we go. Thank you.

18 DR. GARG: Thank you. And again, the  
19 algorithm was given where the patients are receiving  
20 on an average about 35 to 40 units of basal NPH a day  
21 twice a day. And the planned dosages were given prior  
22 to the meals and the incidental dosages for the  
23 postprandial hyperglycemia, whether it's after  
24 breakfast, lunch or the dinner.

25 And this was the algorithm that was given

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1 based on which analysis was made. It's interesting to  
2 note that in a retrospective analysis, more than 99  
3 percent of the decisions were made within one unit of  
4 the insulin dose changes of the pre-meal.

5 So there was hardly any difference in  
6 terms of what the patient would make the decision  
7 based on the blood glucose value using the finger  
8 stick versus the glucose value that is received by the  
9 GlucoWatch.

10 CHAIRMAN NIPPER: Okay, thank you.

11 DR. GARG: Thank you.

12 CHAIRMAN NIPPER: I also would like to  
13 just -- did you have more stuff, Dr. Garg?

14 DR. GARG: No.

15 CHAIRMAN NIPPER: Thank you.

16 DR. GARG: Thank you.

17 CHAIRMAN NIPPER: It has come up several  
18 times about error. And I like Herb Naito's chart that  
19 illustrates the actual numbers that you get when you  
20 have a certain CV. I just did this while I was  
21 sitting at the table there. My math may be wrong.

22 But let's assume we were talking about 150  
23 per dL glucose, and we talk about certain CVs. If you  
24 add -- if you assume that 95 percent of the data is  
25 going to be between plus or minus two standard

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1 deviations, I think that the statisticians would go  
2 along with me on that, and we talk about a -- I think  
3 we were talking 12 percent, 16 percent, somewhere in  
4 there -- 95 percent of the time, your meter, whatever  
5 it is, is going to read between 116 and 186.

6 Now, it's always been amazing to me -- now  
7 that's two standard deviations. It's always been  
8 amazing to me that in this particular field we've gone  
9 along now for a while and not demanded tighter  
10 precision than that.

11 Now, admittedly, plus or minus one  
12 standard deviation, you're going to have 66 percent of  
13 the data. So most of the time your data is going to  
14 be between plus or minus one SD. But if we talk about  
15 95 percent of the time at 12 percent CV, your low  
16 reading is 116, your top reading is 186, and you can  
17 vary all over the map and clinical decisions can  
18 change.

19 Look at 16 percent, 198 to 102. So  
20 anyway, I think it's very important that we keep these  
21 data, these numbers in mind when we're talking about  
22 making clinical decisions. And it's really amazing to  
23 me that clinicians are able to make good decisions  
24 when CVs are large.

25 So I hope we can drive toward smaller

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1 ones. Excuse my editorialization. I already got my  
2 plaque.

3 (Laughter.)

4 Okay, I'd like to also thank the sponsor.

5 If there are no more questions from the panel for the  
6 sponsor, I think we can excuse you briefly and move  
7 toward FDA questions.

8 Anybody got another quick shot while  
9 they're leaving? Okay.

10 Dr. DiGiovanna, let's start with you and  
11 ask if you have any questions that the FDA presenters  
12 could answer.

13 DR. DiGIOVANNA: The only one question I  
14 really have is whether or not there's been any  
15 additional information with respect to the skin  
16 changes that have been described that we haven't seen  
17 -- for example, photographic documentation or  
18 histologic evaluation or anything like that that we  
19 haven't seen?

20 DR. FOURCROY: I presume I get to be the  
21 lucky one to answer that one. We have no photographic  
22 evaluation of this that has been shared with us by the  
23 sponsor.

24 CHAIRMAN NIPPER: Thank you.

25 Yes, Dr. Andrade.

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1 DR. ANDRADE: Can I just follow up on  
2 that? Given that we're interested in a benefit/risk  
3 sort of analysis here, do we have any information on  
4 what sort of skin changes and skin problems we have  
5 with the current technology, some diabetic who's  
6 stabbing himself six to eight times a day on the  
7 fingertips?

8 DR. FOURCROY: Fourcroy. No, I really  
9 don't have any hard evidence on the amount of risk of  
10 stabbings at this point to compare it to even.

11 CHAIRMAN NIPPER: Mr. Reed's microphone  
12 needs to be turned up.

13 MR. REED: I don't have any statistics on  
14 that, but there have been several studies done on  
15 fingertip problems based on finger sticks. And there  
16 really have been -- in fact, the most common practice  
17 is not to change lancets more often than is absolutely  
18 necessary.

19 I suspect mine's been in there at least  
20 six months, and I've never had a single problem and  
21 I've been testing since this technology first came  
22 out.

23 DR. DiGIOVANNA: Just one last comment. I  
24 think there are a number of concerns with respect to  
25 the skin irritation issue. Certainly the least, I

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1 would think from my perspective as a dermatologist, of  
2 those changes is the transient redness or the  
3 transient irritation that's associated with the  
4 application and the removal of the device.

5 I think that's self limited and time  
6 spent, certainly it doesn't seem to be so severe  
7 compared to various alternatives. However, it is an  
8 indicator that a poorly described biological activity  
9 is occurring here.

10 And that activity, besides causing a  
11 current to flow through the skin, a trauma in breaks  
12 and abnormality in the barrier, and a recurrent  
13 inflammation which will lead to the bringing in of  
14 inflammatory cells, sets up a situation whereby either  
15 that change may induce sensitization to the -- some  
16 component of the device or something else applied in  
17 the proximal time, or, over time, will lead to a  
18 difficulty in the device doing what it's supposed to  
19 do because of chronic changes in the skin.

20 I think that's a more serious and weighty  
21 concern because it affects the bottom line, which is  
22 the accuracy of the measurement, number one. And on  
23 the other hand, the ability to continue to use the  
24 device. If 95 percent of the people who use the  
25 device become sensitive to some part of it, then

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1 that's something one would like to know early enough  
2 to be able to change course.

3 CHAIRMAN NIPPER: Thank you.

4 Dr. Everett, do you have any questions for  
5 the FDA?

6 DR. EVERETT: Sure. You mentioned how  
7 often the machine is off. Overall, how often is it  
8 off, but does it miss readings?

9 DR. MEIER: The data I presented is what I  
10 think you're talking about. There were various  
11 reasons for not having readings. Let me see if I'm  
12 understanding your question. They were unable to  
13 calibrate -- is that what you mean?

14 DR. EVERETT: Overall, how often does it  
15 skip readings or turn itself off?

16 DR. MEIER: Skipped readings, 21 percent  
17 of the results were skipped. Every day, every day,  
18 with every use there were at least one skipped result.  
19 Okay, but overall, 21 percent of the points were  
20 actually skipped.

21 You also don't have readings because the  
22 device actually shuts off. That's a separate  
23 statistic, and that was 27 percent of the days it  
24 shuts off early. And then when you don't calibrate,  
25 you fail to calibrate, you don't have any data for

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1 that day, and that happened on 4 percent of the days.

2 Okay, so that was one -- that was sort of  
3 the individual statistics. Then I had presented sort  
4 of overall summaries of -- if you count calibration,  
5 there's 36 possible readings you could have a day for  
6 the GlucoWatch.

7 So if you combine all reasons all together  
8 -- this is assuming you actually calibrate  
9 successfully, however, so these statistics are just  
10 pretty much skipping and shut off results. I had  
11 listed some statistics here that on average you would  
12 have 26 readings per day out of 36, so that's about  
13 three-quarters of the possible.

14 That's an average. Okay, sometimes 12  
15 percent of the days you had less than four results on  
16 a given day. So roughly one every 100 days -- 12 of  
17 those days, you would have less than four results.  
18 Yes, thank you. That's slide nine.

19 And then 28 percent of the days you would  
20 have half those results, 18. There's a variety of  
21 results. Actually, slide nine.

22 CHAIRMAN NIPPER: And Dr. Meier, you're  
23 talking about one part of the study that you  
24 evaluated, right, the Home Environment Study?

25 DR. MEIER: This is just the Home

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1 Environment Study, that's correct.

2 CHAIRMAN NIPPER: Yes, which is 129  
3 subjects over six sites, right?

4 DR. MEIER: Yes, there are actually 111 in  
5 this population.

6 CHAIRMAN NIPPER: Okay.

7 DR. MEIER: One hundred and twenty-nine  
8 were enrolled in this study.

9 Does that answer your question?

10 DR. EVERETT: Almost.

11 DR. MEIER: Okay.

12 DR. EVERETT: In a sense, any given  
13 patient who wears the watch, as a clinician, what can  
14 I generally expect? How many readings out of the  
15 total that it would do in a day -- going into that,  
16 how many would I expect to actually get data for? Is  
17 it the 26?

18 DR. MEIER: The 26 on average per day is  
19 what you could expect. That's an average though.  
20 It's going to go anywhere from zero readings to 36. I  
21 mean some days you will have no readings. In fact --  
22 well, you never got all the points.

23 So the maximum, I guess, would be 35  
24 counting the calibration point. If you don't count  
25 that, 34 points. So that would be the maximum. And

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1 these statistics here give you the range of how often  
2 you can expect a quarter of the points, how often you  
3 can expect half the points, how often you can expect  
4 three-quarters.

5 DR. EVERETT: And as you looked at the  
6 data, were you able to isolate it to any particular  
7 time of day when the machine particularly tended to  
8 fail or skip readings?

9 DR. MEIER: With the skipping, actually it  
10 happened throughout the day and with even the early  
11 shut off. Sometimes it would happen within the first  
12 four hours. Sometimes it happened in the middle four  
13 hours. Sometimes it happened in the last four hours.

14 We weren't -- we didn't note any  
15 particular reason or we never got to the point where  
16 we saw reasons for when it would shut off. But it  
17 could happen at any time.

18 DR. EVERETT: But no identifiable pattern?

19 DR. MEIER: No, we didn't. And I don't  
20 believe the sponsor did, but they -- you could ask  
21 them.

22 DR. EVERETT: Yes. And did you notice if  
23 the accuracy tend to -- I saw on one set of tables  
24 where it looks like it read better after it was first  
25 placed on for the first couple of hours and then, as

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1 time passed, the precision got worse.

2 Is that correct?

3 DR. MEIER: Well, the -- I don't know if  
4 you're referring to my slide 21 on the time of wear  
5 plot. That's what that maybe is getting at. But  
6 overall, over time, if you look at the percent of  
7 points that were -- these are actually the percent of  
8 points in the A plus B range or there was actually  
9 four separate criteria I listed here. You could look.

10 But roughly, it's a measure of sort of  
11 percent agreement, if you will. And what is appears  
12 from at least three of these four plots is that the  
13 percent agreement decreases as a function of time in  
14 the -- of wear.

15 So in other words, here we're seeing  
16 percentages hours three, four and five in the range 60  
17 to 80 percent. As you decrease -- as the time elapses  
18 into hours ten, 11 and 12, the percentages decrease.

19 DR. EVERETT: Okay, so what happens to the  
20 CV over time?

21 DR. MEIER: I'm sorry? Could you repeat  
22 your question?

23 DR. EVERETT: What happens with the CV  
24 over time?

25 DR. MEIER: I don't have an analysis where

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1 I'm actually looking at paired -- for CV, I assume you  
2 mean paired results --

3 DR. EVERETT: Yes.

4 DR. MEIER: -- over time? I don't have  
5 that information.

6 DR. EVERETT: Okay, then my other, and  
7 perhaps last, question was you mentioned -- I can't  
8 remember which one of you mentioned it, but you  
9 mentioned that there was no data to determine if the  
10 skin irritation interfered with the performance of the  
11 instrument, is that correct?

12 DR. FOURCROY: That's basically correct.  
13 And I guess one of the questions that might be  
14 considered is we know that there are skin changes over  
15 the day. Over a period of time, we know there's skin  
16 changes. And there's actually no data that would help  
17 us understand that process either.

18 DR. EVERETT: You may not know the answer,  
19 but do you know how long it takes to wear the watch  
20 before the skin irritation starts to develop?

21 DR. FOURCROY: No, sir, because in the  
22 Home Environment Study where we have most of the data  
23 in the 111 patients, the patients weren't evaluated  
24 until the last day, the fifth day. Most of them were  
25 evaluated on the fifth day if they stayed in, although

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1 some were clearly evaluated earlier than that.

2 DR. EVERETT: And any data to suggest if  
3 the irritation got worse with repeated wearings?

4 DR. FOURCROY: No, because in the Home  
5 Environment data we were only looking at the last day.

6 And the only other time we would be looking at repeat  
7 is the contact sensitization study, which did not give  
8 us that information.

