

FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

ENDOCRINOLOGIC AND METABOLIC

DRUGS ADVISORY COMMITTEE

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MEETING #69

PROPOSED (DRAFT) GUIDANCE DOCUMENT FOR THE

DEVELOPMENT OF DRUGS FOR THE TREATMENT OF

DIABETES MELLITUS

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Thursday, March 12, 1998

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The meeting was held at the Gaithersburg
Holiday Inn, 2 Montgomery Village Avenue,
Gaithersburg, MD, at 8:00 a.m., Dr. Henry G. Bone III,
Committee Chairman, presiding.

PRESENT:

HENRY G. BONE III, M.D., Chairman

JOSE FRANCISCO CARA, M.D., Member

CATHY CRITCHLOW, M.D., Member

ROBERT MARCUS, M.D., Member

ROBERT S. SHERWIN, M.D., Member

JULES HIRSCH, M.D., Member

MARK E. MOLITCH, M.D., Member

JAIME A. DAVIDSON, M.D., Consumer Representative

JOANNA ZAWADZKI, M.D., Consultant

KATHLEEN R. REEDY, Executive Secretary

ALSO PRESENT:

G. ALEXANDER FLEMING, M.D., FDA

ROBERT I. MISBIN, M.D., FDA

SOLOMON SOBEL, M.D., FDA

A-G-E-N-D-A

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

2 (8:09 a.m.)

3 CHAIRMAN BONE: Good morning. I'm calling
4 to order the 69th Meeting of the Endocrinologic and
5 Metabolic Drugs Advisory Committee. I'm Doctor Henry
6 Bone, and I'm sure you all have copies of the meeting
7 agenda.

8 Briefly, we will have -- go around the
9 table to introduce the people at the head table, and
10 then Ms. Reedy will read the meeting statement. The
11 topic for today's meeting is the Proposed (Draft)
12 Guidance Document for the Development of Drugs for the
13 Treatment of Diabetes Mellitus.

14 If we'd just start around and we'll ask
15 the people at the front part of the FDA section to
16 identify themselves as well, please, starting with
17 Doctor Sobel.

18 DOCTOR SOBEL: Saul Sobel, Division of
19 Metabolic Endocrine, FDA.

20 DOCTOR FLEMING: Alexander Fleming, in the
21 Division of Metabolic and Endocrine Drugs.

22 DOCTOR MISBIN: Robert Misbin, Medical
23 Officer.

24 DOCTOR ZAWADZKI: Good morning, Joanna
25 Zawadzki. I'm an Endocrinologist in private practice

1 in this area and Clinical Associate Professor at
2 Georgetown University Medical Center.

3 DOCTOR MARCUS: Robert Marcus, Professor
4 Medicine, Stanford University.

5 DOCTOR SHERWIN: Robert Sherwin, Professor
6 of Medicine, Yale University.

7 CHAIRMAN BONE: Henry Bone, Michigan Bone
8 and Mineral Clinic in Detroit, Michigan.

9 EXECUTIVE SECRETARY REEDY: Kathleen
10 Reedy, Food and Drug Administration.

11 DOCTOR MOLITCH: Mark Molitch, Professor
12 of Medicine, Northwestern University, Chicago.

13 DOCTOR DAVIDSON: Jaime Davidson,
14 Endocrine and Diabetes Associates of Texas,
15 Endocrinologist.

16 DOCTOR CRITCHLOW: Cathy Critchlow,
17 Epidemiologist, University of Washington, Seattle.

18 DOCTOR CARA: Jose Cara, Pediatric
19 Endocrinology and Diabetes, Henry Ford Hospital,
20 Detroit, Michigan.

21 DOCTOR HIRSCH: Jules Hirsch, Rockefeller
22 University, New York.

23 CHAIRMAN BONE: Thank you.

24 Ms. Reedy?

25 EXECUTIVE SECRETARY REEDY: The following

1 announcement addresses the issue of conflict of
2 interest with regard to this meeting and is made part
3 of the record to preclude even the appearance of such
4 at this meeting.

5 Since the issues to be discussed by the
6 committee will not have a unique impact on any
7 particular firm or product, but rather, may have
8 widespread implications with respect to entire classes
9 of products, in accordance with 18 United States Code
10 208 waivers have been granted to each member and
11 consultant participating in the committee meeting.

