

1 issues and reflux that we have in the community
2 now, we need to be looking at antacids, and some of
3 these antagonistic agents for the secretion of
4 acid--I can't think of the name of the group. But
5 at any rate, I think that that is some of the data
6 that we need to have as this develops.

7 I think we do need to stay with the
8 dynamic studies. They have to be in there. So I
9 essentially concur with everyone.

10 Thank you.

11 DR. LASKY: First, I'd like to thank the
12 manufacturers for providing reams of data,
13 literally. Especially as the industry rep, I don't
14 often get to see all the data that the rest of the
15 panel gets to see, so it was very helpful.

16 I think it certainly is appropriate that
17 devices include dynamic as well as steady-state
18 data for their devices. It is consistent with the
19 indications for use of these devices, as was
20 clearly presented by the clinicians and the other
21 panel members.

22 I think the information that was provided
23 with regard to the temporal studies of the various
24 patients who were studied by all the manufacturers
25 was invaluable in helping me understand what the

1 concerns are and also helping to understand what
2 the risks are.

3 From that standpoint, I think that when we
4 look at the data, we also have to be very careful
5 about how it is analyzed and used. It is often
6 very helpful to look at average data across various
7 patients, but as a scientist, I have the advantage
8 of looking at individual data and the disadvantage
9 of not seeing patients. But using average data is
10 often very--it masks concerns. And I think that in
11 almost every case of data that was presented by a
12 manufacturer, there was at least one dataset from
13 one patient that did not look specifically like the
14 rest of the population, and I think there are
15 concerns there that there is no average patient and
16 that from the standpoint of the severity of this
17 problem, the studies and the labeling that go with
18 these products must be considered very carefully.
19 Even if the number of patients that could be
20 adversely is very low, we have to consider what the
21 risk of harm to the patient is.

22 From my way of looking at the data,
23 besides the individual time studies of patients
24 that should be used in the overall analysis, I
25 think the use of agreement tables is also

1 particularly helpful. But again, that is more
2 static than dynamic, and it should just be used as
3 another tool in helping understand what the issues
4 here are and also to consider that, based on a lot
5 of the information that we saw, not every
6 alternative site provides the same kind of
7 information, and certainly the benefits of this new
8 technology I think are enormous based on everything
9 that I have heard.

10 Thank you.

11 MS. LELLOCK: First of all, I'd like to
12 thank the manufacturers for this advancement. In
13 all the years that I have dealt with diabetes, this
14 is quite a great advancement--alternative site
15 testing.

16 After reading everything and look at it, I
17 noticed that there were not many children involved
18 in your studies. As a parent of diabetic children,
19 from an early age, we teach them to test more.
20 Well, if we want them to test more, we need
21 alternative-type testing. But you don't have that
22 in your studies that often. Most of your patients
23 were age 18 and older; you talk about 50-year-olds,
24 calloused hands, and so forth--but what about young
25 skin, changing skin, growing skin--is it different?

1 Do you need to research that more? Do we need to
2 know more about younger patients, because they are
3 the ones who are going to carry on for the future
4 when you get everything together and pull your data
5 together?

6 I do think we need more information. I
7 don't think we should take a step backward; I think
8 everything is wonderful from what I have seen, and
9 I would just like to see more and more with young
10 children.

11 DR. KROLL: Does anybody have any
12 additional comments they would like to make,
13 especially on the latter part of Question 1?

14 DR. ROSENBLOOM: Yes. Now that I have
15 heard everybody's comments, I would certainly like
16 to--and I and others have commented on the
17 individuality that has been noted in the group
18 data, or outside the group data--and I concur with
19 the comments about averages; they are problematic.
20 If there could be some design--and I don't have an
21 immediate suggestion--but some design and
22 suggestion to the clinician on how to identify
23 those individuals who are likely to have
24 discrepancies between alternative sites and finger-
25 sticks, I think that would be very helpful. Just

1 as we have tools for distinguishing who is going to
2 be hypoglycemic, unresponsive, and so on, we
3 individualize a great deal. Everything we do with
4 patients with diabetes is individualized to that
5 particular patient. We heard about the differences
6 in exercise levels and so on. And I think this is
7 one area where we need to, just as we teach people
8 to use finger-stick testing to determine what
9 happens to them with specific exercise or emotional
10 events and meals and so on, I think we need to have
11 some method for individualizing their particular
12 discrepancies between finger-stick and forearm
13 testing.

14 I am intrigued and impressed by the fact
15 that there have been no reported incidents--with
16 extensive use of this technology, there have been
17 no incidents reported of hypoglycemia being missed.
18 That is very reassuring; from a safety standpoint,
19 I think it is extremely reassuring, and I didn't
20 say so before, but I am very positive about this
21 development and intend to review our own use of
22 this technology.

23 I think there are a lot of studies needed
24 with kids, because kids exercise from day to day;
25 it varies tremendously. Studies that we have done

1 in camp have shown that kids can eat twice as much
2 on one day as another day when you are in a
3 position to actually measure what they eat, and you
4 can't detect any difference in their physical
5 exercise or in their blood sugars with twice as
6 much food on one day as another day.

7 So I think kids vary enormously in their
8 physical activity from one day to the next, in
9 their emotional tone, which will affect their blood
10 glucoses, and I think that some real-life situation
11 testing in children is warranted, because that is
12 the group we are most concerned about getting
13 started right, and they need the most information,
14 and it is a changing physiology--what they are
15 doing at age 8 is not necessarily what they need to
16 be doing at age 18 with their altered life
17 situations.

18 So in general, I think more dynamic data
19 is needed. What we saw was very encouraging. I
20 think the companies have acted responsibly in
21 looking at this. I just want to see a lot more
22 data on children.

23 DR. CARA: I'd like to make another
24 comment, and this is again directed more toward the
25 manufacturers, but also perhaps to the FDA.

1 I would encourage that the dynamic nature
2 of blood sugar monitoring be adequately assessed
3 not only from the point of view of the dynamic
4 physiology of blood sugar regulation but also in
5 terms of the dynamic nature of the factors that
6 play a role in decisionmaking as they relate to
7 blood sugar monitoring.

8 In other words, blood sugar monitoring is
9 not if and by itself an isolated number. It is
10 taken in the context of what the person is doing,
11 whether they have eaten, what the pattern of the
12 blood sugar has been, whether they are well,
13 whether they are ill, whether they have exercised,
14 not exercised, their past experiences, and so on
15 and so forth. And somehow I think there needs to
16 be a grip on some of those other factors as they
17 relate to the entire decisionmaking process of how
18 to utilize the blood sugar in terms of optimizing
19 therapy that need to be considered in whatever
20 study design is implemented by the manufacturers.

21 I have no idea how to do that--perhaps
22 through questionnaires; I don't know--but I think
23 something along those lines would be very
24 important. You cannot just take a Clarke Error
25 Grid simply because it does not include any of

1 those other factors. The human brain is much more
2 complicated than that.

3 MS. KRUGER: What comes to mind when you
4 say that, Jose, is whose job is which. I think
5 there is just so much that we can ask of research
6 and the manufacturers. When I sit with a patient--
7 and we each see 30 or so patients a day--I think of
8 what I have learned from the manufacturers and what
9 I read in the PDR and all these other things as
10 what I call "book knowledge," and then, those 30
11 people will respond differently--even if I offer
12 them the same therapy, all 30 of those people are
13 going to respond totally differently.

14 So I think we have to really be careful in
15 what we say is the responsibilities of the
16 manufacturers versus safety versus now I'm going to
17 apply it in my clinic to each of my patients, and
18 how are they going to respond.

19 So it is my responsibility to know which
20 of my patients have gastroparesis and which of my
21 patients have hypoglycemia unawareness, which
22 patients exercise or drive or whatever, and
23 possibly those are the patients who need to be
24 doing finger-sticks versus alternative sites. That
25 is not to say that--we still need to have some

1 parameters, and we still need to have labeling
2 issues. But I think that in practice, diabetes is
3 just not what the book says, so I think we need to
4 be really careful about the burden we place
5 wherever we place it and the realities of what we
6 can expect in our day-to-day practices.

7 So safety, accuracy, responsibility, yes;
8 but then, I've got to take all of that and apply it
9 in my day-to-day practice and how each patient is
10 going to use it.

11 DR. AHMANN: One thing that I noticed and
12 would be curious if other people appreciate it as
13 well is that if you look at most of the data we are
14 presented when they talk about variation, it comes
15 down to inter-individual variation. But I am
16 wondering if that's not because we only have a
17 single test in a single patient, and we're
18 comparing it to a single test in another patient
19 relative to a control.

20 If you look at Dr. Koschinsky's
21 presentation, the other issue to assess is intra-
22 individual variation, because on different days
23 with the repetitive tests, he got different
24 results, and that one, I don't know that we'll be
25 able to do very much with, but it is going to be

1 difficult to separate those two depending on how
2 dynamic tests might be designed, for instance.

3 DR. CARA: In response to your comment,
4 Davida, I think you are right on. It is difficult
5 to know where to draw the line. But I guess what
6 I'm getting to is the fact that whatever device is
7 being evaluated needs to be evaluated in a real-
8 life situation, that you can't just take it out of
9 context. And again, that's a difficult issue, but
10 I think that was the point that I was trying to
11 make.

12 DR. KROLL: Does anybody else have any
13 comments on Question 1?

14 Dr. Gutman, do you think we have
15 adequately answered Question 1?

16 DR. GUTMAN: You'll have an opportunity to
17 come back, but let me keep you an honest panel,
18 because we obviously have a variety of submissions
19 that are on our plate now and that we are hoping to
20 move forward with, and I guess it would be useful
21 for us to understand as much as possible where you
22 net out in terms of--it seems like you are
23 suggesting a dynamic study--where you net out in
24 terms of what would be the minimum parameters of
25 such a dynamic study and the minimum--I realize

1 there are different claims in different studies, so
2 part of this is statistical, but part of this has
3 to do with biologic comfort--so it would be of
4 interest to me personally to know how important
5 time lags as opposed to cross-sectional studies are
6 and if they are important or if cross-sectional
7 studies are enough, and if time lag is important,
8 what kinds of stress might be the minimum stress
9 you would accept--meals or a glucose tolerance
10 test, i.v. insulin--and not statistical, but what
11 would be a bottom-line biological number that you
12 would say the agency plausibly ought to be clearing
13 products for claims and odd sites. We can work
14 around what we don't know; we are very good at
15 working around what we don't know. In terms of,
16 say, pediatric population, we can label the product
17 that it hasn't been studied and hope the companies
18 will get smart and study it and come back with more
19 information.

20 So if you could tell me a little bit about
21 bottom lines; we are kind of looking for bottom
22 lines here.

23 DR. KROLL: Steve?

24 DR. CLEMENT: I think I can help,
25 possibly--maybe not. The question that Steve is

1 bringing up is basically what is the tolerance of
2 error that we can accept with a lag time or
3 fluctuation. Clearly, I think dynamic testing is
4 very helpful. I agree with Dr. Ahmann that if you
5 just measure static blood glucose levels
6 preprandial/postprandial, you get sort of a mish-
7 mash, and it is really difficult to sort out.