9 DR. EVERETT: Okay, thanks.

10 CHAIRMAN NIPPER: Thank you.

11 Dr. Manno, do you have questions of the  
12 FDA?

13 DR. MANNO: No, thank you.

14 CHAIRMAN NIPPER: Dr. Doumas?

15 DR. DOUMAS: I'd like to refer to the same  
16 graph, performance by time of wear. And it seems that  
17 when -- for the entire range really, there is variable  
18 wear. You drop from 100 percent to 90 percent of the  
19 values in the A/B region.

20 The biggest drop is in the hypoglycemic,  
21 and any particular reason for that?

22 DR. MEIER: I can't explain that. That's  
23 a question we had. I don't know what's causing that.

24 DR. DOUMAS: I mean, this is quite  
25 dramatic. For example, for the 20 percent of 20 mg

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1 range hypoglycemic, it drops from about 65 something  
2 percent down to 35 percent, which is 30 percentage  
3 points really down, the number of points in the A/B  
4 region.

5 I wonder, should they recommend that the  
6 sponsor really take a look at that thing or maybe  
7 reduce the time that -- the effectiveness of the  
8 Biographer?

9 DR. MEIER: Yes, I mean, that's a question  
10 for them to think about. I don't have the answer to  
11 what's causing that.

12 DR. DOUMAS: Because it is in an area  
13 really which is the most critical of all of the  
14 glucose concentrations. That's all.

15 CHAIRMAN NIPPER: Thank you.

16 Dr. Clement.

17 DR. CLEMENT: No questions.

18 CHAIRMAN NIPPER: Dr. Rifai.

19 Dr. Rosenbloom, do you have any?

20 Dr. Harrington-Falls, any questions for  
21 the FDA?

22 Dr. Andrade? Mr. Reed? Ms. Kruger? Dr.  
23 Habig, none?

24 Okay, thank you FDA folks. Well, we  
25 appreciate all of the time that the sponsors and the

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1 agency have given us in answering panel's questions.  
2 I think that it's appropriate now for us to start  
3 thinking about the questions that the FDA has asked  
4 us.

5 And I think that we as a group need to  
6 work for a few minutes on the questions. And then  
7 when 5:15 comes, we will suspend our questions -- our  
8 work on the FDA questions and open the public hearing  
9 so that the people who have been so patient with us  
10 can address us.

11 Is the agency ready to put those questions  
12 up on the board? We're getting there I think.

13 Question one, reading a little bit ahead,  
14 do the data support the proposed intended use of the  
15 GlucoWatch Biographer? If not, what adjustments in  
16 intended use or additional data support intended use  
17 might be required?

18 And as is my want, I continue to pick on  
19 various ends of the table. And I haven't picked on  
20 Dr. Clement today, so why don't we work this way  
21 around the table. Then we'll come back this way.

22 If you're not ready, we can skip it. He's  
23 always ready.

24 DR. CLEMENT: I deferred on the last one  
25 because I wanted to show a couple of transparencies.

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1 First of all, the issue of effectiveness. I don't  
2 think anybody in this room can doubt the potential  
3 benefit of more frequent testing.

4 This was data that was published last year  
5 by Dr. Anderson and Dr. Laffel's group up in Joslin  
6 Clinic looking at 89 adolescents. And it was cross  
7 sectional data where they're looking to try to find  
8 the type of critical factors that are associated with  
9 better glycemic control over time -- not over time,  
10 but at least on cross sectional data.

11 And as we all know, is that the more  
12 frequent a person tests -- this is in adolescents --  
13 the better. And of all the data they found, the one  
14 factor that they all found that teased out from all  
15 their data they collected was that the frequency of  
16 blood glucose testing was the most -- was the  
17 strongest factor associated with improved glycemic  
18 control.

19 I don't have a pointer, but, as you can  
20 see here, on the Y axis it shows hemoglobin A1C. The  
21 X axis has frequency of testing. This is on an  
22 average. As you can see, the more frequent a person  
23 tests, the better their A1C is.

24 So, as you can imagine, if the person can  
25 test 23 times or have data for 23 times per day, you'd

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1 get better A1C levels and basically enforce the whole  
2 issue that Steve Edelman talked about, possibly get  
3 through that wall, that barrier that is present to  
4 better control.

5 Next slide.

6 The other issue that has been a big  
7 concern with this is again questions that I was  
8 bringing up was what's the accuracy on the low end.  
9 We heard a lot on the discussions in the open session  
10 about being able to detect hypoglycemic events because  
11 they could be so crucial, sometimes life threatening.

12 Very, very important for a device,  
13 particularly if the labeling is not very precise and  
14 accurate in terms of how it's worded. If this device  
15 is used as a sole agent in order to detect  
16 hypoglycemia, I think there's some major problems.

17 And this is just one example of some of  
18 the data we know. This is from Dan Cox and actually  
19 Dr. Clark's group that pioneered the whole Clark era  
20 grid where they looked at cognitive functioning with  
21 driving, for example, something that we consider  
22 extremely important in terms of risk for someone,  
23 particularly if they're on insulin oral hypoglycemic  
24 agents.

25 And studies that they did found was that,

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1 on the top line, that driving performance -- cognitive  
2 driving performance deteriorates actually quite  
3 dramatically once the blood glucose levels drop below  
4 65 mg/dL. This is very predictable. This is across  
5 all folks that require insulin.

6 And it doesn't really matter whether  
7 they're tight control or poor control. The cognitive  
8 performance does decrease substantially based on what  
9 the blood glucose level is. So measuring blood  
10 glucose in terms of determining a person's risk for  
11 critical functions is extremely important.

12 So I'd suggest in framing these questions  
13 that we think in terms of how close we are to the  
14 actual blood glucose level. The other issue is that  
15 when patients are asked whether or not they feel ready  
16 to drive before they know what their actual sugars  
17 are, they find that people with diabetes are very poor  
18 estimators on determining what their own blood glucose  
19 is based on their symptoms alone.

20 Sixty percent of the time their blood  
21 glucose levels were less than 70, they stated that  
22 they felt functional to drive. And 40 percent of the  
23 time when their actual blood glucose level is less  
24 than 40, before knowing what their glucose level was,  
25 they felt that they were able to drive a car, motor

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1 vehicle, from one point to the other.

2 So clearly being able to discriminate  
3 between fine levels of glucose levels between 40 and  
4 70, for example, is very important for function in  
5 patients.

6 So I think on this first question on  
7 intended use, I agree with Steve Edelman that I think  
8 this device would be a tremendous boon to help look at  
9 patterns, help look at trends in blood glucose; but  
10 I'm a bit worried -- again, this gets on all the  
11 questions in terms of particularly the labeling.

12 If it says that this is indicated for the  
13 use in detection and assessment of episodes of  
14 hypoglycemia -- possibly for hyperglycemia, yes -- but  
15 for hypoglycemia, no. So I think the intended use as  
16 is with the current labeling has a little bit to be  
17 desired.

18 Possibly we can address this on some of  
19 the other questions.

20 CHAIRMAN NIPPER: Dr. Doumas, what do you  
21 think about question one?

22 DR. DOUMAS: I think in part only, I  
23 believe they should be emphasize that this is not like  
24 the glucometer or like a laboratory result; that it  
25 should be used for tracking and trend. I agree with

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1 Dr. Clement about the hypoglycemic level.

2 I wonder, I'm not a clinician, if by  
3 setting the alert level of hypoglycemia higher, if you  
4 can prevent really cases of hypoglycemia because it  
5 will take action on the patient a little earlier. For  
6 example, if you set the alert level -- I don't know if  
7 it can be done. I'm not a physician and I don't treat  
8 patients.

9 Instead of putting 70, you put 90 or 100  
10 or 110. Will that be an additional warning, a safety  
11 mechanism there, a safety margin?

12 CHAIRMAN NIPPER: I think that's in the  
13 labeling, as a matter of fact, that you can set it at  
14 100.

15 DR. DOUMAS: Okay. Also, I feel there  
16 should be somehow a statement there of the confidence  
17 limits of the result from the -- of the biometer.  
18 It's time for people to understand that a variable  
19 result is not that absolute. There is a fringe around  
20 it and I think the size of the fringe should be  
21 printed.

22 This is what Sir Charles Darwin said when  
23 he was director of the National Physical Laboratory in  
24 England. You have to know the plus or minus of the  
25 value.

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1           Also, I think the sponsor should look very  
2 carefully in the time wear of the instrument. I'm  
3 really concerned about that trend over there that the  
4 precision is diminishing as the time goes by. Either  
5 fix it or maybe they should go to a lower -- to a  
6 shorter time for the use.

7           CHAIRMAN NIPPER: Thank you.

8           Dr. Manno, what's your answer to question  
9 one?

10          DR. MANNO: Yes and no. I go along with  
11 the two previous speakers. I think that there is  
12 sufficient reason to consider approving this  
13 instrument with certain reservations. I think they  
14 need to have a very, very strong consumer and  
15 professional health care education program, as they  
16 have mentioned already.

17          I think that there are other populations  
18 that need to be studied. And I think they need to  
19 expand their "n", the number of subjects of the --  
20 based on race, get some more data there. I would  
21 especially recommend if they go on to do -- include a  
22 pediatric population, that very definitely include  
23 body mass index there.

24          This would -- and to consider other sites  
25 of application, especially for application in very,

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1 very young children. I have a friend who has a child  
2 diagnosed less than a year old. How would something  
3 like this do there both in terms of irritation and in  
4 terms of application?

5 Need to include that Type 2 non-insulin  
6 dependent group of people and worry about the  
7 interference studies with all those diabetic drugs  
8 that are used by those people. And I can't quit  
9 without saying this. Clarify the shaving conditions.

10 CHAIRMAN NIPPER: Thank you.

11 Remember, the intended use as stated is in  
12 people 18 years of age or over, and I think use  
13 outside that is not within the purview of the panel.  
14 We understand our -- I think we all understand  
15 concerns about use in children and the fact that  
16 children are being presented to the panel as  
17 beneficiaries of this device indicates the direction  
18 that both the public and the company wish to go in  
19 this particular area.

20 Dr. Everett, do you have -- do you think  
21 the data support the proposed intended use? And if  
22 not, what would you do -- what would you have them do?

23 DR. EVERETT: Well, actually, I think the  
24 data does support the intended use. I do have one  
25 concern, maybe two. But we have not talked about this

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1 alert system. Is the alert system audible or visual  
2 or both? Because I get the impression that this would  
3 work for hypoglycemic patients sleeping, and I would  
4 assume this watch would wake them up. Is it?

5 CHAIRMAN NIPPER: The sponsor should  
6 answer whether it's audible or not and how well it  
7 wakes people up who are sleeping.

8 DR. EVERETT: Can you just fire it up?

9 CHAIRMAN NIPPER: I don't think there's a  
10 battery in it. Is there in that one?

11 DR. PITZER: Let me explain. It is an  
12 audible alarm and a visual message on the display. So  
13 the message clarifies for the user the nature of the  
14 alert situation, whether it's a low, a high, a skip  
15 due to perspiration or so on.

16 The audible alarm is designed to begin  
17 relatively discreetly in case we're at an FDA panel  
18 meeting and we don't want everybody in the room to  
19 hear it. But if you don't respond within 30 seconds,  
20 the pattern of the beeps becomes more and more  
21 disruptive in a series of five steps.

22 So over two and a half minutes, we kind of  
23 ramp it up. In the home simulated study, we had have  
24 an overnight wear period. There were 118 occasions on  
25 which the alarm went off at night and we had study

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1 staff there to verify whether or not the subject woke  
2 up.

3 On 117 of those 118 occasions, the subject  
4 did wake up in response to the alarm. I don't know if  
5 you want to magnify this. That will distort it. But  
6 maybe I should just pass it around. And it's starting  
7 its ramp up now, so it's discreet.

8 By the time it reaches 30 seconds, you  
9 should hear the pattern of beeps escalate. There's  
10 the second step. Third step.

11 CHAIRMAN NIPPER: I'm not awake yet.

12 (Laughter.)

13 Maybe if this thing started serious  
14 iontophoresis on me, it would wake me up.

15 (Laughter.)

16 Here it goes again.

17 DR. PITZER: That's the fourth step.

18 CHAIRMAN NIPPER: That's getting serious  
19 now.

20 (Laughter.)

21 CHAIRMAN NIPPER: Dr. Everett, are we  
22 disrupting your questioning pattern?

23 DR. EVERETT: I don't think so.

24 DR. PITZER: Just press any button when  
25 you're ready to turn it off. Do you want me to start

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1 it again?