12 A copy of these waiver statements may be
13 obtained from the Agency's Freedom of Information
14 Office, Room 12A30, Parklawn Building.

15 In the event that the discussions involve
16 any other products or firms not already on the agenda,
17 for which an FDA participant has a financial interest,
18 the participants are aware of the need to exclude
19 themselves from such involvement, and their exclusion
20 will be noted for the record.

21 With respect to all other participants we
22 ask in the interest of fairness that they address any
23 current or previous financial involvement with any
24 firm whose products they may wish to comment upon.

25 CHAIRMAN BONE: Thank you very much.

1 Doctor Fleming, from whom you will be
2 hearing in a little while, has asked me to make a
3 point to everyone that we are talking about something,
4 a guidance document that's at a fairly early stage of
5 development, so that people should not have the
6 impression that this is necessarily going to reach
7 closure on every issue, that this is a step along the
8 way.

9 And, the next step we're going to take
10 along the way will be the opportunity for people to
11 speak in what's called the open public hearing. As
12 you know, in the United States we have an absolutely
13 unique feature in our regulatory process, which is
14 that, not only are the meetings held in the open when
15 they are involving the Advisory Committee, but the
16 people who are present have the opportunity to make
17 remarks, and we have several persons who will be
18 speaking this morning in this segment of the program.

19 We are going to have an opportunity for
20 the sponsors to have a special section of this open
21 public forum, and we're going to have that between --
22 we have it scheduled for about 9:30, it will come
23 shortly after the presentation of the guidance
24 document.

25 I'm informed that no other individuals

1 have registered with the Executive Secretary to make
2 presentations, so we'll go directly to Doctor
3 Fleming's remarks.

4 DOCTOR FLEMING: Good morning, ladies and
5 gentlemen, and members of the Advisory Committee, on
6 behalf of Doctor Sobel, Doctor Bildstein, Doctor
7 Misbin and other colleagues, at the FDA, we welcome
8 you and look forward to a very interesting day.

9 I think this kind of investment in the
10 future of drug development is one of the best uses we
11 can make of the Advisory Committee. It truly will
12 save a great deal of work in the future, as we discuss
13 with drug developers how they can go about their
14 business.

15 I think there are obvious advantages of
16 having written guidances for sponsors to consider.
17 Clearly, as we are showing today, it invites wide
18 expert input in the process. It promotes, clearly,
19 fairness and consistency when we deal with a number of
20 different sponsors who are seeking the same
21 indication, and I think it provides sponsors with very
22 important information, information that they may not
23 know that they need, and that in itself is a big
24 advantage. It allows them to calculate more
25 accurately how much it's going to cost and how long it

1 will take to develop a particular indication.

2 Ultimately, these guidelines increase the
3 speed, and the quality and efficiency of the drug
4 development process, and that translates, of course,
5 to drugs being available to the people who need them
6 much faster, and at less cost.

7 I thought it would be worth taking just a
8 minute to talk about the kinds of guidances, or the
9 kind of advice that we give at the Agency, so that you
10 on the committee have a context for what we are doing
11 today.

12 First of all, just the types of advice
13 that we give. The first would be the one, the age-old
14 kind of advice that is sort of the one-on-one or the
15 case-by-case discussion with the sponsor. We continue
16 to do that, obviously, but when we are dealing with an
17 indication that will ultimately be pursued by more
18 than one sponsor it certainly makes sense to have a
19 written guidance for that particular indication.

20 Another kind of advice is simply a well-
21 known policy. An example of this would be the
22 recommendation that was made some years ago by this
23 committee, that we should accept nothing less than
24 final adult height in the evaluation of growth hormone
25 or, rather, growth promoting therapies.

1 Then, the next level up, of course, is
2 what we are about today. We are developing what we
3 hope will become a comprehensive guidance for an
4 important therapeutic area, and I'll give you a good
5 example of that in just a moment.

6 We have also a body of agency guidances,
7 and I'd like to show you what I mean by that shortly,
8 and you could consider that even some Agency
9 regulations form, if not advice, at least they provide
10 very important information that pertains to the work
11 that drug developers do. Particularly, in the area of
12 human ethics, there is a body of regulation, and also
13 guidances that are important in the conduct of
14 clinical trials.