8 I think it would be fairly easy to come up
9 with a protocol similar to several that we saw
10 today where you take patients, bring them into an
11 outpatient setting, they get a glucose challenge
12 similar to the data that we saw from Dr.
13 Koschinsky's group, and look for the up-slope.
14 Usually, up-slope occurs within 2 hours,
15 approximately; after 2 hours, give a dose of
16 insulin--it could be given subcutaneously; it
17 doesn't necessarily have to be given intravenously-
18 -and then measure the down-slope and then look at
19 the percent error on both of those curves, and look
20 at it separately, one on the up-slope and one on
21 the down-slope.

22 If, for example, an alternative site such
23 as a palm testing shows numbers plus or minus 20
24 percent in 95 percent of the readings, and the
25 numbers fall right on top of each other both on the

1 up-slope and the down-slope, I would say that that
2 is truly substantially equivalent, and they
3 wouldn't need any additional language in terms of
4 labeling.

5 I think everything else is still okay. We
6 are not ignorant people. We know how to use the
7 data that we have. But I think the labeling would
8 have to be strong enough-- without data showing
9 that close a correlation, the data would have to be
10 strong enough, which I think is the next question
11 we're going to answer, to basically tell patients
12 that they need to use that information with a
13 little bit of a grain of salt, and clearly
14 understanding that the finger-stick is the gold
15 standard.

16 DR. KROLL: I have a comment. I think one
17 of the additional kinds of studies that
18 manufacturers might be able to provide would be if
19 they could characterize the lag and knew that a lag
20 was fairly stable in a person, that that lag was
21 always there, and it was the same from time to
22 time. If that is true, then, could you use a
23 higher value for the alternative site glucose to
24 indicate hypoglycemia--so in other words, you could
25 predict it. If you wanted to pick a value--let's

1 say you're going to get really worried about
2 hypoglycemia at 60, and on the down-slope, it came
3 to 80, and you could say, well, when I hit 80 on
4 the down-slope on alternative site, that's going to
5 be pretty much equivalent to a 60 with a finger-
6 stick. If that were predictive, you could use that
7 as alternative warning.

8 DR. ROSENBLOOM: That's basically what
9 Cygnus has done with the GlucoWatch, and it brings
10 to mind another interesting dataset that could be
11 obtained, and I'm not sure how this could be done,
12 but it would be very interesting to see, using some
13 criterion like that, some altered criterion based
14 on individual discrepancies between finger-stick
15 and alternative site, numbers of episodes of
16 hypoglycemia picked up or missed compared to using
17 finger-sticks. I think that would be very
18 interesting data, and my guess is that there should
19 be no difference, and then, if you put in the
20 factor of more testing, more frequent testing is
21 going to pick up more hypoglycemic episodes.

22 Their comparison was with four times a
23 day. They didn't have--and this is not a
24 criticism--but they didn't have a six-times-a-day
25 comparison group, which would have lowered the

1 difference between the GlucoWatch and the finger-
2 stick testing. So if you are going to six or eight
3 times a day with the forearm versus four times a
4 day with the finger-stick, and using some more
5 liberal criteria, my guess is you're going to be
6 picking up more hypoglycemia. Now, I don't know
7 how you--again, this is a suggestion without a
8 design. That's a tough study to do, but I think
9 that would be very interesting.

10 MS. LELLOCK: One comment I want to make--
11 and this personally happened with my children--we
12 had the normal finger-stick method, and we were in
13 a clinical setting using the same meter, and we got
14 two totally different results from each child, and
15 they did not match the laboratory reference device
16 whatsoever.

17 So in a clinical setting, the current
18 devices are not always clear and accurate; we have
19 to guess. And one thing you are taught from early
20 on is that if you feel hypoglycemic, throw out the
21 blood test and treat it. We all know that you
22 treat the symptoms, and I think we need to keep
23 that in mind if there is not going to be any
24 perfect device out there; but if there is something
25 that will encourage people to test more and perhaps

1 know that they have to use both testing sites, in
2 the long run, we'll have a healthier population.

3 DR. CARA: I would just add a couple more
4 things to what Dr. Clement suggested. First,
5 having some sort of 3- to 6- month real-life
6 experience with a meter I think is important.

7 I was very pleased to see the outcome data
8 from TheraSense in the sense that it was
9 reassuring, as Dr. Rosenbloom indicated, in the
10 sense that there weren't any severe episodes of
11 hypoglycemic or whatnot; I think that having that
12 sort of information is very valuable.

13 DR. LASKY: I would just like to add that
14 with the general parameters that are being
15 discussed here, in discussions that I have had at
16 Advamed meetings with manufacturers or whole blood
17 glucose monitors, of which my company is not one,
18 there was universal agreement among all the
19 manufacturers to work with FDA to use the
20 information that each of the manufacturers has
21 acquired in dealing with this issue, and that there
22 is real benefit to getting general guidelines and
23 an understanding of what kind of clinical data
24 would be needed in order to obtain clearance from
25 FDA in order to advance the use of alternative

1 sites and for new technologies.

2 So that doesn't answer the question, but
3 this discussion should not stop here, at least as
4 far as industry is concerned.

5 DR. KROLL: Are there any other comments?

6 [No response.]

7 DR. KROLL: Then, why don't we go to
8 Question 2, and just to remind people, this is:
9 "Should the FDA require manufacturers to include
10 strong cautionary labeling about this problem
11 unless they provide data demonstrating that the
12 discordance is unlikely to occur with their
13 particular device?"

14 I'd like to start with Diane.

15 MS. LELLOCK: Of course they should. One
16 of the things I liked in the presentation of
17 TheraSense was how they had the red warning label.
18 I think that's fair. As a person who is using a
19 machine, we are not stupid people, we all read--but
20 if you have patients who don't read, that red
21 warning label would really make you take notice.

22 I think that, yes, if your machine has lag
23 time, alert the person--or, alert the user. Alert
24 the diabetic population that there can be
25 discrepancies. If you don't have the lag time, and

1 you can support the data that shows that your
2 machine doesn't, you shouldn't need a warning
3 label, because the evidence would prove that your
4 machine works in conjunction with the finger-stick
5 method.

6 DR. LASKY: Yes, absolutely, I think
7 manufacturers should provide appropriate
8 precautions and warnings in their labeling. And I
9 would like to add, based on some information that I
10 obtained from Diabetes Care and also what Professor
11 Koschinsky mentioned, that at least with forearm
12 testing, unless we begin to better understand the
13 physiology of blood profusion in alternative sites
14 like the forearm, and we need to rely only on
15 empirical data, which is invaluable, but without a
16 fundamental understanding, I think we have to show
17 reasonable caution in providing guidance on how
18 these devices should be used.

19 Also, I'd like to perhaps get a better
20 definition of what "unlikely" means in the
21 question, because I think that has a very important
22 implications on how the labeling should take place
23 and how it is presented.

24 DR. KROLL: Dr Lasky, do you have your own
25 definition of "unlikely"?

1 DR. LASKY: Well, actually, there are
2 standards that we use in terms of risk management,
3 and there are definitions. I don't think
4 "unlikely" is one of them. We have talked about
5 "improbable" and "remote"; maybe "unlikely" is in
6 there. And there are definitions of the
7 possibility of occurrences. These definitions were
8 originally developed I think by the airline
9 industry. So there are standards in place to deal
10 with that--and it is actually, what most
11 manufacturers are using these days to comply with
12 manufacturing regulations dealing with design
13 controls.

14 I hope that answers your question.

15 DR. MANNO: There is an advantage to being
16 in this spot in a way.

17 I would concur with the two previous
18 individuals and their comments, and I don't have
19 anything to add.

20 DR. CARA: Yes, I think any manufacturer
21 desiring alternative site testing as an indication
22 should include a warning label, and I would go so
23 far as to say that any meter being used for
24 alternative site testing should carry the same
25 indication. I don't think we know enough to say

1 that there really is any evidence to suggest that
2 alternative site testing is not going to lead to
3 discordance with other meters. So I would err on
4 the side of caution there.

5 I think that that warning label also needs
6 to carry certain elements--one is that these meters
7 have not been evaluated appropriately as
8 alternative site meters in specific populations,
9 i.e., infants and children--and include what we do
10 know in terms of making sure that the warning label
11 includes information about the need for doing blood
12 sugars by finger-stick if there is any evidence of
13 hypoglycemia, symptoms of hypoglycemia,
14 postprandially, and so on and so forth, but also
15 carry a warning perhaps about what we don't know,
16 that there might be other factors--drugs,
17 situations--in which the discordance may be
18 accentuated.

19 DR. AHMANN: I think you've pretty much
20 covered the bases; it's hard to go beyond that.
21 Clearly, I think there need to be some warnings for
22 now, until we know about this, until we know more
23 about different sites, including more information
24 on the base of the thumb, until we know more about
25 presumably if there is the ability to prove

1 differences, they are based on the collection
2 method and not on the meter itself, and therefore
3 maybe getting some more information on that in the
4 future will lead us. But for the short term, I
5 think we need to be sort of generalized in terms of
6 requiring precautions in a broad sense that can
7 later be narrowed.

8 DR. KROLL: I agree with all the comments
9 and the concerns, especially with Dr. Lasky's about
10 "unlikely"--that makes me a little "un-nervous."
11 But I think if it can be shown that there is a
12 method that is identical to doing a finger-stick,
13 perhaps then, it probably wouldn't require
14 cautionary labeling.

15 So I think cautionary labeling is
16 necessary, and I actually would like to step down
17 one bit further. I was thinking about studies for
18 the manufacturers to do, and I think that
19 cautionary labeling really should stress that the
20 patient needs to work with the physician and the
21 physician with the patient and establish whether
22 the patient has a lag. The manufacturers can't
23 work this out for everybody. Even if you look at
24 thousands of people, you are still not going to
25 know for that individual.

1 And we have crossed the line here. We are
2 starting to see effects that have to do with the
3 individual that are very specific for that person
4 which can end up with wide differences.

5 So it is not like we see with other tests.
6 When you start dealing with these times and these
7 lag effects, that is very specific for that
8 individual. The other problem is that that may
9 change over time, so it periodically has to be
10 reevaluated.

11 There are issues like micro-circulation
12 and micro-angiopathy, other things that may happen
13 as somebody matures or ages, that can definitely
14 have effects. And we don't know where this lag
15 occurs, but I agree with what people said before
16 that it is probably physiologic, and it is probably
17 something major that is going on.

18 So we really just don't understand enough
19 about how this whole system comes together. So I
20 would like to see the cautionary labeling say not
21 only beware that the effect is there, but also test
22 it out as you introduce somebody to use the device,
23 and then maybe recheck it once a year.