2 CHAIRMAN NIPPER: How did you start it?

3 DR. PITZER: Just press the start button  
4 on the lower left.

5 CHAIRMAN NIPPER: Okay.

6 DR. PITZER: Hold it down until you hear.  
7 It's trying to start, but it sees that there's no  
8 AutoSensor.

9 CHAIRMAN NIPPER: Start, read.

10 DR. PITZER: So it's alarming you saying  
11 there's no AutoSensor, you're not connected to the  
12 skin, and that's an off read situation.

13 CHAIRMAN NIPPER: Okay.

14 DR. PITZER: And then it will ramp up.

15 CHAIRMAN NIPPER: Yes. Maybe by the time  
16 we get it around to Dr. Andrade it will be exciting.

17 DR. EVERETT: That was basically my issue.  
18 At this point, that wouldn't wake me up, to be  
19 honest.

20 CHAIRMAN NIPPER: It would not?

21 DR. EVERETT: No. And not any of my  
22 diabetic patients, from what I've seen.

23 CHAIRMAN NIPPER: Did you have any other  
24 questions?

25 DR. EVERETT: No other questions.

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1 CHAIRMAN NIPPER: Okay, thank you.

2 Dr. Janosky, do you have questions?

3 DR. JANOSKY: Sure. My response to  
4 question number one would be yes and no.

5 CHAIRMAN NIPPER: Okay.

6 DR. JANOSKY: It does, but only within a  
7 certain range. And I'm not -- I didn't spend much  
8 time thinking about what range I would feel  
9 comfortable, but just sort of listening to today's  
10 conversation it's probably somewhere between 80 and  
11 240.

12 Either below that or above that, I'm  
13 uncomfortable with giving an exact numerical value --  
14 the exact numerical read value because of the error  
15 that's involved in any of those. And I think that the  
16 average patient wouldn't necessarily take into account  
17 CVs, etc. when they're using those values.

18 So the answer is yes and no to question  
19 one.

20 CHAIRMAN NIPPER: Yes, I understand your  
21 concern. And the thing that worries me about this  
22 whole area is that -- and I think you can see it in my  
23 putting a transparency up that shows how uncertain the  
24 numbers are in the current area with finger stick  
25 blood glucose.

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1           And we are in a situation where we're  
2 caught between the devil and the deep blue, I think.  
3 We're using these devices which are imprecise. Many  
4 of the numbers are okay to use. Many of the numbers  
5 have been quite satisfactory clinically. But we've  
6 also heard -- this panel has heard that there's a  
7 large number of unexplained errors in finger stick  
8 blood glucose use.

9           That doesn't mean that we ought to throw  
10 them out and take them off the market, in my opinion,  
11 but I do think we -- it would be more reassuring to me  
12 as a panel member if we could anchor -- if we had an  
13 anchor in truth, if somebody had gotten up and said  
14 yes, it is possible to use a Lee's Squares rather than  
15 a Deming.

16           But I think we have to take -- we have to  
17 work with what we have. Anyway, excuse me.

18           Dr. DiGiovanna, tell us what you think on  
19 question one.

20           DR. DiGIOVANNA: Well, I think I agree  
21 that my answer would be yes and no. I think we agree  
22 with Dr. Doumas' concern about the time for use  
23 graphs. And basically, that's because I think that  
24 I'm not convinced I understand what's going on in the  
25 interaction between the skin and this device and how

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1 that affects performance over time.

2 And my concern with the errors that we've  
3 seen is that those errors might not be constant and  
4 that there may be factors that, over time, will  
5 increase those errors either at the end of the wear  
6 period or when it's worn chronically over areas where  
7 it's been previously applied many times.

8 And I think the real issue for that is  
9 with respect to having erroneous readings. I think  
10 the issue with shaving is something I'm real sensitive  
11 to because I think that's something that's easily  
12 standardized.

13 But I think it should be standardized  
14 based on some clinical information. Someone should be  
15 able to simply say if you do A, B and C, this doesn't  
16 affect significantly the results. But finally, the  
17 issue that's a little bit awkward for me because most  
18 of my experiences with CDER, which is the drug branch  
19 of the FDA, is your issue of intended use.

20 I think the intended use that I heard at  
21 the beginning of this meeting is that the greatest  
22 need would be in the pediatric population and in those  
23 individuals who would probably want to use this device  
24 every day or maybe even all day during the day and  
25 night.

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1           And I think that that's an area where  
2 there really is a need for more information. And I  
3 guess we're going to talk about the other questions  
4 later on --

5           CHAIRMAN NIPPER: Yes.

6           DR. DiGIOVANNA: -- and address some  
7 specific concerns about that?

8           CHAIRMAN NIPPER: Yes, the idea is to go  
9 around the panel and answer each question one at a  
10 time. And again, the intended use here is in an adult  
11 population. And as admirable as it is and as  
12 desirable as it is to have a device that would work in  
13 the pediatric population, we don't have that in front  
14 of us at this time.

15           Dr. Rifai, how about question one? I'll  
16 even get you my mic.

17           DR. RIFAI: Well, my answer is similar to  
18 what we heard earlier. I think it's yes. It's  
19 certainly -- and when it's used in adults, at least  
20 when shown to be very useful mainly for detecting  
21 trends and give continuous measurements for glucose,  
22 which help better manage patients.

23           I think it's also very important to stress  
24 in the user guide and during training that this is not  
25 meant to replace the existing glucose measurements.

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1 And I think it would be helpful if the sponsor could  
2 refrain from making statements in the user guide like  
3 "a new kind of freedom for millions of people with  
4 diabetes" because it give the impression that you are  
5 doing away with the glucose measurement.

6 CHAIRMAN NIPPER: Yes, go ahead, Dr.  
7 Rosenbloom.

8 DR. ROSENBLOOM: I think that this is a  
9 technology that's certainly -- the timing is  
10 consistent with new insulin delivery systems and new  
11 modified insulin analogs that provide the opportunity  
12 to give truly rapid action and truly non-peak long  
13 action, as well as with the new oral agents in Type 2  
14 diabetes.

15 I think that it's going to be very  
16 important to see what affect this has on actual  
17 practice because although algorithms that provide  
18 additional or variable -- I hate the term sliding  
19 scale because of the disasters that used to occur with  
20 it, and still do in some cases -- because insulin  
21 doesn't work backwards, of course.

22 So if you're treating a blood glucose,  
23 you're treating your inability to control that blood  
24 glucose previously. You're not treating -- you're not  
25 producing excellent control.

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1           And so I think it would be very important  
2 to see how the algorithms and the decisions and the  
3 revisions of the standard and variable dosages before  
4 meals or at various times during the day, how those  
5 decisions affect the overall control and the frequency  
6 of hypoglycemia.

7           I agree with everything else that's been  
8 said about the fact that this is -- that this can't  
9 replace the available technologies, but it certainly  
10 is a step in the right direction.

11           I would also wonder if there might not be  
12 a consideration of having a vibratory model for those  
13 individuals who having hearing difficulty or who sleep  
14 very soundly. Having retired from active practice,  
15 when I would wake up -- before the telephone would  
16 ring, I could hear that first vibration and I would  
17 wake up.

18           Now I would have to have a vibratory or  
19 some kind of maybe extra electrical current or  
20 something to wake up. But I think that's certainly a  
21 consideration. I don't know how many people with  
22 diabetes are deaf or sleep more soundly than others.

23           Or might be sleeping more soundly when  
24 they have hypoglycemia. And I think that I'm a little  
25 concerned about an audible signal providing

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1 overconfidence.

2 DR. HARRINGTON-FALLS: Beverly Harrington-  
3 Falls.

4 I think Dr. Janosky made the most  
5 pertinent point during the discussions earlier in that  
6 this device has been comparing values to glucometer  
7 readings when they are inherently less accurate than  
8 the laboratory readings.

9 So it's almost like we're aiming at a  
10 target that might not be in the right position to  
11 begin with. Overall, I do think that the data as  
12 presented support the proposed intended use. And of  
13 course, I add my two cents worth regarding the need  
14 for child studies.

15 CHAIRMAN NIPPER: Dr. Andrade, question  
16 one.

17 DR. ANDRADE: Yes, we're being asked to  
18 look at a device that has two features that, at least  
19 in my experience, have never been available before.  
20 One is a semi-continuous, wearable device for which  
21 there is really very, very little experience, sort of  
22 anything to compare to or, let us say, calibrate  
23 against.

24 And the other is a minimally invasive,  
25 non-blood derived device. And again, there's very,

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1 very little experience, if any, to compare it to. So  
2 we really have the problem of wanting enormous amounts  
3 of data and information and new research hypothesis  
4 and a whole variety of other things which, having such  
5 a device would, in many respects, actually facilitate  
6 getting that data.

7 So I frankly see this as an enormous  
8 research tool, as well as what's it's being proposed  
9 to do. So, in my estimation, all of the data that we  
10 would love to see, much of it is likely to be  
11 forthcoming if the device is indeed made available.

12 And most of that data would not be  
13 forthcoming, I think, if the device were not made more  
14 readily available. So I think given the application  
15 that they have proposed, that they've put together the  
16 data package that supports that reasonably well.

17 And my hope and expectation is that all  
18 the additional questions, or many of them at any rate,  
19 would be answered as time marches on and the  
20 experience base grows.

21 CHAIRMAN NIPPER: Mr. Reed, we've got  
22 about three minutes before we're going to suspend for  
23 public comments.

24 MR. REED: I'll talk fast.

25 CHAIRMAN NIPPER: Thanks.

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1 MR. REED: The data does support the  
2 intended use. I see a couple areas where this is  
3 particularly important. One for newly diagnosed  
4 diabetics who need an eye opener about what's going on  
5 when they eat, what's going on between the times when  
6 they might test, if you can get them to test with  
7 finger stick methods.

8 It's also something that would be very  
9 important for pump users to analyze where their basal  
10 rates are, what's going on in their body at a given  
11 time. Very important, very important items.

12 It does need to have clear and unequivocal  
13 directions that dosing, particularly for a  
14 hypoglycemic event, should not be done based on a low  
15 reading from the GlucoWatch; that you need to do  
16 finger sticks along with it.

17 CHAIRMAN NIPPER: Thank you.

18 Ms. Kruger, excuse me if we suspend  
19 answers to question one because we'd like to open --  
20 to begin this afternoon's open public hearing. We  
21 have some public attendees who have contacted the  
22 executive secretary prior to the meeting.

23 They're going to address the panel and  
24 present information relevant to the agenda.

25 Speakers, remember, are asked to state

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1 whether or not they have any financial involvement  
2 with the manufacturer of the product being discussed  
3 or with their competitors. So that said, the Chair  
4 recognizes Jack Keating.

5 MR. KEATING: Thank you. My name is Jack  
6 Keating and --

7 CHAIRMAN NIPPER: Turn the mic up a little  
8 bit, Mr. Keating. There you go.

9 MR. KEATING: Is that better?

10 CHAIRMAN NIPPER: Yes, that will work.

11 MR. KEATING: Wow, all this is giving me a  
12 high blood sugar here. Lot of stress here for me.

13 Anyway, I would like to say thank you to  
14 the panel and the FDA for allowing me to speak here  
15 today. I have Type 1 diabetes. I developed the  
16 disease seven years ago actually this month, and I  
17 decided to come here today because I took part in the  
18 clinical studies for the GlucoWatch monitor and I  
19 wanted to talk a little bit about that.

20 And I'll just start by saying that the way  
21 that I see this device and the issues that have been  
22 discussed here today, I believe that the GlucoWatch  
23 could make an enormous difference as far as therapy is  
24 concerned for Type 1 diabetes, which is what I have.

25 And in the spring, summer and fall of

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1 1998, I was in a number of different studies. Most of  
2 them were in the clinical setting. One of them did  
3 involve a home usage study at my house. And the thing  
4 that made the biggest impression upon me, in addition  
5 to seeing how this device, at least in my own mind,  
6 would help me in my therapy decisions, was spending  
7 all day long with other people who I'm assuming most  
8 of them probably had Type 1 diabetes.

9 I didn't go around and ask everyone. But  
10 we spent all day long. If you think this is a  
11 marathon meeting, I can say spending from 7:00 in the  
12 morning until I don't know what time we got out of  
13 there -- we were away from our families all day long.

14 And this is very much a disease that, to  
15 me at least, is a very private disease. I don't hide  
16 it, but, you know, I need to make decisions every day  
17 and, you know, I had never met a lot of other people  
18 that have this disease.

19 And anyway, the thing that just astounded  
20 me were the stories that the people I was in these  
21 trials with told me. And almost to a man or a woman,  
22 people told me stories that to us, because we live  
23 with this disease, maybe I -- we thought were funny,  
24 but many of these stories were tragic -- you know, or  
25 tragedies narrowly averted with the help of other

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1 people.