15 I think the best example of a therapeutic
16 area guidance is that developed by this division and
17 this committee, the guidelines on osteoporosis. I
18 think this is probably the best guidance of its kind
19 in the Agency, and I can brag on it because I was not
20 at all involved in developing it.

21 Now, getting to the Agency level, we even
22 have a guidance on issuing guidances, and here's the
23 example. This was released recently, and one effect
24 of this guidance on guidances is that we will not be
25 using the word guideline very much, and so even in our

1 case we will probably need to amend the title to a
2 guidance.

3 There is now a large body of guidances
4 that have been developed under something called the
5 ICH, the International Conference on Harmonization
6 technical requirements for the registration of
7 pharmaceuticals human use, ICH for short. And, within
8 this body of information they can be looked at in four
9 different groups, safety, which pertains to actually
10 pre-clinical testing, quality pertains to
11 manufacturing and analytical, efficacy pertains to
12 clinical, and then we have the fourth body, a more
13 recent one, pertaining to communicating among
14 different parties.

15 Now, obviously, we don't have time to go
16 into the individual documents that ICH has produced,
17 but this would give you maybe a sense of what exists
18 in the clinical realm. There are basically now ten
19 documents, almost all of them are completed, and they
20 could be grouped according to these four categories,
21 and you can see that these are very pertinent to the
22 work that we bring into the division and, clearly, in
23 all the divisions in the New Drug Review area of CDER.

24 Just to give you a sense of what these
25 documents are about, I'm going to put these titles in

1 front of you without even reading them. You can see
2 that there are a number of fairly pertinent topics
3 that are of use certainly to our drug sponsors, who
4 need to know what to do when it comes to developing a
5 drug.

6 Well, let me just conclude by, again,
7 thanking the committee members for making their time
8 available. We've had a number of three-day Advisory
9 Committee sessions, and this is really well beyond the
10 call of duty.

11 It's a very large investment in the future
12 of drug development, in these various therapeutic
13 areas. This will ultimately make drugs available to
14 those who need them much faster, and we look forward
15 to working with you, not just today, but through
16 coming years as we develop this guideline on diabetes,
17 and thank you.

18 CHAIRMAN BONE: Thank you very much,
19 Doctor Fleming.

20 Next, we will have a presentation of the
21 draft guidance document in its current form by the
22 principal author, Doctor Misbin, from the Division of
23 Metabolic and Endocrine Drug Products. And,
24 subsequently, we will have comments by the prospective
25 sponsors, getting them involved, we'll go on to

1 discuss these different sections on an item-by-item
2 basis. So, I think from the standpoint of going
3 through Doctor Misbin's presentation we will have
4 questions by committee members for points of
5 clarification. Would you prefer to take those at the
6 end, Doctor Misbin, or at the end of each section?
7 Would that be a better way to do that, if committee
8 members have specific questions?

9 DOCTOR MISBIN: You mean in my
10 presentation?

11 CHAIRMAN BONE: Yes, would you like to go
12 straight through or would you like to have questions
13 -- if there's a major point of clarification that
14 seems urgent we could interrupt, but otherwise I'd
15 like to try to go through it.

16 DOCTOR MISBIN: Well, there are a few
17 places where I could pause.

18 CHAIRMAN BONE: All right, why don't we do
19 that then.

20 DOCTOR MISBIN: Okay.

21 Well, what I would like to do is to really
22 begin by talking about how the guidance was developed,
23 and I'm showing here a chronology of that. I'd like
24 everyone really to think about the progress that's
25 been made in the development of drugs for diabetes.

1 If one goes back, really, just three years
2 ago to March, 1995, at that time, really, there were
3 only two drugs, two classes of drugs that were
4 available for the treatment of diabetes in the United
5 States, and they were sulfonylureas and insulin.

6 And, subsequently, over the next several
7 years, three new classes of drugs were introduced in
8 addition to a new type of insulin secretagogue and a
9 new engineered insulin analog in the form of lysepro
10 insulin. So, in going through the guidance there was
11 really a lot of precedent to look over, and that was
12 really how the guidance was developed, to look over
13 those applications and try to extract the essence of
14 what those made -- what made those applications
15 approvable, and also to try to identify what problems
16 there were in the reviews of those applications and to
17 head off those problems from developing in the future.