24 DR. CLEMENT: I think this is probably the
25 most important question, because one of the issues

1 that comes up is what does this labeling look like.
2 It is a black box? Is it included in the
3 Precautions or Warnings sections? Again, I am a
4 clinician, so I'm not involved in that.

5 Black box warnings tend to scare people.
6 They scare patients. Patients are reading these
7 things, and then they come to us and say, "I'm not
8 going to do this."

9 I think there is a lot of value to using
10 alternative site testing because as we heard over
11 and over again, patients are testing more and more,
12 and they are using this, and I think they do get
13 useful information on this.

14 I like LifeScan's proposed labeling. I
15 think they had a lot of very good points in there
16 that I think are very useful and would be a good
17 starting point to be used.

18 I think clearly the whole issue of trying
19 to define whether patients' blood sugars are stable
20 or unstable is a bit of a fantasy, particularly in
21 a Type I patient, because they are never stable.
22 So it may just require refining some of that
23 language to say that at any time, the finger-stick
24 blood glucose reading should be used as the gold
25 standard, particularly if the person is thinking

1 that he or she is hypoglycemic.

2 Some of the issues clearly should be
3 documented as before driving, before, during, or
4 after exercise, or again, if hypoglycemia is
5 suspected, there should be very clearly labeling
6 that the finger-stick method should be used.

7 I think that somehow including that
8 language in the precautions of how the test is done
9 would be worth considering separate from a black
10 box label, which tends to scare patients.

11 MS. KRUGER: I agree with everything that
12 has been said, and I'd like to also point out again
13 that I think the companies have done a remarkable
14 job in moving in this direction without us telling
15 them to do so. We can see that in the
16 presentations that we have had today; we can see it
17 in the marketing materials.

18 I would also say that there will probably
19 be no argument on their part, because in the
20 diabetes community, not only are most of their
21 companies laden with people with diabetes, but they
22 want to do the right thing for people with
23 diabetes.

24 And one other thing is that instead of
25 saying "work with your physician," we say "work

1 with your health care team on an ongoing basis."

2 DR. HENDERSON: I absolutely agree that
3 the labeling should mention some of the lag time
4 episodes, but I agree with Steve--I don't like
5 black boxes, and I don't like alarm warnings in
6 packaging material, because I think it turns people
7 off--one, they don't read what they need to know
8 about it, and they just don't read any of it; or
9 they don't use the product.

10 I think I would tend more toward liking a
11 blurb with bullet points that these are the things
12 you should look out for. As Steve was saying, if
13 you are about to drive, do finger-sticks--in a
14 little blurb, these are finger-stick opportunities--
15 -driving, if you are feeling hypoglycemic, things
16 like that--but not the long pages where you have to
17 open and unfold and you need a magnifying glass to
18 read the tiny print. I think that especially for
19 something like this, where you want people to
20 embrace it and become educated, the labeling really
21 ought to be a jumping-off point for the whole
22 enlarged educational push by the manufacturers, by
23 the educators, and by the health care providers,
24 and that more information is really part of the
25 educational process and should be available and

1 easily disseminated, but not actually a product
2 insert.

3 DR. ROSENBLOOM: This is an even better
4 spot to be.

5 When I saw the word "unlikely," I thought
6 we had an example with thenar testing, the base of
7 the thumb, of a situation where the data indicates
8 that it would be unlikely to occur; and actually,
9 that was referred to earlier as not necessarily
10 requiring special labeling except to indicate that
11 it has been tested.

12 I would add to Dr. Clement's list of
13 situations that needs to be bulleted for finger-
14 stick testing, gold standard testing, sick day
15 management. I would not want a patient to be using
16 an alternative site for their hourly tests when we
17 are trying to keep them out of the hospital and
18 managed at home.

19 DR. KROLL: All right. Dr. Gutman, do you
20 think we have adequately answered Question 2?

21 DR. GUTMAN: Yes.

22 DR. KROLL: All right. Let's go to
23 Question 3--and this one has three points: "Should
24 the FDA rescind the clearance for labeling for
25 alternative site testing if the 510(k)s do not

1 address this new scientific issue; make these
2 products prescription home use; require additional
3 data and labeling changes?"

4 Because I would like to be last once,
5 we'll start with Dr. Ahmann and go around that way.

6 DR. AHMANN: As a rookie here, it is hard
7 for me to respond to the first one, except that I
8 would assume that at some point in time, you'd want
9 to have that as one of the requirements that this
10 would have to be--whatever the conclusions of the
11 panel would be would be adhered to by all for their
12 applications.

13 Secondly, should it be prescription for
14 home use--I think if it were compliant with
15 everything else, I would not see a need for this
16 being prescription, and I think prescription gets
17 into issues too much of branded preferences of
18 physicians or other providers where this should be
19 a patient issue which meter they choose in the end
20 more than any other.

21 I think we have kind of addressed the last
22 one quite a bit already, and I don't think we need
23 to add much to that as to whether there should be
24 additional data and labeling changes.

25 DR. CARA: Can I get some clarification on

1 what you mean by "not address this new scientific
2 issue"?

3 DR. GUTMAN: The sponsors have really been
4 quite interactive and interested, but the
5 theoretical possibility that there might be a
6 sponsor who wouldn't wish to make the labeling
7 changes or provide additional data.

8 DR. CARA: Then, my answer is yes, I would
9 rescind the clearance under those situations.

10 I guess what you're getting at is if a
11 manufacturer is interested in getting approval as
12 an alternative site meter, should they really
13 address these issues--and the answer is yes, they
14 should; otherwise, I would not approve them.

15 Should FDA make these products
16 prescription home use? I like the idea of that in
17 terms of enhancing communication with the care
18 providers. On the other hand, I think it is a bit
19 of a burden, and I think as long as there is a
20 cautionary label where the patients are encouraged
21 to interact with their health care provider, that
22 would probably be enough.

23 And we have already talked about the
24 additional data and labeling changes.

25 DR. MANNO: As far as the prescription

1 home use, I agree with these two gentlemen on that.
2 In an instance in my own family, while one unit was
3 recommended, it turned out that another one was
4 easier to use, and therefore, the person was more
5 compliant.

6 I think we have addressed the additional
7 data and labeling.

8 I think you should rescind the clearance
9 for labeling if they don't provide the data that
10 you need, basically.

11 Thank you.

12 DR. LASKY: The rescinding of clearance,
13 of course, is a difficult thing for me to address
14 because to my knowledge, the companies have been
15 very forthcoming in providing data; but that
16 doesn't mean I'm aware of all of the goings-on in
17 FDA's interactions with manufacturers.

18 Also, as was pointed out before, there
19 have been no adverse event reports, so we aren't
20 dealing with an epidemic type of issue. And as we
21 have heard here, I think the manufacturers have
22 been responding effectively and responsibly.

23 How's that for an equivocal politically
24 correct answer?

25 Number 2, make these products prescription

1 home use--I think definitely not. We found today
2 and most of us were aware that these patients are
3 very aware patients, they are knowledgeable
4 patients, they care a lot about their own self-
5 care, and making the products prescription would
6 add a burden, I believe, to patients and make it
7 much more difficult for them to have access to the
8 products they need in order to care for themselves.
9 In circumstances where they may not be near their
10 physician, and could just go to a drugstore and
11 pick up the blood testing materials they need, if
12 they are required to get a prescription under those
13 kinds of circumstances, there are issues that I
14 would be very concerned about.

15 And Number 3 on labeling, we already
16 talked extensively about.

17 MS. LELLOCK: Yes, I do believe that we
18 should rescind the clearance if they don't have the
19 alternative site testing in their 510(k)
20 application.

21 About the prescription home use, in all my
22 years of living with the disease, I don't know of
23 anybody who goes to the store and picks up a meter
24 for the heck of it. They get a new meter because
25 their health care provider recommends it.

1 We just stated here earlier that as long
2 as you work with your health care provider, this
3 machine would be a nice thing to keep on the
4 market, and we talked about labeling. So yes, I
5 think that you should need a prescription to get it
6 so that you know how to use it properly, so if they
7 have a hypoglycemic episode, they can't say, "I
8 didn't read the paperwork," because somebody would
9 have sat down with them and explained how to use it
10 before they ever got their hands on it.

11 DR. ROSENBLOOM: One question that I guess
12 did come up in relation to labeling is those meters
13 that have not been tested for alternative site use-
14 -will they require labeling saying this device has
15 not been tested for, is not approved for anything
16 but finger-stick testing?

17 DR. GUTMAN: I suppose we could explore it
18 if there were a thought that it would be a problem.
19 Normally, we don't look at off-label use, so if
20 there is no claim that it is being used for a
21 particular purpose, we don't generally try to
22 second-guess people who would use the product off-
23 label. It's not absolutely unheard of; if we
24 thought there were going to be some terrible
25 crisis, there is some potential to do that, but it

1 is not a usual measure.

2 DR. ROSENBLOOM: I would think that if, as
3 we have heard, this is becoming a popular
4 alternative, and people are going to just assume
5 that whatever meter they have--and this may be
6 true--can be used for this purpose, perhaps
7 somebody representing--perhaps the lady from
8 Diabetes and Children might know something about
9 this--but if people are using any old meter,
10 perhaps it should be noted in that labeling--it
11 would seem only fair that if these companies are
12 spending a lot of research dollars developing
13 alternative site testing data that that should not
14 accrue to those companies who have not made this
15 investment and demonstrated that their machines are
16 equally accurate.

17 It would be very easy to imagine their
18 representatives going around saying, "Oh, yeah, you
19 can use this for alternative site testing." So
20 that is part of my response to this--yes, it should
21 be part of the labeling and required, but I think
22 it should also be part of the labeling of any blood
23 glucose testing methodology if we are going to be
24 that restrictive that those who have not been
25 tested for this purpose, it should indicate so in

1 their labeling as well.

2 On prescription home use, there is so much
3 abuse. People write prescriptions for meters and
4 send people to the drugstore assuming that they are
5 going to read how to use them or that the
6 pharmacist is going to teach them how to do it. I
7 don't think we're going to improve that with
8 prescriptions, so I think it just adds a burden to
9 the consumer. If I thought that it would assure
10 good training and good teaching, I would favor it,
11 but I don't think we have that information.

12 On requiring additional data and labeling
13 changes, I think we have already addressed that.

14 Thank you.

15 DR. HENDERSON: I do not believe that
16 requiring prescriptions would be useful. I
17 probably write somewhere on the order of 10 to 20
18 prescriptions a week for glucometers. The patients
19 get educated regardless of where they get the
20 meters, whether they pick it up or borrow it from
21 someone or if they get it from the pharmacy--they
22 certainly don't get any education there--and then
23 they come back to either my practice if it is a
24 referral patient, or to the clinic, where we have
25 diabetic educators and nutritionists and other

1 people who provide education about how to use it,
2 how to administer insulin, what diet and how to do
3 exchanges, and all that stuff.

4 I think that by requiring prescriptions,
5 one would certainly increase the cost. It will
6 make it less available for a lot of people. For a
7 lot of people, it is very difficult to go to the
8 pharmacy and pick it up, and who is going to pay
9 for that.