2 And I'm talking specifically about  
3 hypoglycemic attack episodes where, you know, you get  
4 blindsided and you don't know what your blood sugar  
5 is. The next thing you know, you know, you're either  
6 on the verge of unconsciousness or someone's helping  
7 you out.

8 And I guess I hadn't planned on bringing  
9 this issue up with my comments, but since a lot of the  
10 questions have been about the skin irritation, I  
11 wanted to just speak about myself and the trials.

12 And I believe I had seven actual  
13 applications of the watch. At one time I had a couple  
14 of them going. But I have very sensitive skin, and I  
15 believe, looking at the slides we saw this morning,  
16 that I would fall into the category of the slight and  
17 moderate skin irritation.

18 But what a lot of us found that are also  
19 on insulin pump therapy is that the pump sites that we  
20 change every three days with the adhesive tape or  
21 whatever it all comes together causes like a dermal  
22 burn or irritation or whatever, and I see the  
23 irritation from the watch is extremely minimal.

24 I mean, we're talking about the extraction  
25 sites that actually -- excuse me -- the irritation

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1 area about the size of two dimes. And I guess I would  
2 fall into the camp that, you know, I'm sure I could  
3 have put some cream on it if I wanted, but, you know,  
4 they went away in a couple of days.

5 And I know I'm speaking just for myself,  
6 but in terms of looking at the pros and cons of what  
7 something like this would offer, I see it, for myself  
8 at least, as not an enormous thing. But one thing  
9 else I wanted to say is that in diabetes therapy, many  
10 of us try to attain the best hemoglobin A1C values  
11 that we can in, you know, the six or seven percent  
12 range, or depending upon your physician.

13 But a lot of people don't realize that  
14 there's a cruel paradox that follows. When we follow  
15 physician directed orders to attempt good control, we  
16 place ourselves at significantly greater risk of  
17 incidence of severe hypoglycemia. And it's kind of  
18 crazy. You know, by following the doctor's orders,  
19 you can literally put yourself in harm's way.

20 And I would say today, as I see this  
21 device and I see, you know, the information that's  
22 been presented, if it's -- you know, the average is to  
23 blood sugars a day that people are checking or four,  
24 the incidence of, you know, missing these hypoglycemic  
25 episodes -- I guess all I would say is to me, if

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1 information is power, the lack of information, as it  
2 pertains to this disease, is a lack of power.

3 And you know, I see this disease as  
4 managing a lot of important information. It's a  
5 tightrope walk every day balancing, you know, your  
6 diet, your exercise, your activity and your insulin.  
7 And I believe we're the types of people, as -- I  
8 believe it was Ms. Kruger said you trusted your  
9 patients and not the practitioners.

10 I don't know how you said that, but -- I  
11 have to believe, meeting with these other patients at  
12 this clinic in this setting, I really think that we're  
13 competent -- or at least with the education and  
14 everything else, that this could certainly be  
15 incorporated as a key tool for diabetes management.

16 And I truly hope that the features that  
17 the watch offers would be approved or seriously  
18 considered today. So I hadn't planned to answer  
19 questions; but since I was in the trials, if anyone  
20 had any questions for me, I would be happy to answer  
21 them.

22 CHAIRMAN NIPPER: The information was  
23 available to you from the watch, at least in part of  
24 the trial?

25 MR. KEATING: No, sir.

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1 CHAIRMAN NIPPER: Oh, okay. So you --

2 MR. KEATING: I was in a completely  
3 blinded study, so we -- believe me, I think everyone  
4 in the room would have been jumping up and down if we  
5 knew -- because we did, most of the studies that I was  
6 in, we pricked our fingers twice an hour and we loved  
7 it.

8 CHAIRMAN NIPPER: And it was all sent to  
9 the data center directly?

10 MR. KEATING: Right.

11 CHAIRMAN NIPPER: So there was no trial, I  
12 guess, that had -- that made data available to people?

13 MR. KEATING: That I wouldn't know.

14 CHAIRMAN NIPPER: Okay, thank you very  
15 much, Mr. Keating, and good luck to you.

16 MR. KEATING: Thank you.

17 CHAIRMAN NIPPER: Our next listed speaker  
18 is Cynthia Wood. Is Ms. Wood here? We'll come back  
19 to her if she's still here. Debbie Ellington. Ryan  
20 Harvey. Here we go. Now we're ready.

21 MR. HARVEY: Hello. My name is Ryan  
22 Harvey. I'm 11 years old. And just two years ago, I  
23 was diagnosed with diabetes. The reason I'm here is  
24 because of Cygnus's GlucoWatch, which I hope will end  
25 finger sticks. For the last two years, I've had to

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1 prick my finger with a needle six to eight times a  
2 day, even more on days when I play sports, to check my  
3 blood sugar.

4 Sometimes I wake up in the morning very  
5 tired and I have a headache because I went low during  
6 the night, so I end up missing school. Not that  
7 missing school is bad, but with such a bad headache, I  
8 sleep most of the day.

9 Also, when I play sports, I sometimes have  
10 to pull myself out of the game because I feel low. If  
11 I have the watch, my whole life will become easier.  
12 Instead of pricking my finger seven times a day, with  
13 just a press of a button I can get an accurate blood  
14 reading.

15 Also, I could program it to beep when I am  
16 at 100 -- when I am below 100. Who knows, maybe the  
17 watch will even lead to insulin in a pill for Type 1  
18 diabetics. Another reason I'm here is that because  
19 after learning about the watch, I have invested in  
20 Cygnus's stock using my money I make selling  
21 newspapers at Dunkin' Donuts and a little of my  
22 birthday money.

23 I invested in this because I believe in  
24 it. Almost every day I look up how Cygnus does in the  
25 paper or on the Internet.

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1 (Laughter.)

2 I really hope Cygnus will get the watch  
3 approved because it will make a lot of other diabetics  
4 and me happy not having to prick ourselves and make  
5 tight control easier. Now that I have told you what I  
6 hope to happen, I will tell you a little bit about  
7 myself.

8 I live in Holliston, Massachusetts, an  
9 hour from Boston, with my mom, who is sitting right  
10 over there; my dad, Scott, who stayed home with my ten  
11 year old brother; and my adorable five year old dog,  
12 Maggie.

13 Ever since I was diagnosed with diabetes,  
14 my family and I have done almost every Walk-A-Thon and  
15 Bike-A-Thon and raised about \$10,000 for ADA. Also,  
16 my dad and I are going to bike 150 miles next summer  
17 with our new tandem bicycle for the ADA.

18 I have also been to Camp Joslin twice and  
19 hope to go again next year. Thank you and have a  
20 great Christmas or Hanukkah, and have a great New  
21 Year.

22 (Applause.)

23 CHAIRMAN NIPPER: Thank you, Ryan.

24 Our next speaker is Michael Komondy.

25 I hope I've pronounced your name

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1 correctly.

2 MR. KOMONDY: Komondy, correct.

3 CHAIRMAN NIPPER: Yes.

4 MR. KOMONDY: Good afternoon.

5 I'd like to thank you for the opportunity  
6 to speak before you for what I hope is the approval of  
7 the GlucoWatch and all of its features. On March 4,  
8 1993, I lost my father due to complications of  
9 diabetes. I lost my father, my mentor and my best  
10 friend.

11 I watched the last five of his years  
12 wither away. There was a man who was strong, alert,  
13 intelligent and witty deteriorate in front of my eyes.  
14 To add insult to injury, on December 19, 1998, my two  
15 year old son Donald was diagnosed.

16 As you can tell, this disease has consumed  
17 the majority of my life. I remember as a child  
18 waiting anxiously for my father to come home. Of  
19 course it was because we loved him, but it was also  
20 because we weren't sure if he was going to bottom out  
21 and black out on the way home.

22 As far as I could remember, this happened  
23 about eight times. There was that dreadful phone call  
24 about 8:30 when he was already an hour past his  
25 arrival time. But times have changed. Now technology

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1 is different.

2 People watch their sugars much more  
3 closely. And people are much more aware of the  
4 complications associated with diabetes. Therefore,  
5 more and more people are beginning to use intensive  
6 therapy for insulin.

7 A friend of mine is a salesman and he's  
8 told me countless stories of how he blacked out in the  
9 middle of the day while driving, at a meeting, with no  
10 warning of a crash. My brother-in-law Tom is a  
11 diabetic for 40-some-odd years.

12 He also has the same thing happen to him.  
13 Without reason, all of the sudden the numbers go low,  
14 you pass out. If you're lucky, if you're lucky,  
15 someone is around you who knows and is able to take  
16 care of you.

17 If you're unlucky, as so many are, there  
18 is nobody around. As a volunteer fireman and an EMT  
19 in the small town of Basking Ridge, New Jersey, we go  
20 on at least half a dozen calls a week related to  
21 diabetic problems.

22 People are at their cubicles and they  
23 crash because they go too low. No indication  
24 whatsoever it's going to happen. They didn't do  
25 anything wrong. Took their insulin, they ate. All

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1 the sudden, we show up, face first in a desk.

2 Or maybe they ran off the road. Or maybe,  
3 God forbid, they even hurt and killed somebody as a  
4 result. As many of you know, a diabetic with a cold  
5 has their blood sugar levels all over the place. They  
6 may crash in the middle of the night without any  
7 reason.

8 We may stay high due to an infection.  
9 Again, my brother-in-law Tom shared with me how he  
10 checks his blood sugar every two hours when he has a  
11 cold. Every two hours, he sets his alarm to get up.  
12 If that alarm rings three times and he doesn't get up,  
13 his wife panics.

14 Gets up to check because he's afraid.  
15 He's afraid he may not wake up in the morning. So  
16 picture that glucometer with that noise that it makes  
17 in the dead of the night will wake you up. It will  
18 wake up your loved ones who have your monitors on.

19 Every two hours, for a five to ten day  
20 period, that man checks his blood sugars. And even  
21 with doing that, he still has missed lows. We live in  
22 a society today where we have every kind of early  
23 warning detection device known.

24 On the way down here, I knew if there was  
25 radar up ahead.

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1 (Laughter.)

2 My gas tank was running low, the light  
3 came on and there was a beep. I knew to pull over and  
4 get gas. We have CO<sub>2</sub> detectors, smoke detectors, heat  
5 detectors. I have alarms on my doors and windows so,  
6 if somebody enters, I know my children are safe.

7 And now we finally have the GlucoWatch  
8 that can simply give us an indication, an early  
9 warning indication, of where we're going -- too high  
10 or if we're going too low.

11 So now visualize that salesman driving  
12 down the road and suddenly his GlucoWatch starts  
13 beeping. He knows that his sugars are out of whack.  
14 He can pull over and react. He can pull something out  
15 of his bag to eat or give himself a dose of insulin.

16 Or when Tom is sleeping in the middle of  
17 the night and his watch goes off, he can simply get up  
18 and take care of himself. The quality of life for the  
19 diabetic, the spouse, the family and the safety of the  
20 community as a whole will be much improved by this  
21 device.

22 Maybe those early indications will keep  
23 those from passing out and going into a coma. Or  
24 maybe that alarm will help someone -- help someone  
25 with their highs and keep them under control to avoid

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1 loss of sight, kidney disease, or loss of limbs.

2 Many people that I have told that I'm  
3 coming here to speak before you said this is great,  
4 sign me up, where do I go. I'll take that 20 percent  
5 difference. I'll take that indication that I'm on my  
6 way down as opposed to I check myself at 2:00 in the  
7 morning, I'm 125.

8 Four o'clock, I'm 275. Did I bottom and  
9 am I rebounding, or is my insulin wearing off? This  
10 will give us a tracking indication that will help us  
11 out. The positives are outstanding. And if you lived  
12 with diabetes around you for as long as I have, you  
13 know that this is such a great, great device.

14 It would be a godsend just not to the  
15 people directly affected with diabetes, but in the  
16 entire community in which they live.

17 In conclusion, I asked a friend with  
18 diabetes how he felt about the GlucoWatch and the  
19 possibility of a small rash.

20 He said, "Geez, let me see. The choices  
21 here are between crashing and possibly going into a  
22 coma in the middle of the night, or highs that  
23 deteriorate my body. or a watch that gives me an early  
24 indication and possibly gives me a small rash? Well,  
25 since the last time I crashed I had a rug burn on my

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1 forehead, nose and chin, I think I'll take my chances  
2 with the possibility of that small rash."

3 I have no financial connections with this  
4 firm, any of its competitors. The only financial  
5 connection I have is, hopefully, when I become an old  
6 man, my son will still be around to take care of me.

7 Thank you.

8 CHAIRMAN NIPPER: Thank you very much.

9 In concluding the public hearing, I have  
10 two letters and a statement to read. In addition,  
11 there were 38 letters received from all over the  
12 United States, Brazil, the Netherlands and Singapore.