18 The first draft of the guidance, I think
19 was written in November of 1996, and when I gave it to
20 Doctor Sobel, and then went through an in-house review
21 and there were some revisions made, of course, as
22 people in the division commented.

23 The first actual public presentation was
24 in July of 1997, when it was given -- presented at a
25 meeting of PHARMA, and comments were solicited,

1 really, from the people who heard that presentation at
2 PHARMA, and we requested written comments from
3 industry in an attempt, really, to come to some kind
4 of consensus on the way new drugs should be developed.

5 In addition, we sent the guidance to the
6 American Diabetes Association, to Richard Kahn and
7 Mayor Davidson, Mayor Davidson being the President of
8 the ADA at that time, and requested that they make
9 comments as well.

10 Now then, all of these comments were then
11 sent back to our office and they were incorporated
12 into the revised document in September, 1997.

13 Now, I think I would say that there were
14 many, many comments that were made, both by the ADA
15 and by members of industry, and I think all of these
16 comments were incorporated in one way or another into
17 the revised document.

18 The ADA had a number of comments and
19 these, in fact, were -- there were many comments and
20 all of these, really, were taken quite seriously and,
21 in fact, incorporated into the revised document.

22 The comments by industry, though, many of
23 them were included and they were all really taken
24 seriously, as I said, but there were many comments
25 that were given to us by sponsors, although we took it

1 seriously, we did not agree with those comments, and
2 still do not agree with those comments.

3 The document was revised to include
4 reasons why we did not agree with those points raised
5 by industry, but I think if anything the revised
6 document actually takes a harder line on these points
7 than the original document, and I shall, in the bulk
8 of my presentation, actually go through these issues
9 which I think still are areas of controversy.

10 In February of 1998, there were some new
11 additions made. These were, this was just last month,
12 and this was based on problems that had developed just
13 over the months during which time the guidance was
14 being developed, and then, of course, we have the
15 meeting today.

16 Now, in anticipation of this meeting, we
17 thought it appropriate to invite members of industry,
18 those very people who had submitted written comments
19 before, to present their cases before this committee,
20 and in a hope to discuss these, potentially debate
21 them, and I hope to resolve them, and I'm quite happy
22 that there are many sponsors who are here and will be
23 addressing you directly about why they feel we have
24 not taken the line that they would like us to take.

25 This is really the areas that I think we

1 should be discussing today. The first really is the
2 criteria for the basis of approval of a new drug, then
3 the types of trials and the types of patients that we
4 would like to see have done, and within this category,
5 really, are the major areas of controversy, and I'll
6 discuss these in some detail.

7 Then after that, I think the other points
8 that I think the Division really needs a lot of help
9 on I've listed here, and there are four of these that
10 I've identified. The first really is the definition
11 of hypoglycemia, and this, I have to say that I
12 wrestled with this for two years and I really do not
13 have a good handle upon how to come up with a
14 satisfactory definition of hypoglycemia that we can
15 use in clinical trials.

16 On the one hand, we would like to capture
17 all of the clinically relevant events. On the other
18 hand, we need to have criteria that are objective,
19 quantifiable and not really subject to individual
20 interpretations, subjective reporting, bias reporting,
21 whatever, which I think is a major problem with
22 respect to reporting of hypoglycemia. And, I think
23 this, to me, is really the major issue that I really
24 think we need some input from the experts, really, on
25 the committee.

1 The second area is the use of all
2 hypoglycemic agents in children. This is something
3 which we are asked, which the Division is being asked
4 to comment on specifically, and is, I think, a major
5 public health issue. I mean, we do not ordinarily
6 think of the use of oral hypoglycemic agents in
7 patients with type 2 diabetes, I think we should think
8 about it, but the decisions that are made will affect
9 those patients for the rest of their lives and really
10 transform, potentially, the way diabetes is treated in
11 this country. And so, this, I think, is a major area
12 that needs to be discussed.

13 The use of antiobesity drugs in diabetes,
14 and I think we would all recognize that if we could
15 cure obesity we would cure most patients with type 2
16 diabetes. And, many drugs are being developed which
17 would have activity, really, in both areas, but I
18 think there is the question, if a new agent is really
19 an antiobesity agent, and doesn't actually have a
20 specific antidiabetic activity, then, really, in what
21 category should it be placed or what should be the
22 criteria for approval. The criteria for approval of
23 an antidiabetic agent, even in this draft guidance, is
24 less stringent than that for an antiobesity drug, and
25 so I think that there is the potential for some

1 conflict here.