10 I am asked several times a week to write
11 prescriptions for people because they can't get to
12 the doctor, they can't afford the medication,
13 and/or whatever it is and the doctor visit.

14 I think our system really doesn't help
15 that be a nice oversight; in fact, I think it helps
16 it to be more of a burden, which is unfortunate.

17 I think that these requirements should
18 certainly be in place for new applications. I am
19 not convinced that should a manufacturer not
20 provide that data, either because they don't have
21 it or maybe in a rare situation, they may not be up
22 to it. I think that's the exception rather than
23 the rule. So I would not rescind the approval
24 because of that one bad apple, because I think for
25 the most part from what we've seen today, the

1 manufacturers have been fairly supportive.

2 The other thing, I'd like to go back--I
3 didn't comment on the "unlikely". I don't think
4 "unlikely" is a hard concept, because I think that
5 in all the testing and all the screening that we
6 do, we present issues of risk and chances of. And
7 to Dr. Lasky's position, certainly risk management,
8 in many aspects of our lives, we talk about chances
9 of and risk and how do you decrease your risk, and
10 I think that "unlikely" falls into that category.

11 MS. KRUGER: On the first issue in terms
12 of rescinding the clearance, I think we need to
13 move forward, and I'd hate to see us rescind
14 anything that we now have in place. I think that
15 maybe for future applications, I would agree, but
16 not for anything that has been approved to date.

17 I do not agree with making the product
18 prescription. I think we need to continue to
19 remember that diabetes is a self-care disease, and
20 patients need to have opportunities to improve
21 their outcome, and blood glucose monitoring is
22 certainly one of the best ways for them to do it.

23 In terms of labeling, I think we have
24 probably beaten that horse to death, but I would
25 like to say that I don't think we need a label on

1 the meters that are not for alternative sites.
2 It's like if you buy a new car, and it has
3 different bells and whistles, you learn the bells
4 and whistles on that particular model. So if we
5 have one model that says "Warning: This is for
6 use....," and go through these things, I don't think
7 we need to go back and spend the money to put it on
8 the blood glucose monitors that you shouldn't be
9 using for alternative sites.

10 DR. CLEMENT: Being the last one--or,
11 almost the last one--I think most of them have been
12 answered.

13 I think we answered most of the questions,
14 and I agree with all the panelists. I think
15 sponsors that currently have devices out there
16 should be given one of two options. One is to
17 accept the labeling as discussed; and Option B is
18 to demonstrate data using dynamic testing that
19 there is no systematic bias during up-slope or
20 down-slop of glucose levels in the difference
21 between a YSI result and their device. I think
22 that's a very rigorous test.

23 DR. KROLL: Thank you.

24 For the first part of the question, I
25 agree, yes, rescind the clearance.

1 For the second part, I was leaning toward
2 wanting it to be prescription home use, mainly with
3 the thought that it would improve education between
4 the health care team and the patient; but it all
5 depends--if people don't think that's going to be
6 effective, I don't see a reason to do it. Maybe we
7 could just have a very strong label that says you
8 need to work with your health care team before you
9 use this device and make it big enough so that it's
10 like a hammer, because even though the people who
11 presented today and the patients who have been
12 represented are all very intelligent, greatly self-
13 motivated people, we know there are lots of
14 patients out there who don't fall into that
15 category. They are partially motivated. They have
16 a lot of trouble understanding these health care
17 issues, so they do need a lot of help. They need
18 somebody to lead them by the hand and show them
19 what to do.

20 I work in a VA hospital, and we have a lot
21 of patients there, and we see the results. They
22 wind up getting bounced around the community, and
23 their health gets to be a mess because no one has
24 spent the time to lead them through it because
25 these concepts are very difficult for them. So I

1 think that somehow we need to get the message out.
2 Maybe prescription is not the way; maybe it needs
3 to be. I am mixed on that.

4 On the last one, require additional data
5 and labeling--yes, like everyone else.

6 Dr. Rosenbloom?

7 DR. ROSENBLOOM: I know we are not
8 supposed to consider these issues, but one reason
9 for prescription might be third-party payment--
10 Medicare, Medicaid, and other third-party payment.

11 I have a great deal of difficulty--I
12 direct the Children's Medical Services Program for
13 a 16-county area of Florida, and I have a great
14 deal of difficulty with over-the-counter
15 medications which are prescribed by physicians,
16 which are essential to patients with cystic
17 fibrosis and other disorders, but they are over-
18 the-counter. I get a great difficulty from third
19 parties who don't want to pay for them because they
20 are over-the-counter.

21 So I don't know if that is a major issue
22 or not, but that would certainly be one reason to
23 make it a prescription item.

24 DR. CLEMENT: I'd like to comment. This
25 whole issue of prescription or non-prescription is

1 almost a moot point, because almost all insurers
2 require a prescription for payment, for
3 reimbursement, for either glucose strips or meters
4 and so forth. So even if all these things are
5 currently over-the-counter, we still have to write
6 prescriptions for anyway, so it's a huge burden to
7 the health care system.

8 So I agree with the other panelists. I
9 don't think that making it a regulatory issue that
10 it has to be prescription is really necessary,
11 because generally, we have to do it anyway, and if
12 they can't reach us by phone, or if we can't leave
13 a message, I wouldn't want that to prevent them
14 from getting it on their own.

15 DR. KROLL: Dr. Gutman, do you think we
16 have answered this one sufficiently for you?

17 DR. GUTMAN: Yes.

18 DR. KROLL: Okay, good.

19 DR. CARA: Sorry. Just for the sake of
20 argument, I assume that alternative site testing is
21 anything else other than the fingers.

22 DR. GUTMAN: Yes.

23 DR. KROLL: All right. We'll go to
24 Question 4: "Are there other activities or issues
25 that the FDA should consider with regard to this

1 important public health issue, such as a public
2 health alert, targeted postmarket surveillance,
3 educational outreach activities to stakeholders and
4 other Government and non-Government entities to
5 promote additional research in this area?"

6 I guess to be fair, I ought to start.

7 I would actually say yes to all three of
8 these points, but I do have a comment on the last
9 one, that we can see that one of the issues is that
10 we're dealing with a dynamic process, and it is
11 also time-dependent. This is an area that is not
12 really that well-known to many areas of the health
13 care field and how to adapt to it.

14 We can see that the old statistical
15 techniques that we would commonly use in a sense
16 have sort of failed us. So I think it is important
17 that additional educational outreach activities
18 occur, because now we are getting into sort of a
19 new area, and there need to be new approaches and
20 new ways to think about it.

21 DR. CLEMENT: I agree. I think the more
22 education, the better for everyone. I think the
23 FDA can very well work with the American Diabetes
24 Association and the Juvenile Diabetes Federation
25 and other organizations that have wonderful

1 websites and other patient education ways to alert
2 consumers--us--and professionals as well that there
3 are issues that can be used to everyone's
4 advantage.

5 So I agree that all those would be very
6 helpful.

7 MS. KRUGER: I think that any way we can
8 educate the public about the importance of blood
9 glucose monitoring and use of these devices in a
10 positive way, there is no down-side to it.

11 DR. HENDERSON: I agree and would say
12 "yes" to all three of these, but particularly with
13 the targeted postmarket surveillance, I think is
14 very important to look at groups like pregnant
15 women, also those who have concurrent medical
16 illnesses, to look at the interaction between the
17 medications they are on and other things that are
18 physiologically going on with them.

19 DR. ROSENBLOOM: And children.

20 I agree with you--and children.

21 MS. LELLOCK: Yes, and as far as the
22 public health alert, I would like to make this
23 comment. I called a particular person who I knew
24 from his mother who had a machine--and I'm not sure
25 which one, but one that is already on the market--I

1 called his place of work--he is a pharmacist--and
2 asked, "How do you like that meter?"

3 He said, "Oh, it's great."

4 I asked, "So you use the alternative site
5 testing?"

6 And he said, "I have a little bit of
7 trouble with that."

8 And I said, "Did you know that there is a
9 lag time?"

10 And he said, "What? No."

11 So here was a professional who probably
12 has those in the store that he works with, an
13 educated man who didn't know there was a lag time.
14 Whether he didn't read the insert, I don't know;
15 whether it is in the insert, I don't know. But
16 yes, there should be a public health alert out
17 there that for those who already have them, yes,
18 they need to be aware that there is lag time. Yes,
19 I think that any postmarket surveillance is great.
20 And yes, more education.

21 DR. LASKY: I'd like to answer these as 1,
22 3, and 2.

23 First, the public health alert I don't
24 think is warranted, because a public health alert
25 from the FDA would have the impact of I think

1 virtually a panic situation. And we have already
2 talked about the fact that we do not want to have
3 patients stop using alternative site testing. The
4 way I believe the question is worded, we have to
5 look at that very cautiously.

6 However--I'll go now to Number 3--
7 definitely, additional education is warranted, and
8 as we have heard from several of the manufacturers,
9 they expect to continue to work with the diabetes
10 associations and their general means of educating
11 users and health care providers in terms of how to
12 use their devices appropriately, and also to deal
13 with this specific issue of lag times. I don't
14 think any of us want to dismiss the importance of
15 that.

16 And number two, on targeted postmarket
17 surveillance, I would like to separate postmarket
18 surveillance from postmarket clinical studies. The
19 postmarket clinical studies for pregnant women and
20 children and geriatrics, for instance, I think
21 certainly are warranted. As we are all aware,
22 diabetes is a growing concern, and the demographics
23 of the population are shifting, and we have to
24 understand that better without question.

25 However, surveillance from an industry

1 standpoint has the connotation of regulatory
2 consequences, and there are already mechanisms in
3 place under regulations for medical device
4 manufacturers in which surveillance is obtainable
5 by FDA. I want to be careful how I phrase that,
6 because we have certain requirements that we must
7 adhere to. MDRs, which I think you are all
8 familiar with, are when manufacturers or users must
9 report to the FDA in the event of an adverse event
10 or when an adverse event could possibly have
11 occurred, or an allegation of an adverse event
12 could possibly have occurred or has the potential
13 to occur. It is not a perfect system but one that
14 is often used to monitor the safety and
15 effectiveness consequences of the devices out
16 there.

17 In addition, manufacturers are required to
18 track every, single complaint that comes into the
19 facility, and for manufacturers of self-testing
20 devices, this is an enormous task. Manufacturers
21 are required to track them, to understand and to
22 solve any of the failures that may have caused the
23 complaints. Now, obviously, many of the complaints
24 have to do with using the devices effectively or
25 training; those cannot be ignored. But the bottom

1 line is that there are postmarket surveillance
2 techniques that are already in place.

3 I think it would be warranted for the FDA
4 to ask questions about the effectiveness of
5 alternative site testing when complaints are
6 reviewed and when the manufacturers put programs in
7 place in order to deal with any issues that may
8 arise as these technologies improve and more sites
9 are studied for this disease and for other diseases
10 in which self-testing is warranted.