13 Most of these letters were from mothers of  
14 diabetic children. All supported the approval of  
15 GlucoWatch or non-invasive monitors or minimally  
16 invasive monitors for the improvement in quality of  
17 life, for better management of disease, for continuous  
18 monitoring and tracking of fluctuations, and the need  
19 for read out and alarm especially for hypoglycemia.

20 This is a statement to the Clinical  
21 Chemistry and Toxicological Devices Panel of the  
22 Medical Devices Advisory Committee supporting pre-  
23 market approval of the GlucoWatch monitor.

24 "Please will you accept the GlucoWatch. I  
25 and other kids and other people really need it badly.

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1 I understand if you can't do it if it doesn't work or  
2 if you don't think it's ready yet. The reason I need  
3 the GlucoWatch is because I have been getting low.

4 "For instance, in gym class I have been  
5 down to 48 and 32. I think when I am running around,  
6 I don't concentrate on how I am feeling low or high.  
7 When I am low, I don't know because I am running  
8 around and playing and active.

9 "So when the GlucoWatch beeps, I think it  
10 would help me and other people a lot. I think it is  
11 so cool how the GlucoWatch works. One of the parts I  
12 like is that you don't have to carry it around in your  
13 pocket. You have it on your wrist.

14 "It's just like a watch, except it keeps  
15 track of your blood sugar. You have the opportunity  
16 to make one of the best things right now, so please  
17 try to do it. Thank you."

18 And it's signed Isabel Gordon, who is  
19 Isabel Rose Sumara Gordon, 3208 North 49th Street,  
20 Milwaukee, Wisconsin. And she attached a picture,  
21 which I'll circulate to the panel.

22 The second letter is from the Juvenile  
23 Diabetes Foundation, a statement by the Juvenile  
24 Diabetes Foundation International regarding non-  
25 invasive and minimally invasive blood glucose

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1 monitoring.

2 "Non-invasive and/or minimally invasive  
3 blood glucose measurement have the potential to  
4 provide valuable information that could result in  
5 significant improvements in the treatment of insulin  
6 dependent diabetes and have a positive impact on the  
7 quality of life of people with this disease.

8 "The JDF believes that there is a pressing  
9 need for devices capable of measuring blood glucose  
10 levels non-invasively and/or minimally invasively, and  
11 we have strongly supported research in this area.

12 "We welcome the efforts by industry to  
13 develop these technologies and believe that devices  
14 judged by the FDA to be safe and effective could lead  
15 to improvements in the management of diabetes.

16 "Further, the JDF believes that studies  
17 should be undertaken as expeditiously as possible in  
18 order to determine the potential role and value of  
19 these devices in the management of children with  
20 diabetes." Dated November 24, 1999.

21 Finally, a statement was given to us today  
22 from the American Society of Clinical Pathologists  
23 dated December 6, 1999.

24 "The American Society of Clinical  
25 Pathologists appreciates this opportunity to comment

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1 on the pre-market approval application of a device  
2 intended for frequent, automatic and non-invasive  
3 monitoring of glucose levels in adults with diabetes.

4 "ASCP is a nonprofit medical specialty  
5 society organized for educational and scientific  
6 purposes. Its 75,000 members include board certified  
7 pathologists, other physicians, clinical scientists,  
8 and certified scientists and technicians.

9 "These professionals recognize the society  
10 as a principal source of continuing education in  
11 pathology and is the leading organization for the  
12 certification of laboratory personnel. ASCP's  
13 certifying board registers more than 150,000  
14 laboratory professionals annually.

15 "ASCP is not here today to speak in favor  
16 of, nor in opposition to, this particular device.  
17 However, we do have concerns regarding the quality of  
18 clinical data sets for non-invasive glucose  
19 monitoring. Non-invasive glucose monitoring devices  
20 should have analytical performance that is roughly  
21 equivalent to existing conventional point of care  
22 glucose devices.

23 "The accurate analytical performance and  
24 precision of any device is essential for patient care.

25 Technical performance and correlation with laboratory

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1 methods should be evaluated. The American Diabetes  
2 Association defines accuracy goals for the technical  
3 performance of glucose meters.

4 "In 1987, the ADA recommended that glucose  
5 concentrations determined with portable meters should  
6 fall within 15 percent of the laboratory values for  
7 meters available at that time, and that the future  
8 goal should be to reduce this variability within 10  
9 percent at glucose concentrations between 30 and 400  
10 mg/dL.

11 "In 1994 and 1996, the ADA recommended  
12 variability of within 5 percent of laboratory values  
13 for future glucose meters. To our knowledge, these  
14 guidelines have never been met in any independent  
15 evaluation of glucose meter performance.

16 "Guidelines of the National Committee for  
17 Clinical Laboratory Standards recommends that glucose  
18 meters fall within 20 percent of the laboratory value  
19 for glucose concentrations higher than 100 mg/dL. The  
20 ADA states that the exact accuracy recommendations for  
21 clinical management have not been defined rigorously.

22 "Possibly the clinical guidelines would be  
23 less stringent; but until clinical accuracy and  
24 precision guidelines are set, the above cited  
25 technical guidelines must be used.

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1           "The results of technical evaluations such  
2 as the study published in April of 1999, American  
3 Journal of Clinical Pathology, demonstrates that the  
4 use of the meters under normal conditions likely  
5 introduces greater variability in test results than  
6 the results used to gain approval for the devices.

7           "Thus, the technical guidelines are not  
8 being met. If the data the Food and Drug  
9 Administration receives for approval purposes are  
10 indicative only of what an instrument is capable of  
11 achieving under optimum operating conditions, there is  
12 reasonable cause for concern regarding the quality of  
13 clinical data sets.

14           "Again, thank you for your consideration  
15 of our comments on non-invasive monitoring of glucose  
16 devices."

17           To the best of my knowledge, that  
18 concludes the people who wish to testify at the open  
19 public hearing. I might call on the two people who  
20 did not answer to call initially, Cynthia Wood or  
21 Debbie Ellington.

22           Okay, seeing no response, the public --  
23 open public hearing is now closed.

24           Ms. Kruger, we were back on question  
25 number one for you. And my question one is, do the

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1 data support the proposed intended use of the  
2 GlucoWatch Biographer? If not, what adjustments in  
3 intended use or additional data to support intended  
4 use might be required?

5 MS. KRUGER: I would agree that it does.  
6 However, I would still like to see data with Type 2  
7 individuals on oral agents.

8 CHAIRMAN NIPPER: Okay, thank you.

9 Dr. Habig.

10 DR. HABIG: I also agree the data support  
11 the intended use. I don't feel adjustments or  
12 additional data to support that are needed. The three  
13 intended use statements that are in the slides I think  
14 are specific enough and carefully worded such that the  
15 indications are appropriate and the data to support  
16 them are adequate.

17 CHAIRMAN NIPPER: Thank you.

18 My answer to question one is that the data  
19 does support the intended use. I don't believe  
20 additional data to support intended use is required at  
21 this time. I think it's obvious that if the intended  
22 use is broadened in any way, I think that appropriate  
23 data should be submitted to the FDA, but that goes  
24 without saying.

25 Question two: What controls might be

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1 applied to this product to ensure safe and effective  
2 use? There are several suggestions from the FDA:  
3 that the intended use be modified to -- only so that  
4 GlucoWatch Biographer readings be used only to decide  
5 when extra finger stick testing is indicated; (b)  
6 should real-time readings for high and low GlucoWatch  
7 values be replaced by error codes; (c) should special  
8 educational efforts be put into place to ensure proper  
9 understanding of the use of the device.

10 And then they cite the Pro-Time Home Use  
11 Kit. And other labeling or use controls that might be  
12 appropriate for this device.

13 You might as well keep going, Bob.

14 DR. HABIG: Thank you. I have actually  
15 considered answers for all of the (a), (b), (c) and  
16 (d) parts. I think that parts (a) and (b), the answer  
17 is no, the current intended use is adequate and the  
18 real-time values are okay.

19 I like the idea of special education with  
20 the prothrombin time as the model, particularly as we  
21 stated before to involve clinicians who are going to  
22 prescribe the device. And for part D, I have no other  
23 specific suggestions.

24 CHAIRMAN NIPPER: Ms. Kruger.

25 MS. KRUGER: For part A, I stated no,

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1 there's no changes needed. B, no also. I've already  
2 spoken to the issue of education and pretty adamant  
3 about making sure that that's accomplished. And as  
4 far as D, just as long as the labeling is consistent  
5 and pretty fanatical about saying if you have low  
6 blood sugar rechecking, or if you're going to adjust  
7 medication based -- it should not be based on just the  
8 reading, I'm fine.

9 CHAIRMAN NIPPER: Thank you.

10 Mr. Reed.

11 MR. REED: I agree with Davida that (a)  
12 and (b) are no. (c), there should be some strong  
13 educational material. And as far as (d), unequivocal  
14 statements about treating hypos especially.

15 CHAIRMAN NIPPER: Thank you.

16 Dr. Andrade.

17 DR. ANDRADE: I basically agree with the  
18 previous two speakers.

19 CHAIRMAN NIPPER: Thank you.

20 Dr. Harrington-Falls.

21 DR. HARRINGTON-FALLS: For question two,  
22 (a) would be no. Two, that's already included in the  
23 features of the monitor showing less than and greater  
24 than. Three, my main concern there is that there be a  
25 step-wise educational process so that patients

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1 understand how to use a glucometer rather than simply  
2 starting on the watch so that they know how to  
3 correlate those values.

4 And for other labeling, not at this time.

5 CHAIRMAN NIPPER: Thank you.

6 Dr. Rosenbloom.

7 DR. ROSENBLROOM: Yes, under (a) I think  
8 that making sure that the decision process requires  
9 glucose monitoring, blood glucose monitoring, will  
10 cover that; real-time readings be replaced by error  
11 codes; no, but I agree with the earlier comment that  
12 the educational materials should very clearly state  
13 what the error is for a specific number.

14 We have that problem all the time with  
15 blood glucose meters. People think that's a real  
16 number. C, most emphatically yes, along with  
17 everybody else. Are there other appropriate labeling  
18 or use controls that might be appropriate?

19 I do have some comments about the manual,  
20 but I think that's going to be changed so much that I  
21 don't want to go into detail about that.

22 DR. RIFAI: I agree also with what's  
23 already been said. Really the success of this product  
24 in large is going to be dependent on the educational  
25 materials that's going to be provided by the company.

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1 CHAIRMAN NIPPER: Thank you, Dr. Rifai.

2 I believe that 2(a) should be no, 2(b)  
3 should be no, 2(c) yes. I am -- don't have enough  
4 brain cells left to remember the home use prothrombin  
5 time meters model, but I assume it's pretty rigorous  
6 and I hope it works.

7 And if it works and is applicable to this  
8 device, I think something that is -- that does not  
9 interfere with the distribution of this device as  
10 appropriate to people who need it, but, on the other  
11 hand, ensures that the patient care population and the  
12 patient knows how to use it is appropriate.

13 And I'd like to see the FDA work with the  
14 sponsor to develop appropriate educational efforts.  
15 Other labeling or use controls -- I think this is --  
16 the labeling is adequate now. I've got some minor  
17 changes that I'm going to submit to the FDA.

18 For example, you can nitpick a lot, but I  
19 noticed that in the labeling and the presentations  
20 today we refer to glucometer readings as a standard B  
21 traditional or B routine. I think we ought to figure  
22 out what these are.

23 I don't think they're standard. They may  
24 be traditional. So anyway, I think we can get our  
25 language cleaned up so that the patients will

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1 understand it and maybe the doctors will, too.

2 Dr. Clement.

3 DR. CLEMENT: Sure. Basically, I agree  
4 with all the other panel members.

5 CHAIRMAN NIPPER: Speak into the  
6 microphone, please.

7 DR. CLEMENT: No for (a), no for (b), yes  
8 for education for clear purposes. On terms of the  
9 labeling again, I think the data as presented looks  
10 very impressive except on the hypoglycemic range. And  
11 I don't think the data supports the use of this  
12 machine to detect hypoglycemia on majority of the  
13 cases.

14 It may miss it, and I'm concerned about  
15 that. And possibly the labeling could be modified to  
16 account for that.

17 CHAIRMAN NIPPER: Dr. Doumas.

18 DR. DOUMAS: I agree fully with Dr.  
19 Clement's comments.

20 CHAIRMAN NIPPER: Thank you.

21 Dr. Manno.

22 DR. MANNO: Two(a) is no.

23 CHAIRMAN NIPPER: Speak into the  
24 microphone, please.

25 DR. MANNO: 2(a) is no; however, you've

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1 got the warnings in there for not depending on the  
2 number when the alarm goes off and recommending finger  
3 stick, but it needs to be highlighted in some way, put  
4 in a box or some way to really draw attention to it,  
5 to emphasize it.