2 And then finally, the area of diabetes in
3 pregnancy and the use of drugs in gestational
4 diabetes. I think we all recognize that we need more
5 data in this area, but the fact that we recognize it
6 does not mean that we are able to get it. This is a
7 very, very sensitive area, and whenever it has come up
8 we really have great difficulty in getting studies
9 done in this area, and here I think a statement from
10 the committee would be extremely helpful.

11 Now, I've listed other areas, and I don't
12 mean to indicate that these are less important than
13 anything else, but I think since time is limited, I
14 think -- these areas, I think, are the really urgent
15 ones, and these, I think, are, to my mind, really of
16 importance, but really of less importance. I've just
17 listed them, the use of insulin analogs and mixtures
18 of insulin, insulins given by non-parenteral means,
19 the changes in drug use that have occurred or may
20 occur because of the revisions in the diagnosis of
21 diabetes that was approved by the ADA and the World
22 Health Organization last year, which actually makes
23 more patients covered under the diagnosis of diabetes
24 than had been previously, and finally, the thrust
25 toward the treatment of patients with impaired glucose

1 tolerance, the impact of the NIH study and how we
2 should meet the challenge of the treatment of impaired
3 glucose tolerance.

4 I think it's now time to get right into
5 the areas of major contention, I believe, and this is
6 really categorized as the criteria for the basis of
7 approval and the types of trials and patients that
8 would lead to approval of a new product.

9 The criteria for the basis of approval,
10 well, we recognize, really, in the draft of the
11 guidance, that there were three bases for approval.
12 The first is the one that we've used, really, in all
13 other drugs that are approved for this indication, and
14 that is -- at least all recent approvals -- and that
15 is a reduction in hemoglobin A_{1c}, which is clinically
16 significant and sustained for a period of 12 months.
17 A second potential basis for approval would be a
18 reduction in the frequency of major hypoglycemic
19 events. We recognize, I think, as I think most
20 diabetologists, that the hypoglycemia is the major
21 limiting step in achieving near normal glucose levels,
22 and we would really like to see a thrust directed
23 specifically at lowering hypoglycemic events. And
24 then finally, and by no means last, an improvement in
25 the decrease in the development of complications

1 directly. This would be independent of changes in
2 glycemic control.

3 Now, with respect to the type of trials,
4 we recognize that there is still importance of doing
5 placebo-controlled trials. There's no -- absolutely,
6 no doubt about that. But, on the other hand, there
7 are some ethical considerations here, which I think
8 cannot be ignored. The reason we develop these drugs
9 is that sustained hypoglycemia is harmful. If we
10 recognize that sustained hypoglycemia is harmful, then
11 how can do a placebo-controlled trial, in which
12 patients are given a placebo and their hypoglycemia is
13 not treatment, now this, I think, raises some ethical
14 issues which have to be considered and have really not
15 been considered up until now.

16 In order to address this, we are really
17 urging the use of positive comparators, something like
18 glyburide or acarbose are given as examples of well-
19 established positive comparators that could be used
20 versus a new drug in a new trial.

21 And then finally, we would like to say
22 that in all trials we are assuming that there will be
23 continued attempts at good glycemic control. This
24 really gets back to the ethical issue that I was
25 talking about earlier, and this comes up in many, many

1 guises, but I think the simplest way of looking at it
2 is this. Let's say that a sponsor had a new compound
3 that they wished to test to see if it decreased the
4 development of microvascular complications independent
5 of changes in glycemia. The most efficient way to do
6 a study like that would be to use patients with type
7 1 diabetes, and type 1 diabetes who are poorly
8 controlled, say that had Glycohemoglobins of 12.
9 These are the very patients that have the high risk of
10 developing microvascular disease.

11 Now, the other way of -- another point of
12 this would be that if one entered patients into a
13 trial and altered their insulin regimen, or altered
14 their glycemc control, then that would be another
15 variable which would be difficult to factor out in the
16 final analysis. And so, the simplest trial would be
17 to take patients with poorly controlled type 1
18 diabetes and to say, once they are in the trial their
19 insulin regimen and their glycemc control should be
20 kept constant for the duration of the trial, that
21 would be the simplest way of investigating this
22 question.