11 That's a long answer, but there was a lot
12 there to cover. Thanks.

13 DR. KROLL: It's 2:45. We're going to
14 come back later and have the rest of the panel give
15 their answers to Question 4, but right now, we're
16 going to take a--do you want to finish? Okay,
17 we'll go ahead and finish.

18 Dr. Manno?

19 DR. MANNO: I'll make it quick. I agree
20 with Dr. Lasky about the health alert. I have seen
21 too many frightened people lately with some of the
22 things that are going out there in the newspapers,
23 so to speak.

24 I agree with the targeted postmarket
25 surveillance. I think that any new studies should

1 very definitely be separated from the postmarket
2 surveillance as described by Dr. Lasky.

3 On the last one, I think this is a rich
4 area. We need to have the educational outreach
5 activities not only to the patients, to the
6 physicians, to the nurses, but they have to get to
7 the pharmacists--the whole health care industry in
8 terms of the person who gets with the patient or
9 provides any type of service to them that way.

10 And I would just like to comment that I
11 see this as such a significant change in being able
12 to find the multitude of descriptors for a patient
13 to individualize their care, and I see a great deal
14 of research coming out of this, both primary and
15 ancillary research, because one thing will lead to
16 another--in other words, one question will lead to
17 another vascular-wise and so on. So I see this as
18 a very significant thing.

19 DR. CARA: I agree with Dr. Manno's
20 comments.

21 I have a couple of comments of my own. I
22 would encourage the FDA to work with other
23 agencies, especially organizations like the
24 American Diabetes Association, to get this
25 information out there.

1 I would make sure that that information is
2 targeted in a sort of overkill manner to make sure
3 that everybody and his brother out there knows
4 about the potential issues related to alternative
5 site testing.

6 I would make sure that dieticians,
7 certified diabetes educators, physicians, pediatric
8 nurse practitioners, nurse practitioners, are all
9 informed of this phenomenon.

10 The other issue is that I would be careful
11 about trying to--well, not trying to--I have a
12 problem with the whole concept of time lag in the
13 sense that I think it tends to soften the actual
14 phenomenon that we see in hypoglycemia, and that is
15 that alternative site testing measures blood sugars
16 that are two or three times the value of the actual
17 blood sugar when patients are hypoglycemic, or at
18 least they can. That needs to be made very clear.

19 I think this issue of time lag tends to
20 soften the blow, and I think I would just make it
21 clear that when patients have any signs or symptoms
22 of hypoglycemia, the only real option is finger-
23 stick monitoring.

24 DR. AHMANN: First, it isn't because I
25 want to say "me, too," but the public health alert

1 issue I think is one that has to be done very
2 cautiously. It is more of an education; it is not
3 really an alert inasmuch as we are not trying to
4 frighten people. It doesn't really make much
5 difference what is said here; it is what is said in
6 the media, and the media have a habit of trying to
7 make the points that are going to have the biggest
8 impact, which will usually be the negative points.
9 So education, but not to the point of an alert
10 somehow.

11 On targeting and postmarket surveillance,
12 I would say that personally, my bias is that I am
13 highly skeptical of MDRs in this kind of setting.
14 I would think it would be extremely unusual for
15 anybody to report that they had a blood sugar of 90
16 and then went into a coma 30 minutes later and that
17 somebody would say, "Oh, it was the meter." There
18 are too many other events, too many uncertainties;
19 this is too complex of a dynamic for us to really
20 make those conclusions. So I don't think MDRs are
21 going to be particularly helpful except maybe to
22 look at some trend; if there were some trend that
23 maybe had to do with difficulty of use and seemed
24 to be seeing something strange. But I don't have
25 any other suggestions, and I don't think it will be

1 something for us to come to easily as to a better
2 surveillance methods.

3 I do think that several things that have
4 to do with the basis of study and postmarketing
5 studies are important. One, it would be
6 interesting to see a lot more companies look at the
7 base of the thumb, for instance, to see--this could
8 be a solution to everything if everybody found out
9 the same results.

10 I also think that it would be useful--and
11 again, I applaud all the companies, because I think
12 it is because of their integrity and their
13 dedication to the group that we are serving that we
14 are here in the first place--but I would like to
15 see some independent reviews of what happens 6
16 months after a patient is given a meter of this
17 type and how they adhered to the use of it, because
18 my suspicion is that a lot of them don't use
19 different sites; they'll use the alternative site
20 most of the time. But I think that is data that we
21 would like to know, because there is a significant
22 educational component here, and I think there are
23 different issues about how samples might be
24 collected.

25 So I think there is lots of fertile

1 ground, but overall, I think things are headed in
2 the right direction. I think this is an important
3 technology that will benefit patients and patient
4 care.

5 DR. KROLL: Thank you.

6 We'll take a break now and come back at 3
7 o'clock.

8 [Recess.]

9 **Open Public Hearing**

10 DR. KROLL: If you'll please take your
11 seats, we'll continue now with the open public
12 hearing.

13 Now we're going to begin the open public
14 hearing. As a part of that, there is a letter that
15 was sent by Sonia Cooper, but she couldn't be here,
16 so I'm going to go ahead and read it. Some of it
17 was already read by Ms. Laura Biletdeaux, so I'll
18 read the first part very quickly and then get into
19 the additional parts.

20 It is addressed to Dr. Bernard Statland
21 and Dr. David Feigal, Director of the Center for
22 Devices and Radiological Health.

23 It says: "Dear Board of Review Members,
24 as President of Children With Diabetes Foundation,
25 I would like to thank you for giving

1 TheraSense/FreeStyle the opportunity to discuss the
2 Roche/AccuChek paper."

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

13 "Although the TheraSense meter is not
14 'continuous and alarmable,' yet it is a step
15 closer. Because it is pain-free, a parent can test
16 a child in the middle of the night without waking
17 the child. The developmental advantages of
18 allowing the child to have uninterrupted sleep are
19 tremendous. Because of this, they are more likely
20 to test the child at all."

21 "Adults are more likely to test themselves
22 before falling asleep. My own son could squeeze
23 his fingers and get blood out without even using a
24 lancing device prior to alternative site testing.
25 The practical reality is that in 'home' use, kids

1 don't always wash their fingers. The carbohydrates
2 from the last potato chip they consumed can cause a
3 reading to be off by over 60 points. Fortunately,
4 kids don't eat using the sides of their arms.
5 Comparative studies need to include home use."

6 "We were extremely fortunate to try the
7 GlucoWatch monitor. The continuous readings helped
8 us adjust basal rates on this insulin pump, and now
9 his hemoglobin A1c is down to 6.9, and he has not
10 had any severe low blood sugar levels. His only
11 major complaint was that for the purposes of the
12 trial, he had to go back to the finger poke. I
13 cannot stress enough how important it is to
14 encourage and support very company working toward
15 continuous monitoring."

16 "Three other American companies--JNJ,
17 Abbott Laboratories, and Amira Medical--have also
18 launched alternative site testing monitors. Their
19 monitors were not cited by Roche, but their goals
20 of limiting pain are similar."

21 "The American companies providing an
22 alternative to the painful finger poke methods have
23 been very well-received by people with diabetes.
24 It was apparent at trade shows. People were lined
25 up in long lines to test themselves in front of the

1 TherAsense and JNJ (Ultra) booths, but this wasn't
2 the case for the meter companies still requiring a
3 large drop of blood from a finger poke."

4 "An interesting anecdotal observation was
5 regarding people who didn't know they might be
6 getting diabetes. They were lined up to test
7 because it was pain-free. Some were sent over to
8 the DPT-1 booth for additional information and
9 testing as their numbers were higher than would
10 have been expected. Alternative site testing may
11 be an important tool for early detection and
12 prevention of this epidemic."

13 "The bottom line is that people with
14 diabetes need to test more often. Their fingers
15 need a break, and the reality is that they will
16 test more often if it doesn't hurt. I still
17 remember when my son was one year old, and he would
18 scream and cry as we went through sometimes six
19 pokes and six strips because the meter kept reading
20 "Not enough blood." Often, we had to resort to his
21 large toe as my husband and I would struggle to
22 hold him down."

23 "Unfortunately, I am unable to make the
24 trip to testify personally, but I would like to let
25 you know that I am not an investor in the company,

1 TheraSense, and I work as an unpaid volunteer in my
2 position as president of the nonprofit Children
3 With Diabetes Foundation."

4 She also states that she is not an
5 investor in the alternative site meter companies in
6 question--Amira, JNJ, and Abbott--and that is per
7 her email.

8 This is signed "Sonia Cooper, President
9 and Chairperson, Children With Diabetes
10 Foundation."

11 On that note, I'd like to proceed and have
12 Dr. C. Kurt Alexander come forward and speak.

13 DR. ALEXANDER: I would like to thank the
14 panel for allowing me to address them today.

15 [Slide.]

16 I am not an employee of any meter company.
17 I am not on any speakers' bureau for any meter
18 company. I was an investigator for Roche on this
19 alternative site testing study. I am not receiving
20 any payment from Roche for testifying today, but
21 they did pay my travel expenses.

22 [Slide.]

23 In keeping with a long, time-honored way
24 of doing a talk, I am going to tell you what I'm
25 going to tell you I'm going to tell you, and I

1 don't want to go back and tell you what I told you.

2 So to start off, I am representing as a
3 clinical endocrinologist in central Indiana. I am
4 not representing Roche whatsoever. I would ask
5 that the panel not restrict patient access to new
6 technology.

7 I am going to tell you what I learned from
8 participating in this clinical trial, and I am
9 going to put an emphasis on education.

10 [Slide.]

11 New technology in diabetes testing is
12 essential. I feel that in my practice, it enhances
13 patient adherence. Patients actively seek new
14 opportunities in testing. They will do this either
15 by word-of-mouth, by way of the internet, by way of
16 advertisements in magazines or journal articles.

17 Those of you who are in clinical practice
18 I am sure have a lot of patients who like to play
19 the game of "Gotcha." This means that they like to
20 come in and try to one-up you, try to find
21 something that you don't already know. So they are
22 always actively looking for new ways of taking care
23 of their diabetes.

24 [Slide.]

25 In terms of access to technology, a well-

1 informed patient expects it, and physicians and
2 certified diabetes educators want to provide it.
3 Providing access to the newest technologies improve
4 patient interest and generally leads to an
5 improvement in glucose control.

6 Studies have shown, for instance, that
7 whenever you change anything on a patient with
8 diabetes in terms of a new meter or a new pen
9 device, generally the hemoglobin A1 goes down
10 temporarily thereafter.

11 [Slide.]

12 Having said that, when they came to me and
13 asked us to consider doing this study, I went down
14 and started reading some of the package inserts on
15 the various alternative site testing. Up until
16 that point in time, I hadn't realized that there
17 were some caveats in there, and I have quoted a few
18 from some of the package inserts. The Ultra
19 package insert says, "Consult your health care
20 professional before using the arm for testing." I
21 thought, well, that's kind of a typical cover your
22 you-know-what type of statement.