6 2(b) is no, (c) is yes, and (d) is -- I  
7 think the shaving instructions -- (laughter) -- beat a  
8 dead horse.

9 CHAIRMAN NIPPER: You're saying shaving is  
10 a hairy issue?

11 (Laughter.)

12 This is getting late in the day. I  
13 apologize.

14 Dr. Everett, how about question two?

15 DR. EVERETT: 2(a) is no. 2(b) is no.  
16 But as it relates to 2(c), I would like to see some  
17 effort -- I'm not sure at this point exactly what, but  
18 one of the things I am sure of, and that is if you  
19 give a patient a number for his blood sugar, he's  
20 going to try and treat himself based on that number  
21 sooner or later, particularly those guys who can't  
22 afford the sticks for the Accucheck machines.

23 Those are relatively expensive. So once  
24 this watch goes on and they look at their number,  
25 they're -- sooner or later, somebody's going to try

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1 and treat themselves based on that number.

2 So I think somewhere in there, there  
3 should be special emphasis, whether it's put into the  
4 educational component or changing that very high  
5 number or that low number which seems to be built in  
6 already to a code as opposed to an actual blood sugar.

7 And then (d), I would say no. In its  
8 current stage, I think it's appropriate for what is  
9 intended, but not for anything else at this time.

10 CHAIRMAN NIPPER: Dr. Janosky.

11 DR. JANOSKY: Yes, for part (a) I would  
12 say no. For part (b) I would say yes. Just very  
13 similar to what Dr. Everett is saying, but I come to a  
14 different conclusion in that, instead of saying error  
15 codes for (b), either some categorization, whether  
16 that categorization is hyper or hypo, or high or low,  
17 or an asterisk with the actual value that the patient  
18 then knows they need to do some further action.

19 (c) would be yes. And (d) -- one of the  
20 issues that I hear most of the public in open public  
21 forum talking about is using this device either  
22 eventually or perhaps very shortly as somewhat of a  
23 continuous monitor.

24 And my understanding of the data is, for  
25 the most part, it only has been tested for a maximum

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1 of 12 hours. So I'm very concerned about that. What  
2 happens in the 13 hour, seven day, what happens in  
3 that respect?

4 So I don't know if that's appropriate for  
5 (d) in terms of labeling or where that would be. But  
6 given that it only has been tested in a maximum of 12  
7 hours, from what I understand, that should be stated  
8 somewhere within the labeling.

9 I might be mistaken and it was more than  
10 12 hours, but --

11 CHAIRMAN NIPPER: Do we have a question  
12 for the sponsor?

13 DR. JANOSKY: Well, that is a question,  
14 how about that?

15 CHAIRMAN NIPPER: Okay.

16 DR. PITZER: This is Ken Pitzer.

17 Yes, after the 12 hours, the device will  
18 automatically stop glucose monitoring and it will say  
19 off/end. If the patient wants to continue, they would  
20 need to get out another AutoSensor, select a different  
21 site and start the whole process over again.

22 DR. JANOSKY: Okay, so it automatically  
23 shuts off and nothing else can happen?

24 DR. PITZER: Absolutely.

25 DR. JANOSKY: So to get it going again,

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1 they have to replace the sensor, is that correct?

2 DR. PITZER: Replace the AutoSensor and  
3 start the warm up process all over again.

4 DR. JANOSKY: Okay, so then the issue goes  
5 away?

6 CHAIRMAN NIPPER: Yes, I thought it was a  
7 moot issue, but I wanted to hear from the sponsor.

8 Dr. DiGiovanna, how about question two?  
9 And you're going to go ahead and answer question three  
10 after that because I know you're going to want to,  
11 okay?

12 DR. DiGIOVANNA: Okay, I'll accept that  
13 challenge.

14 2(a) no, 2(b) no, 2(c) yes. 2(d) I agree  
15 with Dr. Manno. I think that it will be nice to have  
16 some clinical assessment as to whether or not shaving  
17 is going to affect the readings, because I think  
18 that's going to be a very frequently used procedure  
19 from what I have heard about the use of this device.

20 The other thing that I would think should  
21 be included in the labeling, they give some somewhat  
22 specific direction as to the application of a cream  
23 after use, and I would probably think that they'd be  
24 better off being a little more specific to use a cream  
25 without various kinds of additives which might

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1 confound the readings.

2 With respect to three, question three,  
3 with respect to should performance of this device be  
4 assessed in additional studies of skin irritation and  
5 sensitivity either as a pre or post market condition  
6 of approval, I think the issue isn't so much the fact  
7 that there is an irritation that the device is  
8 associated with; it's the fact that there is some kind  
9 of a physiological phenomenon that's occurring.

10 And with the use that's intended, which is  
11 short term, that seems to not have an effect. But  
12 with the use that I think will be -- the way it will  
13 actually be used, I think it very well may have short  
14 term subacute and chronic effects.

15 And the assessment of that really is  
16 twofold. Number one, when one looks at a risk/benefit  
17 ratio, clearly this device has a tremendous amount of  
18 benefit compared to what's available. And the short  
19 term risk seems rather minimal.

20 The risk over longer term depends upon  
21 what may be precipitated by these events, whether it's  
22 a contact sensitization with some agent that may make  
23 the patient miserable for the rest of their life  
24 because they've become allergic to something they  
25 can't get rid of or other effects with respect to

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1 being able to use the device.

2 And I think that's reasonably easily  
3 testable either currently pre-market or in a phase  
4 four type environment with a simple study of more  
5 frequent use to determine whether there is or is not  
6 the development of contact sensitivity.

7 Preferably that would be sort of a study  
8 that would have some kind of clinical data with it  
9 since that's what we're talking about, both clinical  
10 photography and histologic evaluation, which I think  
11 several times today people have remarked that that's  
12 not been present and it's not clear exactly what is  
13 going on here.

14 And for the short term, that's probably  
15 not of an enormous concern. Over the long term, it  
16 may be of concern with respect to the accuracy of the  
17 measurements, with respect to the development of  
18 contact sensitization to various components that may  
19 have other implications for the person using it that  
20 they may not be aware of.

21 And the last issue is -- the two last  
22 issues are with respect to the only experience I'm  
23 aware of with chronic iontophoresis is chronic  
24 intermittent iontophoresis for hyperhidrosis. With  
25 the daily use over a very long period of term, no one

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1 is really -- I believe has a lot of experience with  
2 carcinogenic potential or other sorts of issues that  
3 may be related.

4 That might be something that's worthwhile  
5 to at least record in some way in a phase four venue.

6 The last of my issues is with respect to -- I think  
7 at some point this device is going to be widely used  
8 in children. The concern that I have with that is  
9 with -- children are smaller, but they're also  
10 different and they're not small big people.

11 Their skin is also very different. And  
12 many of the diseases we see in adults appear  
13 differently in children. And younger skin blisters  
14 far more easily than adult skin. So if we're seeing a  
15 large percentage of the adult patients blistering, we  
16 probably should expect to see more of that in the  
17 pediatric population.

18 So I think studies in children would need  
19 to be done if that's going to be widely used.

20 CHAIRMAN NIPPER: Thank you.

21 Does anyone on the panel have anything to  
22 add to what we heard from our dermatologist in answer  
23 to question three?

24 Yes, Dr. Habig.

25 DR. HABIG: I actually think the emphasis

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1 on some of the testing would be mitigated by the usual  
2 medical device reporting and the sponsor's complaint  
3 handling procedures, so I don't go quite as far into  
4 assuming we should have studies.

5 The phase four kind of thing is more of a  
6 drug kind of model, I suppose. I think it needs to be  
7 monitored, but I don't support specific studies either  
8 pre or post market, to answer number three.

9 CHAIRMAN NIPPER: Okay.

10 Are there any other additions to question  
11 three? Okay, you answer question four since you spoke  
12 up. We want to know what, if any, pre or post market  
13 conditions of approval -- and I would like to ask the  
14 panel to be as brief as possible, otherwise we may be  
15 waiting tables for a banquet of 200 people starting at  
16 7:00.

17 (Laughter.)

18 And so I'm not trying to cut off  
19 discussion, but let's be focused. If you suggest a  
20 pre or post market study, tell us what it is and  
21 whether it's pre or post.

22 Thank you.

23 DR. HABIG: I have no suggestions for pre  
24 or post market approval studies.

25 CHAIRMAN NIPPER: Good, thank you.

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1 Ms. Kruger.

2 MS. KRUGER: I have none either.

3 CHAIRMAN NIPPER: Mr. Reed.

4 MR. REED: None.

5 CHAIRMAN NIPPER: Dr. Andrade.

6 DR. ANDRADE: None.

7 CHAIRMAN NIPPER: Okay.

8 Dr. Harrington-Falls.

9 DR. HARRINGTON-FALLS: Of course, one of  
10 my patient populations would be gestational diabetes.

11 CHAIRMAN NIPPER: Pre or post?

12 DR. HARRINGTON-FALLS: Post, I'm sorry.

13 DR. ROSENBLOOM: And as I stated earlier,  
14 I think the effect on controls since we've really not  
15 seen any of that kind of data yet. And I would think  
16 that that would be obviously in the economic interest  
17 of the sponsor.

18 CHAIRMAN NIPPER: Thank you, Dr.  
19 Rosenbloom.

20 Dr. Rifai.

21 DR. RIFAI: No, I just want to bring out  
22 the issue again of they use the device in children,  
23 and I just hope this sponsor will be thinking about  
24 that on their way home tonight.

25 CHAIRMAN NIPPER: Thank you.

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1 I'd like to see the sponsor do some post  
2 market data gathering, not necessarily a study or a  
3 condition of approval, to focus on the hypoglycemic  
4 issue.

5 Dr. Clement.

6 DR. CLEMENT: I concur with Dr. Nipper. I  
7 think following incidence of hypoglycemia at night,  
8 that's a possibility by this device. Also, just a  
9 suggestion. It is more expensive to do, but it does  
10 give a lot more data -- is doing some type of plant  
11 study of either hyperglycemia or hypoglycemia.

12 In that case, that's totally independent  
13 of what the standard glucose level is and you can  
14 actually measure time of occurrence of reaching  
15 certain thresholds we talked about.

16 CHAIRMAN NIPPER: Thank you.

17 DR. DOUMAS: I agree with Dr. Nipper.

18 CHAIRMAN NIPPER: Thank you.

19 Dr. Manno.

20 DR. MANNO: I agree with the previous  
21 panel members who have spoken. I do have some concern  
22 over the alarm intensity. I think it would be very  
23 hard, as someone's already pointed out, to hear that  
24 if you are hypoglycemic.

25 It would be difficult to respond even at

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1 that higher level. I can't hear my Timex travel  
2 alarm, which sounds much like that. I cannot depend  
3 upon it to get up in the morning. So I think that  
4 that needs to be looked at as time goes on.

5 CHAIRMAN NIPPER: Thank you.

6 Dr. Everett, do you have pre or post  
7 market conditions of approval?

8 DR. EVERETT: No additional ones. I agree  
9 with you and Dr. Manno. That is, the hypoglycemic  
10 issue and the audible alarm, even though they  
11 mentioned the majority of patients could hear it, it  
12 did appear to be a bit soft.

13 For a person who is depressed, centrally  
14 depressed because of hypoglycemia, I find it difficult  
15 they would hear it. Of course, if you are not  
16 hypoglycemic, then you wouldn't be centrally depressed  
17 and you could hear it.

18 So my question really deals with whether  
19 people who truly are hypoglycemic can hear that alarm.

20 But I have no additional suggestions.

21 CHAIRMAN NIPPER: Thank you.

22 Dr. Janosky.

23 DR. JANOSKY: For the current indication  
24 of use, no.

25 CHAIRMAN NIPPER: Okay, thank you.

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1 Dr. DiGiovanna.

2 DR. DiGIOVANNA: Nothing in addition to  
3 what I've already mentioned.

4 CHAIRMAN NIPPER: Thank you.

5 With regard to question five, it appears  
6 that we have a yes or a no answer to this question.  
7 Since the device is known to occasionally skip  
8 readings and have unexpected shut offs, is the low  
9 glucose alert reliable enough to warn of hypoglycemic  
10 events, especially while sleeping?

11 We've had some of our panelists who have  
12 already addressed this. May we have a show of hands  
13 for yes votes? One, two, three, four, five, six,  
14 seven. Seven yes. How many no? One, two, three,  
15 four. And some people have abstained.