23 The next one from FreeStyle says: "Blood
24 glucose in forearms and fingertips are not always
25 the same." That was kind of the first time that I

1 went, "Huh?" One of my mentors at Indiana
2 University where I did my endocrine training was
3 Dr. Feinberg, and Feinberg did a lot of these types
4 of studies with the Yellow Springs Instrument, and
5 we'd bring people into the clinical research labs
6 and show that there was good correlation. That's
7 the first time I had ever seen that; Dr. Feinberg
8 never mentioned that to me.

9 [Slide.]

10 I couldn't figure out why they were doing
11 disclaimers, because if you go back through the
12 rest of the package inserts--now, again, I am
13 speaking as a clinical endocrinologist out there
14 taking care of patients--looking at the package
15 inserts, the information that I have available to
16 me. MediSense says that the results compare well
17 with the laboratory reference method, and I think
18 it was they who would about the Yellow Springs
19 Instrument, and I'm very familiar with that. It is
20 extremely accurate.

21 FreeStyle also said it compared well with
22 the standard laboratory method.

23 So I am sitting there, scratching my head,
24 saying, okay, we can do this study, but why would
25 we find anything?

1 [Slide.]

2 I think Roche selected the four doctors
3 because we have very active practices. Roche was
4 interested in entering into the AST market. And I
5 got the feeling from the previous reading of the
6 last letter that perhaps someone thinks that Roche
7 wants people to have their fingers hurt, and I
8 don't think any of the companies wants that.

9 Roche wanted to find out if there was a
10 difference, and this whole study was designed to
11 find out if there is a difference between finger-
12 stick and forearm.

13 [Slide.]

14 This just goes back to recapitulate that
15 that is the case. Could we predict who might
16 demonstrate difference? Some of you have made
17 comments about that, and I want to address those in
18 just a moment.

19 [Slide.]

20 At the post-study investigators' meeting,
21 it was shown that there was a delay on some
22 patients between forearm and finger-stick glucose,
23 and I asked specifically the question of the
24 statisticians who ran the data--could we predict
25 who did that; was it a consistent person all the

1 time? It was not. We could not identify from our
2 data, which had a fair number of data points, any
3 consistent pattern.

4 So when we talk about having the patient
5 show that there was a lag, the lag wasn't always
6 there on a patient-per-patient basis. Sometimes it
7 was, sometimes it wasn't; we could not predict.

8 [Slide.]

9 So what did I learn from the study? Well,
10 it would appear that the glucose results that were
11 used in the preparation of these package inserts
12 did not include the one-hour postprandial blood
13 sugars, because we discovered in our study that
14 there were sometimes significant differences in
15 that one-hour time point.

16 [Slide.]

17 Probably for the 15-second soundbite, one
18 thing I learned was that a drop of blood is not
19 always a drop of blood, which up until that point
20 in time, I thought it would have been. I figured
21 it really didn't make any difference if you got a
22 drop of blood out of the finger versus the forearm
23 versus the earlobe, which sometimes people use, and
24 versus the toe, which we have heard some people
25 use. But that is not the case.

1 [Slide.]

2 I almost feel like this is anticlimactic
3 because you guys have already been through this,
4 but I am going to go through these individually.

5 Next slide.

6 [Slide.]

7 It sounds like from what the committee has
8 already said that you are not going to outlaw AST,
9 and that's great, because I think there are several
10 things that would happen if you did.

11 First of all, the information is already
12 out there. People would continue to use it, but
13 they would do so without knowing the limitations.
14 In fact, from what I understand of the rules and
15 regulations, the companies would be forbidden from
16 discussing that; if they didn't have approval for
17 that, they couldn't tell you that there was a
18 shortcoming there. I think that would be bad.

19 Also, it is not just children--I know
20 there were some children here earlier--it is not
21 just children. I had a patient last Thursday.
22 This guy works for General Motors. He is a skilled
23 tradesman; a big, burly guy--bigger than I am. He
24 came in with blood sugars over 300.

25 I said, "Look, you've got to go on

1 insulin, and you've got to start doing self-blood
2 glucose monitoring."

3 He said, "I can't do that. I tried poking
4 my fingers. It hurts. I'm not going to do it."

5 This guy is big, you know. We showed him
6 alternative site testing, and he went home a happy
7 man, and I think his blood sugars are already doing
8 better, according to the nurse I just talked to a
9 few hours ago.

10 [Slide.]

11 By prescription only--somebody already
12 alluded to this--and maybe I have kind of a warped
13 practice--but I am already having to write
14 prescriptions for these. Is it required by law?
15 No. But in essence it is, because all the
16 insurance companies require it. In fact, for most
17 the Federal Government patients, I have to not only
18 fill out an insurance form, but I also have to fill
19 out another piece of paper that tells them how many
20 times and Type I or Type II diabetes, and have they
21 been seen in the last 6 months, and do they do
22 blood sugar monitoring. I have to fill that out in
23 order to get their supplies for them.

24 So I am already doing that. Now, that
25 having been said, most meters are not prescribed by

1 endocrinologists or those specializing in diabetes
2 management.

3 [Slide.]

4 In my county in central Indiana--it is not
5 Indianapolis; it is one county north of
6 Indianapolis--the year 2000 population figure was
7 roughly 167,000 people. If the prevalence of
8 diabetes is roughly 10 percent, that means there
9 are 16,700 people with diabetes. There is one
10 endocrinologist in the county, and I can take care
11 of about 2,000 patients. That means there are
12 14,000 patients who are either going out of the
13 county or seeking an internist or family physician.

14 Having said that, let me also tell you
15 that there are some well-respected internists in
16 town--in fact, one of them is the head of the HMO
17 who sees 60 patients in a day. Some of you talked
18 about 30 patients a day; this guy is seeing 60.
19 Tell me that he is going to be able to take the
20 time to educate the patients. That is not going to
21 happen.

22 Where you are going to get the education
23 is from the certified diabetes educators.

24 [Slide.]

25 So I think that education is key, and I

1 think the educational effort needs to be directed
2 to the end-users and the diabetes educators.

3 Another thing I did in my fellowship was
4 we tried to change things. We tried to go out into
5 Indiana as part of our research study and see what
6 we could do to actually change practice patterns,
7 and we found that we couldn't.

8 There are two things that change practice
9 patterns. Number one is direct-to-consumer
10 education--bring patients in and teaching them.
11 The second thing that changes practice patterns--
12 and this is a bad reflection on doctors--is
13 malpractice suits. That changes it faster than
14 anything else.

15 How about direct advertising to the
16 certified diabetes educators? In all due respect,
17 I was one of the 90,000 doctors who got the little
18 program from LifeScan, and it was very nice, and I
19 read it. It was kind of nice, because they
20 basically confirmed our previous studies. But the
21 average doctor is not going to read that.

22 In fact, just Saturday, I was at an
23 education conference in Hamilton County that was
24 attended by about 50 or 60 doctors. The doctor was
25 talking about alternative site testing and

1 mentioned that these were not equal--and it was
2 news to those 50 or 60 doctors. Five or six of
3 them came to me later on in the hay ride and asked
4 is that really true, is it important, could it be a
5 reason for what they are seeing. And I had to say
6 that, yes, it is.

7 So I'm assuming those people got the flier
8 too, and they probably round-filed it very quickly.

9 The other thing that Dr. Clement made a
10 point of is that the trend is toward more
11 postprandial testing, which makes education along
12 these lines even more important.

13 One other thing that I want to make
14 mention of because someone talked about it is this
15 shouldn't be used in hypoglycemia. In children, I
16 guess hypoglycemia unawareness doesn't happen all
17 that much, but in my adult population, autonomic
18 neuropathy and hypoglycemia unawareness are fairly
19 common. So I wouldn't know how to tell them; I
20 would probably just tell them between zero and 2
21 hours to avoid alternative site testing.

22 [Slide.]

23 Some additional recommendations--when new
24 information becomes available concerning patient
25 safety, please try to make it allowable for

1 companies to immediately distribute this
2 information. I was kind of surprised when we got
3 the information back--someone talked about some of
4 the adverse reports. When we were doing the study,
5 I was asked on several occasions why did my finger-
6 stick say this, and my arm said that. And I just
7 assumed, because no one had told me, and I didn't
8 know that this was a problem, that it was probably
9 operator error. As it turned out, it wasn't. So
10 you aren't going to get those reports until you get
11 the information out into the practicing physicians'
12 hands.

13 I would also ask that before alternative
14 site testing be allowed in specific populations
15 that it be tested in those populations. One of you
16 made the comment earlier today, a pediatrician--I
17 don't think he is here right now--that there is
18 probably not a child who is in a steady-state
19 period. Speaking for my two children, I can say
20 that that's probably the case except maybe for when
21 I first wake them up in the morning.

22 [Slide.]

23 In review, the potential benefit of
24 increased frequency of testing I think is
25 compelling. I feel that the risk of using

1 alternative site testing inappropriately should be
2 better-explained to patients with diabetes and
3 their caregivers.

4 I would ask you to continue making
5 innovative products available to the diabetes
6 community, but to provide more information to the
7 health care providers.

8 [Slide.]

9 One of the general rules of all of us--and
10 I am convinced, after having heard you folks talk
11 and discuss, that you will do this--as long as you
12 always put patient safety first, it is very
13 difficult to find fault or point fingers, and what
14 you are doing is doing right by the patient.

15 Thank you very much.

16 DR. KROLL: Thank you.

17 The next speaker is Maria Matas-
18 Chamberlain.

19 MS. MATAS-CHAMBERLAIN: Good afternoon to
20 the panel.

21 My name is Maria Matas Chamberlain, and I
22 have a personal and professional interest in
23 today's subject. I have lived with Type II
24 diabetes for 20 years. I am a native
25 Washingtonian, and I am also, hopefully, a

1 certified diabetes educator--I'll know in 6 weeks--
2 with the Washington Hospital Center with MedStar
3 Diabetes Institute.

4 A little bit about me personally--I have
5 been pumping insulin for 3 years now, and having
6 the option of alternative site testing has been
7 very beneficial to me. Even the educators don't
8 want to test their blood sugars 4 to 10 times a
9 day, but sometimes we do, and we need to especially
10 after exercise or periods of hypoglycemia.

11 We are regular people aside from being
12 educators, so I can't stress enough that I find
13 having this option to test my blood sugars in
14 several different ways very uplifting, so to speak.

15 On a professional level, I see inpatient
16 and outpatient people with diabetes at Washington
17 Hospital Center, and you get mostly adults who run
18 the gamut from having diabetes for 10, 20, 30
19 years to people who are newly-diagnosed with
20 diabetes.

21 I have found that it doesn't matter who I
22 am teaching--if it is someone who has just stopped
23 testing because the finger-sticks are too painful--
24 when you show them any of these meters, they are
25 much more relieved to see that they have an option,

1 and they want to start testing their blood sugars
2 again; they seem very motivated.

3 People with new-onset diabetes who have
4 been in the hospital, after experiencing the
5 hospital lancets, when they see you coming at them
6 as a diabetes educator, and you pull out the lancet
7 from a meter that you are showing them, they
8 immediately say, "I am not going to go home and do
9 that." But when you show them how different a
10 hospital lancet is, and when you have the option of
11 alternative site testing, they are put a little
12 more at ease, and they are more motivated to go
13 home and to self-manage their diabetes.

14 I know my time is short, so the bottom
15 line is that whatever labeling you put out, I think
16 it is definitely the educators who really need to
17 be informed on how we should be teaching our
18 patients. Our practice at MedStar is to tell the
19 patient you may have different numbers from arm to
20 finger and to always in periods of hypoglycemia
21 take the finger as the number that you are looking
22 for.

23 This is my first time in front of a panel,
24 and I just want to say it has been a very good
25 experience for me, and I hope I get to come back.

1 Thank you very much.

2 DR. KROLL: Thank you.

3 Before you leave, did you mention if you
4 have any financial interest?

5 MS. MATAS-CHAMBERLAIN: No. That's what I
6 forgot. I have no financial obligation, and I was
7 not paid to come here by any of the companies
8 today.

9 Thank you.

10 DR. KROLL: Thank you.

11 The next speaker is Natalie Bellini. I
12 will just remind everybody to please disclose any
13 financial interest you may have.

14 MS. BELLINI: Hi. My name is Natalie
15 Bellini. I am not being paid by anyone--as every
16 educator knows. We don't get paid.

17 [Laughter.]

18 MS. BELLINI: I came at this from two
19 angles. One, I am a patient. I have been diabetic
20 for 32 years, and as I was sitting there thinking
21 about what really needs to be said again, I have
22 been on a pump for 16 years, but I have been
23 diabetic for 32. Before I got my pump, I had taken
24 18,000 shots.

25 So then, I'm thinking, wow, that's a

1 pretty big number. What else can I tell them that
2 would make them really let us do this still? In my
3 lifetime, I have taken approximately 60,000 blood
4 tests. Being able to do it wherever you can makes
5 a huge difference; it makes a difference to me, it
6 makes a difference to my patients.

7 As much as diabetes is a disease, it is a
8 psychological issue, too, because it never goes
9 away. And being able to say to a patient, "Just do
10 it" and having them say, "Okay, I can do that," is
11 what we need.

12 That's it.

13 DR. KROLL: Thank you.

14 The next witness is Carolyn Jones.

15 MS. JONES: It is sort of interesting
16 being the last speaker up here.

17 I am Carolyn Jones, and I am with
18 AdvaMED. AdvaMed is a trade association, and we
19 represent medical device manufacturers.

20 [Slide.]

21 Some of the companies that we represent as
22 a trade association are listed here. Many of them
23 have made presentations today.

24 We have a Glucose Monitoring Working Group
25 within AdvaMed, and they support the development

1 and use of new technologies that allow individuals
2 with diabetes to test their blood sugars from sites
3 other than their fingertips.

4 As you have heard today from the speakers
5 who have preceded me, fingertip testing can be
6 painful, and many patients may not test as
7 frequently as recommended because of the pain. A
8 number of patients also prefer alternative site
9 testing to avoid potential injuries to their
10 fingertips.

11 There is clinical evidence to demonstrate
12 that samples collected from alternative anatomical
13 sites give blood glucose readings that can be
14 accurate and compare well with fingertip samples.
15 During times of rapid changes in glucose
16 concentrations, the results of samples taken from
17 certain sites may differ from the blood glucose
18 concentrations measured at the fingertip.

19 There is also evidence indicating that
20 this difference is not apparent in samples taken
21 from all alternative sites, such as the palm of the
22 hand, or seen with all test systems.

23 For the information on alternative site
24 testing to be of real value and benefit to
25 patients, it is important that evaluations simulate

1 real-life conditions as opposed to the extreme
2 conditions used in the Jungheim and Koschinsky
3 studies. It is also important that all
4 instructions in the manufacturer's labeling be
5 followed.

6 AdvaMed supports the development of a set
7 of evaluation criteria that can be used for better
8 assessment of device response in diabetic patients
9 under typical conditions of use.

10 The assessment would include evaluation of
11 any differences in results from samples taken from
12 the fingertip and other anatomical sites in non-
13 steady-state patients.

14 [Slide.]

15 We recommend the following points to
16 consider in evaluating blood glucose monitoring
17 systems labeling for alternative site testing.

18 When evaluating the significance of
19 differences in the results of change between
20 glucose results from samples taken from the
21 fingertip and other anatomical sites, a
22 manufacturer should apply the same accuracy
23 criteria they use to assess differences between
24 glucose meter and laboratory results obtained from
25 fingertip capillary blood samples.

1 Regardless of anatomical site used for
2 meter testing, the reference sample should be
3 obtained from the finger-stick, as this is the
4 value commonly used by the patient for therapeutic
5 decisions.

6 Because studies have suggested the
7 possibility of physiological differences in blood
8 glucoses at various anatomical sites, studies done
9 to confirm the acceptability of an alternative site
10 should gather data under the proposed conditions of
11 use.

12 For instance, if a meter is labeled for
13 alternative site use at a time when blood glucose
14 levels may be changing rapidly, testing should be
15 done at that time, such as after a meal when blood
16 glucose changes are likely to be occurring. If
17 testing is not done, the meter labeling should
18 indicate that the alternative site should not be
19 used at such times. In diabetic subjects showing
20 the typical range of glycemic control, blood
21 samples drawn before and following a normal meal
22 can be expected to expand a range of rates of
23 glucose change from minus 0.2 mg/dL per minute to
24 plus 2.0 mg/dL per minute, with some values outside
25 this range.

1 This physiological stimulus provides an
2 adequate range of glucose change to evaluate
3 glucose monitoring systems' performance in non-
4 steady-state situations. Sponsors may propose
5 other types of studies that look at the rate of
6 change in a slightly different way.

7 Performance claims should be supported by
8 a statistically sound study. The size of the study
9 and number of data points will be determined by the
10 nature of the performance claims made and the
11 precision of the particular glucose monitoring
12 system.

13 Data specific to each proposed alternative
14 site, such as the arm, palm, or thigh, should be
15 obtained, and the labeling claims for use limited
16 to the specific sites that have been evaluated.

17 We in the AdvaMed Glucose Working Group
18 are willing to work with FDA to further develop
19 these points to consider, but we do consider that
20 each manufacturer will be responsible for
21 submitting data obtained in a manner consistent
22 with the points to consider and that demonstrate
23 their systems' performance.

24 All labeling claims would be supported by
25 data. Where the meter system performance data

1 demonstrate a clinically significant lag, AdvaMed
2 believes that it is appropriate to establish a
3 specific set of precautionary statements that would
4 be included in the product labeling of the affected
5 device or devices.

6 It is the responsibility of each
7 manufacturer to provide FDA valid scientific
8 evidence to support their product labeling.

9 AdvaMed supports the continued use of
10 currently marketed systems as well as FDA clearance
11 of new systems provided manufacturers inform users
12 about the possible limitations of alternative site
13 testing, or the manufacturer can demonstrate or has
14 already demonstrated that its test system is not
15 affected.

16 As is the case with any question related
17 to diabetes self-management, issues around
18 alternative site sampling can be explained in clear
19 and easily readable labeling that has been assessed
20 for clarity using readability evaluation procedures
21 as suggested in the FDA Guidelines for Home Use
22 Device Submissions.

23 AdvaMed believes that where a lag is
24 demonstrated, labeling statements and the proper
25 education and training can be best communicated to

1 the health care community and consumers by
2 manufacturers. Manufacturers would be responsible
3 for disseminating the information to customers
4 through efficient communication channels. They
5 should also provide supplemental materials to
6 health care professionals that explain, for
7 example, the specific studies, the scientific basis
8 for the results, and recommendations regarding
9 patients who may not be suitable candidates for use
10 of some alternative site testing--that is, patients
11 with hypoglycemic unawareness.

12 [Slide.]

13 AdvaMed does not believe that prescription
14 use is warranted for these devices. It is
15 impractical. It will create an undue hardship for
16 diabetics, and it would be impossible to administer
17 because a number of these devices are also approved
18 for finger-stick testing.

19 [Slide.]

20 For test systems and body sites that
21 demonstrate a clinically significant lag, the
22 following information written in simple language so
23 that all users can understand their meaning should
24 be included in the labeling.

25 For example, indicate the site being

1 tested. If it is the arm, the results may be
2 different from the fingertip when glucose levels
3 are changing rapidly, indicating after a meal,
4 taking insulin, or during exercise. And you are
5 going to state to the user: Do not use the arm
6 site or whatever site you collected your data on;
7 use the finger-stick if you think your blood sugar
8 is low, if you have been diagnosed with
9 hypoglycemic unawareness, or if the site results do
10 not agree with the way that you feel.

11 [Slide.]

12 In conclusion, AdvaMed strongly believes
13 that the use of alternative site testing technology
14 provides important patient benefits and is safe and
15 effective when used with the manufacturer's
16 instructions and precautions. Again, the AdvaMed
17 Glucose Working Group is willing and open to
18 working with FDA to further clarify the points to
19 consider and to develop the appropriate criteria
20 for submissions on these devices.

21 Thank you.

22 DR. KROLL: Thank you.

23 I and the rest of the panel members would
24 certainly like to thank all the people who spoke in
25 the Open Public Hearing, and we would also like to

1 thank all the speakers from the sponsors and the
2 sponsors' efforts and all the information that they
3 have provided.

4 Now, I'd like to open up the committee
5 discussion again, especially in light of what we
6 have just heard from these people in the public
7 hearing, and ask if people have any additional
8 comments or questions or if they want to make any
9 changes in what they have said.

10 So I'll just open it up, and it looks like
11 Dr. Henderson wants to speak.

12 **Open Committee Discussion**

13 DR. HENDERSON: I just have a question,
14 and I guess it's for the FDA, I'm not sure for
15 whom.

16 I am confused about the controversy. I
17 don't really see that there is one. Everything
18 that I have heard today suggests that this is a
19 good tool. It's not perfect, but medicine is an
20 art, not a science, and you use everything you
21 have, and you kind of tweak it. Patients are not
22 machines, do you do the best you can with whatever
23 information you have.

24 I don't see the dilemma. I am really
25 confused. And it seems as though everyone on the

1 panel is in agreement that this is a good thing to
2 have, yet there are some problems. But in
3 medicine, there is nothing that we have that
4 doesn't present some problems. You make the best
5 of it and try to maximize the outcome.

6 I'm sorry, I just don't get it.

7 DR. GUTMAN: Well, I guess that's one of
8 the uses of a panel to perhaps pacify or calm down
9 FDA.

10 [Laughter.]