16 Is that okay with the FDA to do it what  
17 way? Thank you.

18 Are there any other -- Dr. Gutman is  
19 egging me on here, silently egging me on.

20 I'd like to open the floor to see if any  
21 of the panel has any additional remarks they'd like to  
22 make before we decide to vote. Okay, are we ready for  
23 the vote?

24 Now, do I do this thing or do you do this?

25 Okay, we have some new voting procedures. If you

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1 thought things were confusing before, I think these  
2 things may clarify them. I hope they do. Dr. Gutman  
3 has reminded me to ask the sponsor if they have  
4 anything they -- if the sponsors have anything you'd  
5 like to add as a result of our comments?

6 I don't hear any hypoglycemic alarms going  
7 off over there, so does any of the FDA -- did any of  
8 the FDA presenters have anything you'd like to add?  
9 Okay, thank you.

10 Okay, now our esteemed executive secretary  
11 can read her statement.

12 MS. CALVIN: The Medical Device amendments  
13 to the Federal Food, Drug and Cosmetic Act, as amended  
14 by the Safe Medical Devices Act of 1990, allows the  
15 Food and Drug Administration to obtain a  
16 recommendation from an expert advisory panel on  
17 designated medical device pre-market approval  
18 applications that are filed with the agency.

19 The PMA must stand on its own merits and  
20 your recommendation must be supported by safety and  
21 effectiveness data in the application or by applicable  
22 publicly available information.

23 Next.

24 Safety is defined in the Act as reasonable  
25 assurance, based on valid scientific evidence, that

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1 the probable benefits to health under conditions on  
2 intended use outweigh any probable risks.  
3 Effectiveness is defined as reasonable assurance that,  
4 in a significant portion of the population, the use of  
5 the device for its intended uses and conditions of use  
6 when labeled will provide clinically significant  
7 results.

8 Your recommendation options for the vote  
9 are as follows: number one, approval, if there are no  
10 conditions attached; number two, approvable with  
11 conditions. The panel may recommend that the PMA be  
12 found approvable subject to specified conditions such  
13 as physician or patient education, labeling changes,  
14 or a further analysis of existing data.

15 Prior to voting, all of the conditions  
16 should be discussed by the panel. Number three, not  
17 approvable. The panel may recommend that the PMA is  
18 not approvable if the data do not provide a reasonable  
19 assurance that the device is safe or if a reasonable  
20 assurance has not been given that the device is  
21 effective under the conditions of use prescribed,  
22 recommended or suggested in the proposed labeling.

23 Following the vote, the Chair will ask  
24 each panel member to present a brief statement  
25 outlining the reasons for their vote.

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1           As a reminder, the voting members,  
2 including the temporary voting members for today, are  
3 Drs. John DiGiovanna, Janine Janosky, James Everett,  
4 Barbara Manno, Basil Doumas, Stephen Clement, Nader  
5 Rifai, Arlan Rosenbloom, Beverly Falls, Joseph  
6 Andrade.

7           Thank you.

8           CHAIRMAN NIPPER:   Okay, now the change  
9 that we are going to operate under here has to do with  
10 the possibility of approvable with conditions. In  
11 panel meetings that I've chaired and been in before,  
12 the conditions issue has been a little bit hazy and  
13 not completely defined.

14           There are three main motions that you can  
15 -- that we can operate under, and it depends on who  
16 makes the motion. Someone who is a voting member will  
17 move either approval of the PMA without conditions, or  
18 approval with conditions, or not approvable.

19           At that time, the Chair will entertain a  
20 second to the motion. If the motion is seconded,  
21 there will be discussion. If there is -- if the  
22 motion is approvable with no conditions, we will then,  
23 after discussion, proceed to a vote up or down.

24           If that motion is defeated, we'll move to  
25 a different motion. And the same happens if someone

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1 moves not approvable. If that's defeated, we'll move  
2 to a new motion. If the motion is approvable with  
3 conditions, we may discuss that, and then each  
4 condition will be considered an amendment to the  
5 motion, as is required by Robert's Rules of Order.

6 We will then vote on each one of the  
7 conditions as an amendment to the motion. So  
8 therefore, we'll have a clear voting statement of who  
9 on the panel approves or who disapproves of each one  
10 of the conditions.

11 And therefore, if we decide to use  
12 conditions or to attach conditions to our approval, we  
13 need to state them clearly so they can be recorded and  
14 read back to the panel before we vote on them.

15 So at this time, the chair will entertain  
16 a motion to approve, to approve with conditions, or to  
17 not approve the PMA as presented today.

18 DR. ROSENBLOOM: I'd like to move approval  
19 with conditions.

20 CHAIRMAN NIPPER: Dr. Rosenbloom has moved  
21 that we approve with conditions. Is there a second?

22 DR. HARRINGTON-FALLS: Second.

23 CHAIRMAN NIPPER: Dr. Harrington-Falls has  
24 seconded.

25 Is there discussion at this time?

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1 Dr. Andrade.

2 DR. ANDRADE: This is more of a point of  
3 information. If we vote particular conditions, whose  
4 responsibility -- is it the FDA's responsibility to  
5 formulate those conditions and to set up a schedule  
6 and to see to it that they're met?

7 CHAIRMAN NIPPER: Dr. Gutman is nodding in  
8 the affirmative. Okay, other discussion?

9 Okay, does any -- is there an amendment to  
10 the motion that would state a condition of approval?

11 Dr. Rosenbloom.

12 DR. ROSENBLOOM: I'd like to suggest --

13 CHAIRMAN NIPPER: You need to speak in the  
14 microphone, please.

15 DR. ROSENBLOOM: I would like to suggest  
16 the following conditions, which I believe are  
17 consistent with the previous discussion. First that  
18 there be an extensive education program using the  
19 model for prothrombin time that was previously alluded  
20 to.

21 Secondly, that the labeling be revised  
22 according to recommendations from several of the panel  
23 members that would be furnished to FDA. And thirdly,  
24 that there be a post marketing evaluation of the  
25 effective -- the use of this device on hypoglycemia

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1 detection and frequency, hypoglycemia detection, and  
2 overall diabetes control as reflected in  
3 glycohemoglobin levels in Type 1 and Type 2 diabetes.

4 CHAIRMAN NIPPER: Is there a second to  
5 that amendment?

6 DR. CLEMENT: I'll second.

7 CHAIRMAN NIPPER: Dr. Clement has  
8 seconded. Is there discussion to those particular  
9 post market studies or to the amendment as Dr.  
10 Rosenbloom has made his motion on? The studies are  
11 education -- pardon me. The amendments and the  
12 conditions are the educational program, revised  
13 labeling to reflect a panel discussion, post marketing  
14 studies for hypoglycemic control, hyperglycemic  
15 control.

16 Yes.

17 DR. DiGIOVANNA: Question. Is this the  
18 limit of the conditions or can we add conditions?

19 CHAIRMAN NIPPER: You can add conditions,  
20 but we add them one by one. We'll vote up or down on  
21 these conditions. Then if there's a second amendment  
22 to add other conditions, we'll go through the same  
23 procedure.

24 And remember, we have a fairly tight  
25 deadline in here to do it.

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1 Other discussion or questions? Okay,  
2 we're ready for -- has the question been called?  
3 We're going to vote on the amendment of Dr. Rosenbloom  
4 seconded by Dr. Clement. So Dr. DiGiovanna?

5 DR. DiGIOVANNA: I agree, yes.

6 CHAIRMAN NIPPER: Dr. Janosky?

7 DR. JANOSKY: Need a point of  
8 clarification, please.

9 CHAIRMAN NIPPER: Yes.

10 DR. JANOSKY: The studies, are those post  
11 market?

12 CHAIRMAN NIPPER: Yes.

13 DR. JANOSKY: And would you please just  
14 state them again? I got lost in the --

15 CHAIRMAN NIPPER: Okay, education -- the  
16 education has to be -- education program has to be in  
17 place. Labeling needs to be revised according to the  
18 suggestions made by the panel. The post marketing  
19 study about the effectiveness of hypoglycemic control,  
20 hyperglycemic control and -- did I miss something, Dr.  
21 Rosenbloom?

22 DR. ROSENBLUM: Yes, let me clarify that.  
23 Hypoglycemia detection --

24 CHAIRMAN NIPPER: Hypoglycemia detection,  
25 thank you.

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1 DR. ROSENBLOOM: -- and frequency.

2 CHAIRMAN NIPPER: Okay.

3 DR. ROSENBLOOM: And hyperglycemia  
4 detection --

5 CHAIRMAN NIPPER: And frequency?

6 DR. ROSENBLOOM: -- and the effect of the  
7 use of the device on clinical outcome as reflected in  
8 glycohemoglobin concentration.

9 CHAIRMAN NIPPER: Okay, good. I apologize  
10 for missing the big pieces of that, but I was trying  
11 to write fast.

12 DR. ROSENBLOOM: And in Type 1 and Type 2  
13 diabetes.

14 CHAIRMAN NIPPER: Okay. Yes, Dr. Gutman.

15 DR. GUTMAN: Could we just get a little  
16 specificity on the nature of the labeling changes  
17 you're asking for? There's been a lot of material  
18 floating around here. Is there specific comments that  
19 were submitted or is there something in particular in  
20 the discussion that we should point to?

21 DR. ROSENBLOOM: I think Dr. Nipper and I  
22 referred to comments that we had made that we were  
23 going to submit, but I haven't submitted mine yet.  
24 And they're not -- they're things like frequent  
25 references to extracting glucose from the body.

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1 DR. GUTMAN: So you're talking about  
2 advice that you'll submit to the record that we can  
3 use as we negotiate final labeling with the company?

4 CHAIRMAN NIPPER: Yes.

5 DR. GUTMAN: Okay, thank you.

6 CHAIRMAN NIPPER: Okay, so we have Dr.  
7 Janosky.

8 DR. JANOSKY: Yes, I have a question. In  
9 the first --

10 CHAIRMAN NIPPER: I don't want to be too  
11 rigorous here about points -- about Robert's Rules,  
12 but we're voting and discussion has been cut off.

13 DR. JANOSKY: I asked for a clarification  
14 of --

15 CHAIRMAN NIPPER: Okay, okay.

16 DR. JANOSKY: So it's going back to that  
17 clarification.

18 CHAIRMAN NIPPER: Okay.

19 DR. JANOSKY: The first time I don't  
20 remember hearing the issue of a clinical study of  
21 outcomes. Was that just added or did I not hear that  
22 before and I'm --

23 CHAIRMAN NIPPER: I think he was -- I  
24 can't speak for Dr. Rosenbloom, but I think he was  
25 clarifying what he said. Is there a problem with

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1 that?

2 DR. ROSENBLOOM: No, no, I specifically  
3 indicated. I just didn't describe it as outcomes. I  
4 said the effect on glycohemoglobin the first time and  
5 I referred to it as outcomes the second time.

6 DR. JANOSKY: Now do I have to vote as a  
7 package?

8 CHAIRMAN NIPPER: Yes. I'm sorry, but  
9 that's the way the motion is --

10 DR. JANOSKY: It was fine until you added  
11 that part.

12 CHAIRMAN NIPPER: You'll have to vote as a  
13 package.

14 DR. JANOSKY: You have to vote as a  
15 package. And I'll vote yes.

16 CHAIRMAN NIPPER: Okay.

17 Dr. Everett?

18 DR. EVERETT: Yes.

19 CHAIRMAN NIPPER: Dr. Manno?

20 DR. MANNO: Yes.

21 CHAIRMAN NIPPER: Dr. Doumas?

22 DR. DOUMAS: Yes.

23 CHAIRMAN NIPPER: Dr. Clement?

24 DR. CLEMENT: Yes.

25 CHAIRMAN NIPPER: Dr. Rifai?

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1 DR. RIFAI: Yes.

2 CHAIRMAN NIPPER: Dr. Rosenbloom?

3 DR. ROSENBLOOM: Yes.

4 CHAIRMAN NIPPER: Dr. Harrington-Falls?

5 DR. HARRINGTON-FALLS: Yes.

6 CHAIRMAN NIPPER: Dr. Andrade?

7 DR. ANDRADE: Yes.

8 CHAIRMAN NIPPER: And Mr. Reed, Ms. Kruger  
9 and -- you can sit on your hands for a little while.  
10 You don't have to do another thing.

11 Okay, are there other conditions that  
12 anyone on the panel would like to add to the approval  
13 motion?

14 DR. DiGIOVANNA: Yes. This is Dr.  
15 DiGiovanna.

16 I would like to add that an assessment be  
17 done of the irritation and potential for contact  
18 sensitivity. I'm not certain what the options are for  
19 how they be done. I'm familiar with drugs having  
20 these studies done as phase four.

21 In other words, as a continuation or  
22 requirement, but something that's done after  
23 marketing, and whatever the equivalent of that is.