11 DR. GUTMAN: But it actually is our job to
12 look at issues with broad public health impact.
13 This is a learning experience for the agency and
14 perhaps for the panel and for the industry as well.
15 The course of our understanding of this issue is
16 one in which it becomes increasingly complicated
17 and enriched by knowledge, and what seemed like
18 something that was actually quite alarming perhaps
19 6 or 8 month ago and in part, to be honest, because
20 it was our perception when we were first aware of
21 this that nobody knew about it, and it always
22 alarms us when there is some interesting
23 physiologic quirk which might have impact on
24 insulin therapy or other therapy when the
25 community--and by "community," I speak in the

1 broadest terms, the health care providers as well
2 as patients--didn't know about this.

3 I don't know if that's the case now; if
4 that is the case now, I hope the panel has been a
5 marker to help make this publicly perhaps more
6 prominent. I do think that the industry has been
7 increasingly responsive and, as they understand the
8 issues better, have been trying to communicate
9 them.

10 It doesn't have to be a problem. You can
11 put this to bed. I actually do see it still as a
12 challenge to the agency, and AdvaMed has been kind
13 enough to offer some support--a challenge to the
14 agency to make sure that a very complex physiologic
15 process that has different interactions at
16 different sites and different actions with
17 different devices leads to a fair and even playing
18 field in terms of allowing products to go through
19 with clear labeling and honest data so that
20 patients and their health care providers can make
21 intelligent choices.

22 So I'm not sure it actually is a no-
23 brainer.

24 DR. CLEMENT: I have just one small
25 comment. We have heard this term over and over

1 again, and just in the last presentation, it came
2 up again, and I had lots of notes and circles
3 around it. We use this term "hypoglycemic
4 unawareness" as if everybody knows what this is,
5 but--and I'm sure Davida could comment on this--it
6 is clearly not a term that is in seventh grade
7 education in terms of labeling--an I mean when
8 actually putting in terms for actual writing for
9 labeling and instructions for patients.

10 Most physicians don't know what the term
11 means. So I think that how that language is put in
12 the educational materials is extremely important.
13 I mean, just putting a label on and saying this
14 should not be used if you have hypoglycemic
15 unawareness--I don't know any of my patients,
16 unless I have actually instructed them, who knows
17 exactly what that means, even though it has
18 tremendous implications.

19 So I think trying to iron out the
20 language, defining what it is--some of the terms
21 that have previously been used to define
22 "hypoglycemic unawareness" are if you have passed
23 out, if you have had a coma or seizure, if you have
24 ever required assistance and treatment of
25 hypoglycemia; those are obviously clear red flags

1 to us that this patient cannot detect symptoms.

2 I'll be interested to hear if Davida has
3 any other ideas about that.

4 MS. KRUGER: I would just make the comment
5 that I have been in this field for 20 years--I was
6 actually brought in to do the diabetes control and
7 complications trial, and that was my awakening to
8 this--and 20 years ago, our biggest challenge was
9 when urine testing was moved to blood glucose
10 monitoring, getting people not to pee on the blood
11 glucose strips. That was a big issues.

12 So I am just thrilled to have any new tool
13 that will really move the care forward because we
14 know so much more about diabetes and what needs to
15 happen, and still it is not happening in terms of
16 average hemoglobin A1c's and blood glucose in the
17 community and education.

18 I have the same experience when I present
19 this to patients as an awareness, that they can now
20 test in various places and do more blood glucose
21 monitoring. And I would agree with Steve that we
22 just need to be careful with the labeling because--
23 I always say to my patients, "I understand what I'm
24 telling you, so stop me if you don't understand"--
25 because what I have done for 20 years, other people

1 have not. And it is true that most people--as one
2 of the presenters showed us today, we have 35,000
3 people in the health system that I work in, and we
4 only have four endocrinologists, so most of our
5 patients also go to internal medicine, and that's
6 the thing that we have to remember in terms of
7 education and products and labeling, that most of
8 us who work in the field of just diabetes are not
9 going to be the ones who are going to have the
10 issues with what are the right patients. We need
11 to make sure that we're clear on those things.

12 DR. LASKY: I just wanted to talk a
13 little bit about the question that FDA asked about
14 help in assessing the parameters and the studies.

15 It occurred to me that there has been a
16 lot of interest in standardization of in vitro
17 diagnostic products, particularly on an internal
18 basis. There is an ISO Technical Committee on
19 IVDs that has as one of its work items a document
20 on the criteria for whole blood glucose monitoring,
21 and FDA has been very active in this process; Dr.
22 Gutman has been on the working group, and he has
23 also been very critical of the drafts, critical in
24 terms of critiquing, to be sure that it truly
25 satisfies the needs of diabetologists and patients.

1 So I would suggest that any criteria that
2 are developed for alternative site testing use at
3 least in part this document which is up for
4 approval in order to deal with some of the issues
5 that we talked about today.

6 DR. KROLL: Do any other panel members
7 have comments or questions?

8 [No response.]

9 DR. KROLL: Then, let me ask Dr. Gutman
10 and Dr. Cooper and anybody else from the FDA
11 whether there are any questions that we have left
12 unanswered or that you would like us to elaborate.

13 DR. GUTMAN: No. I think you have done a
14 fine job of helping us here. If any of you on your
15 routes home or in the next day or two have any
16 insights you'd like to share with us, I do
17 encourage you to do so.

18 This has been a very rich day; there has
19 been a lot of data presented and a lot of
20 interesting perspectives, and Dr. Cooper and I
21 would be happy to hear from any of you if you have
22 any insights. We clearly are anxious to see if
23 AdvaMed can come to the table and help us, and we
24 want to move the submissions that are in our house
25 through quickly and try to keep what is obviously

1 an important new technology properly labeled,
2 properly grounded, but alive.

3 DR. LASKY: I do have one more comment,
4 and that is that I'd like to thank FDA for
5 providing the extensive--when I first got this, I
6 thought intimidating--amount of documentation; but
7 it enabled us--I can speak for myself only, of
8 course--to do some homework beforehand, so I had a
9 complete appreciation of what the issues were. And
10 also, the information that was presented, I did not
11 have to be concerned about the details, but I
12 learned a great deal about the interpretation and
13 use of these products, and it was only because I
14 was able to do my homework beforehand.

15 So I thank the FDA for doing that.

16 DR. GUTMAN: We always like to give the
17 final word to our statisticians, and it is my
18 understanding that the statistician does have a
19 question, so you aren't off the hook yet.

20 DR. KONDRATOVICH: I have a question about
21 naming the study design single point measurement.
22 The typical scheme of this study design is that the
23 sponsor invited, for example, 100 subjects, and
24 these subjects were tested only once during the
25 normal scheduled visit. So, in this situation,

1 there can be built time profiles for these
2 subjects, and we have a mixture of patients; some
3 patients may be in steady-state, some may be
4 dynamic.

5 Can we consider that this is an
6 appropriate design to evaluate the equivalence of
7 alternative sites, or do we need to consider that
8 this is not a good study design, and you need to
9 have some kind of time series measurement, maybe
10 monitoring or measurement of some patients during
11 special time points.

12 What is your opinion about this problem--
13 because we saw a lot of study designs with single
14 point measurements.

15 DR. KROLL: First, let me open this up to
16 the panel members.

17 Does anybody have an opinion?

18 DR. CLEMENT: I think it's pretty clear
19 that some kind of dynamic testing of individual
20 patients tested serially with some provocative
21 tests to cause either hyperglycemia and/or
22 hypoglycemia would help to sort out these problems.

23 If you just do single point testing in a
24 large population, you get individual points, but it
25 really doesn't tell you lag time, it doesn't tell

1 you individual differences. Everybody gets
2 clustered on this Clarke Error Grid, and the
3 differences get totally lost in the data.

4 I scribbled out for Dr. Gutman a little
5 proposed dynamic study I think very similar to what
6 Roche did, very similar to what was done in
7 Germany, on how to analyze it that would help
8 amplify some of those differences.

9 DR. KONDRATOVICH: I am very happy to hear
10 this, because I am of the same opinion.

11 Thank you.

12 DR. KROLL: Let me just comment that I
13 agree with Dr. Clement. I think the time series
14 studies are absolutely necessary. The single
15 points are totally inadequate. The time is another
16 variable, and it is going to be different. You
17 have at least four or five different points that
18 are very critical, so they are absolutely required.

19 You can't go back to the old way of just
20 picking out a point here or there.

21 The other thing you have to be very
22 careful about is using any averages. I think that
23 when patients are studied, they need to be
24 classified individually, and then you can put them
25 together and say how many patients didn't agree

1 well, how many patients turned out to be
2 potentially hypoglycemic, and we missed it, or how
3 many patients had very sky-high glucose, and we
4 missed that.

5 Again, is time a factor--they have these
6 time lags, and they need to be evaluated as well.

7 DR. KONDRATOVICH: Okay. Thank you very
8 much.

9 DR. ROSENBLOOM: The single point
10 measurements, of course, are useful for your
11 accuracy studies. It was mentioned that accuracy,
12 of course, is a very different issue. I don't see
13 a problem with using the error grid or single point
14 measurements in determining the accuracy of
15 alternative site testing as opposed to the
16 correlation of alternative site testing with the
17 primary site or with the gold standard site.

18 DR. KROLL: Let me just make one comment.
19 You can use paired single point values if you have
20 the same sample. That is what is critical here.
21 The real question is we don't always have the same
22 sample. We know we have a different fraction of
23 blood. The blood is not mixed the same way, and
24 that is critical. And it may be that it's in all
25 patients or just a few patients. So that is where

1 you run into that accuracy issue.

2 If you took--

3 DR. ROSENBLOOM: Yes. I'm not talking
4 about matching on the grid with finger-stick, but
5 matching with the reference standard.

6 DR. KROLL: Well, the problem is that you
7 have one drop of blood, and you can only--if you
8 could put it in two different devices, and you are
9 checking the device out--but I think the question
10 here has really been if we collect sample two
11 different ways, we actually don't have the same
12 sample, and again, that is no longer an accuracy
13 issue.

14 But I agree with you that you can use it
15 to match up between meters, but I think you have to
16 be very careful. That's what we're trying to
17 clarify.

18 DR. ROSENBLOOM: But what you are
19 measuring is different from the accuracy question.
20 I mean, the Clarke Error Grid is an accuracy
21 device, is it not? The Clarke Error Grid was
22 originally developed for measuring a specific meter
23 against the YSI or a laboratory standard.

24 DR. KROLL: Assuming you had the same
25 sample.

1 DR. ROSENBLOOM: Yes, right. And that's
2 really the only way you can use it in this context.
3 I agree with that.

4 DR. KROLL: Are there any other comments
5 or questions for the panel?

6 [No response.]

7 DR. KROLL: Is there anything else that
8 the FDA wants us to do?

9 DR. GUTMAN: No. Thank you all very much.

10 DR. KROLL: Okay. Then, I hereby say we
11 can adjourn the meeting, and I thank everyone. I
12 thank the panel members and thank the FDA and the
13 sponsors and the public speakers.

14 [Whereupon, at 4:00 p.m., the proceedings
15 were concluded.]