24 CHAIRMAN NIPPER: That would be post  
25 market, if I understand it.

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1 DR. ROSENBLOOM: Yes, post marketing.

2 CHAIRMAN NIPPER: Yes.

3 DR. ROSENBLOOM: But something that would  
4 include an assessment of contact sensitivity and the  
5 nature of the changes that are seen --

6 CHAIRMAN NIPPER: Okay.

7 DR. ROSENBLOOM: -- clinically and  
8 histologically. The skin changes.

9 CHAIRMAN NIPPER: Skin changes.

10 Is there a second to the motion?

11 DR. MANNO: Second.

12 CHAIRMAN NIPPER: I'm sorry, who was that?

13 DR. MANNO: I seconded.

14 CHAIRMAN NIPPER: Dr. Manno has seconded.

15 Okay, is there discussion of the motion?

16 Hearing none, let's vote.

17 Dr. Andrade?

18 DR. ANDRADE: No.

19 CHAIRMAN NIPPER: Dr. Harrington-Falls?

20 DR. HARRINGTON-FALLS: No.

21 CHAIRMAN NIPPER: Dr. Rosenbloom?

22 DR. ROSENBLOOM: No.

23 CHAIRMAN NIPPER: Dr. Rifai?

24 DR. RIFAI: No.

25 CHAIRMAN NIPPER: Dr. Clement?

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1 DR. CLEMENT: No.

2 CHAIRMAN NIPPER: Dr. Doumas?

3 DR. DOUMAS: No.

4 CHAIRMAN NIPPER: Okay, Dr. Manno?

5 DR. MANNO: Yes.

6 CHAIRMAN NIPPER: Dr. Everett?

7 DR. EVERETT: No.

8 CHAIRMAN NIPPER: Dr. Janosky?

9 DR. JANOSKY: No.

10 CHAIRMAN NIPPER: Okay, so the motion  
11 fails.

12 Dr. Janosky, if you are unhappy with any  
13 of the items in Dr. Rosenbloom's motion, --

14 DR. JANOSKY: I am.

15 CHAIRMAN NIPPER: -- you can ask -- you  
16 can make a move to alter that motion.

17 DR. JANOSKY: Okay. Let me just make sure  
18 that I understood what you added as the last one for a  
19 clinical study. Clinical study was then to see the  
20 impact of the use of the GlucoWatch on HbA1C values,  
21 is that correct?

22 DR. ROSENBLOOM: On diabetes control as  
23 reflected in glycohemoglobin levels.

24 DR. JANOSKY: But that's not one of their  
25 intended uses. Their intended uses doesn't say

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1 anything about being better control in terms of  
2 controlling diabetes. So then it's almost like coming  
3 back -- if I understand it correctly, it's like they  
4 can then come back with a new claim.

5 DR. ROSENBLOOM: Well, improved control  
6 would be fewer hypoglycemic episodes or no great -- no  
7 increase in hypoglycemic episodes with better diabetes  
8 control. If one of the goals is not improved control,  
9 then there's no point in having the device unless it's  
10 just to replace some other predicate device, and it  
11 isn't replacing the predicate device.

12 I mean, that's all we've heard is that  
13 it's going to improve diabetes control by changing the  
14 decision bases.

15 DR. JANOSKY: Right.

16 DR. ROSENBLOOM: So it would be worthwhile  
17 seeing if it actually does that. I would imagine the  
18 manufacturer would be very anxious to see if it  
19 actually does that.

20 DR. JANOSKY: I agree that that's the  
21 ultimate, but their intended use isn't saying anything  
22 about controlling diabetes.

23 DR. ROSENBLOOM: Well, that's why it's a  
24 post marketing. It's not a preapproval. This not a  
25 preapproval requirement.

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1 DR. JANOSKY: Right.

2 DR. ROSENBLOOM: This is a post marketing  
3 recommendation.

4 CHAIRMAN NIPPER: Dr. Doumas.

5 DR. DOUMAS: I think we voted on better,  
6 more efficient detection of hypoglycemia, not control.  
7 The control depends on the patient, whoever is using  
8 it. I don't think the sponsor can be held responsible  
9 for control of hypoglycemia. For detection, yes.

10 DR. JANOSKY: That's exactly my point.

11 DR. DOUMAS: And that's what we voted for.

12 DR. JANOSKY: That's exactly my point.  
13 But his motion -- the amendment to that, my  
14 understanding was that then the study would go on to  
15 show that this does lead to better controlled  
16 diabetes, and that's not their intention.

17 CHAIRMAN NIPPER: Dr. Gutman, can you help  
18 bail us out here?

19 DR. GUTMAN: Well, I can offer some FDA  
20 perspectives. And this is new technology. We  
21 assembled you here to get an honest appraisal. In the  
22 history of the division, to be perfectly honest, it is  
23 rather unusual for us to ask for outcome studies.

24 And in the context of this intended use,  
25 it would be somewhat unusual to ask for outcome

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1 studies. If that was the sense of the committee, we  
2 would certainly be prepared to work with the sponsor  
3 to figure out if there were user friendly ways to do  
4 it, perhaps using historical controls or using some  
5 kind of survey methods to maintain the spirit of at  
6 least burdensome thresholds.

7 One would presume that -- and I can't  
8 remember, someone at that end of the room said that  
9 approval of this product will probably spark use,  
10 which will probably spark research.

11 `And I'm pretty comfortable in thinking  
12 that there will be independent assessments of this  
13 tool over the next few years that will answer that  
14 question, so I'm not -- I'm not supposed to lead or  
15 mislead you, but the truth of the matter is we would  
16 not normally ask for an outcome study.

17 If you were really hung up about this, we  
18 could work on an outcome study. And we're not stuck  
19 with your recommendation, whether it's brilliant or  
20 terrible, in that we -- you are an advisory group.

21 (Laughter.)

22 CHAIRMAN NIPPER: Dr. Rosenbloom.

23 DR. ROSENBLROOM: Yes, I was drawing my  
24 amendment from the statement the pre-market approval  
25 applications, the last line, "effectiveness is defined

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1 as reasonable assurance that in a significant  
2 proportion of the population, the use of the device  
3 for its intended uses and conditions of use will  
4 provide clinically significant results."

5 And to me, as a diabetologist, clinically  
6 significant means to improve diabetes control.

7 CHAIRMAN NIPPER: And detection of  
8 hypoglycemic episodes and hyperglycemic episodes.

9 DR. ROSENBLOOM: That's part of improving  
10 diabetes control.

11 CHAIRMAN NIPPER: Yes. But those are the  
12 three things that you mentioned. So we're at a  
13 situation where we've had discussion about a potential  
14 amendment to the conditions that were voted in.

15 Does anyone wish to modify those  
16 amendments?

17 Dr. Doumas. Dr. Clement.

18 DR. CLEMENT: I would like to respectfully  
19 disagree about the outcome issue. I think I agree  
20 with Dr. Gutman that I think these will be done  
21 independently, which should not be coupled to  
22 approval, even post market approval.

23 Because even assessment and making  
24 conclusions from outcomes studies may or may not be  
25 related to the device itself or the increased

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1 attention that the patient may receive.

2 CHAIRMAN NIPPER: Okay. Well, if you feel  
3 that way, are you making that as a motion?

4 DR. CLEMENT: Yes, I would like to motion  
5 that one not be put in for --

6 CHAIRMAN NIPPER: Okay, could you spell  
7 out what you would like the amended motion to read?  
8 Dr. Rosenbloom was asking for a post market -- for a  
9 stringent education program. I hope I'm saying this  
10 correctly. Revised labeling according to material to  
11 be submitted to the FDA.

12 And for post marketing studies to  
13 determine the effectiveness of hypoglycemic detection,  
14 hyperglycemic detection, and a clinical outcome study,  
15 etc.

16 So what would you like it to be?

17 DR. CLEMENT: I'd like to amend the  
18 amendments to the first three, the education program,  
19 the labeling changes and the post marketing study to  
20 assess the efficacy of the device for determining  
21 hyperglycemia and hypoglycemia, but without the  
22 outcome studies.

23 CHAIRMAN NIPPER: Okay. Is there a second  
24 to that further amendment?

25 DR. MANNO: Second.

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1 CHAIRMAN NIPPER: That was Dr. Manno.  
2 Okay, is there further discussion? Can we repeat the  
3 motion? Okay, what I understood was that the panel  
4 would recommend that a stringent education program be  
5 instituted, that labeling would be revised according  
6 to submissions to the FDA from the panel after the  
7 meeting, that post marketing -- a post marketing study  
8 of effectiveness of hypoglycemic detection -- and of  
9 episodes of hypoglycemia and detection of episodes of  
10 hyperglycemia be done.

11 Did I state that correctly?

12 DR. CLEMENT: Yes.

13 CHAIRMAN NIPPER: Okay. All right, are we  
14 ready for the vote?

15 Dr. DiGiovanna?

16 DR. DiGIOVANNA: Yes.

17 CHAIRMAN NIPPER: Dr. Janosky?

18 DR. JANOSKY: Yes.

19 CHAIRMAN NIPPER: Dr. Everett?

20 DR. EVERETT: Yes.

21 CHAIRMAN NIPPER: Dr. Manno?

22 DR. MANNO: Yes.

23 CHAIRMAN NIPPER: Dr. Doumas?

24 DR. DOUMAS: Yes.

25 CHAIRMAN NIPPER: Dr. Clement?

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1 DR. CLEMENT: Yes.

2 CHAIRMAN NIPPER: Dr. Rifai?

3 DR. RIFAI: Yes.

4 CHAIRMAN NIPPER: Dr. Rosenbloom?

5 DR. ROSENBLOOM: Yes.

6 CHAIRMAN NIPPER: Dr. Harrington-Falls?

7 DR. HARRINGTON-FALLS: Yes.

8 CHAIRMAN NIPPER: Dr. Andrade?

9 DR. ANDRADE: Yes.

10 CHAIRMAN NIPPER: Okay, thank you. I  
11 think we have a motion.

12 All right, now are there further  
13 conditions that the panel would like to move that we  
14 attach to the approval? Hearing none, are we ready  
15 for the vote on approval with conditions? Yes, okay.

16 Dr. Andrade.

17 DR. ANDRADE: Yes.

18 DR. HARRINGTON-FALLS: Yes.

19 DR. ROSENBLOOM: Yes.

20 DR. RIFAI: Yes.

21 DR. CLEMENT: What is happening?

22 CHAIRMAN NIPPER: We're voting on approval  
23 with those conditions.

24 Dr. Clement?

25 DR. CLEMENT: Yes.

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1 CHAIRMAN NIPPER: Dr. Doumas?

2 DR. DOUMAS: Yes.

3 CHAIRMAN NIPPER: Dr. Manno?

4 DR. MANNO: Yes.

5 CHAIRMAN NIPPER: Dr. Everett?

6 DR. EVERETT: Yes.

7 CHAIRMAN NIPPER: Dr. Janosky?

8 DR. JANOSKY: Yes.

9 CHAIRMAN NIPPER: Dr. Di -- I'm sorry,  
10 it's late in the day.

11 DR. DiGIOVANNA: Yes.

12 (Laughter.)

13 CHAIRMAN NIPPER: I need a drink of water.

14 Okay, we have approved this motion with  
15 the conditions as shown. I think we're down to  
16 closing remarks.

17 Who's going to close this thing out, you  
18 and I? I have a couple of personal remarks I'd like  
19 to make.

20 MS. CALVIN: I just want to thank the  
21 sponsors. They've been really great to work with in  
22 preparation for this meeting. The FDA staff, all of  
23 their hard work. All of the public attendees,  
24 particularly the public speakers. Cannot forget to  
25 thank the panel, as always, for all of your advice.

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1                   CHAIRMAN NIPPER: I was shocked to get my  
2 plaque. These four years have gone by very quickly.  
3 It's been an honor to work with the FDA as a panel  
4 chair. The sponsors that I've worked with have  
5 uniformly been professional and very helpful, even  
6 when we told them things they didn't want to hear.

7                   The panel members that I've worked with  
8 have been a joy to meet and get to know. And for some  
9 that I've known for years, it's been a joy to work  
10 with them still. I'd like to thank all of you for all  
11 the hard work that you've done that got us to this  
12 point today.

13                   In particular, I'd like to thank the Food  
14 and Drug Administration reviewers. I thank the  
15 sponsor for a highly professional job. If we went by  
16 weight, it was a pain. If we went by quality, it was  
17 a joy. Thank you very much.

18                   If there's no further business to come  
19 before the panel, we stand adjourned.

20                   (Applause.)

21                   (Whereupon, the proceedings were adjourned  
22 at 6:24 p.m.)

23  
24  
25