23 But, to our mind, that would be an
24 unethical trial, because there would be no
25 justification for saying that patients should be

1 enrolled on the trial under conditions which we
2 recognize to be harmful. And so, we would require
3 that in that setting those patients actually have, be
4 allowed to have a change in their insulin regimen so
5 as to bring this glycosylated hemoglobins further
6 toward normal. We would not accept as ethical saying
7 that their hypoglycemia should be maintained
8 intentionally just for the sake of being able to do a
9 placebo-controlled trial.

10 Now, I think this -- to me, this seems
11 really quite evident that that would be an unethical
12 trial, but we still deal with this issue over and over
13 again, and I would hope that the committee members
14 would address this issue specifically.

15 Now, I would like, really, to engage in
16 the major area of controversy, which is really right
17 up here, what is the basis of approval based on a
18 reduction in hemoglobin A_{1c}. Now, I've indicated a
19 placebo in parenthesis, and this is intentional. We
20 recognize that a treatment effect is really determined
21 based on a change in what happens to a placebo.
22 There's always a certain placebo effect in any trial,
23 so the effect of the drug is really what is observed
24 with the drug minus what is observed with the placebo.

25 But, I think we are unwilling to actually

1 approve a drug just on the basis of a change in
2 glycemic control versus a placebo, and one of the
3 other criteria which is in the guidance is that the
4 glycemic control, the hemoglobin A_{1c} actually
5 decreased itself in any individual patient, not just
6 a decrease in glycosylated hemoglobin versus placebo.

7 Now, this is the major area of comment
8 that we got from sponsors, and the argument that was
9 made really goes something like this. Diabetes -- now
10 we are talking here about type 2 diabetes, type 1
11 diabetes is, of course, a very different situation,
12 but type 2 diabetes is a progressive illness, glycemia
13 gets worse over time, patients fail on their diet, the
14 sulfonylurea ceases to be effective, there's betacylic
15 exhaustion, all of these things happen to lead to a
16 progression and a decay, really, in glycemic control.

17 And, if then one had a drug that
18 interfered with this progression and, therefore, was
19 kind of changing the natural history and development,
20 or the decay in glycemic control in these patients,
21 that that, of itself, should be adequate to sustain a
22 recommendation of approval.

23 And, there is, really, some validity, I
24 think, in this way of looking at it, but I think there
25 are also some major problems with this way of looking

1 at it, and that's what I'm going to illustrate now.

2 Now, let's just consider some hypothetical
3 data. This is not actually hypothetical, this is real
4 data, but we are not -- it doesn't matter what
5 products it is, and I'm not going to identify that
6 because it doesn't really make any difference. I just
7 want to illustrate this for the sake of making the
8 point.

9 This is a trial, a six-month trial, with
10 a one-month run in of an oral agent used for the
11 treatment of type 2 diabetes, and it's a dose response
12 trial where patients are getting increasing doses of
13 the drug versus a placebo, and the placebo is shown
14 here by the little circles on top, and then you have
15 the very lowest dose of the drug, the intermediate
16 dose and two high doses of the drug.

17 And, if you say, well, what is the effect
18 of this drug, was this effective, how would you
19 evaluate that, well, if you look at six months you can
20 see that the patients on placebo had a glucose of 260,
21 that was pretty much the same at low dose, but in the
22 intermediate dose it was around 220 and at the high
23 doses you were around 200. So, clearly, this drug was
24 effective in lowering fasting blood sugar versus
25 placebo, a difference of about 200, a difference of

1 about 60 milligrams percent, and these were all
2 statistically significant down here.

3 So, you could say that this really was an
4 effective treatment, but I think if you look at this
5 curve you have some problems with this, and that the
6 problem is that although the patients were lower than
7 placebo, here is placebo at 260 and the patients on
8 the drug were around 200, the patients that received
9 the drug and had a glucose of 200 at the end of six
10 months, that blood sugar of 200 is exactly the same as
11 it was at the beginning. So, in fact, the drug did
12 not actually lower the blood sugar in these levels, it
13 just -- in these patients, it just prevented the rise
14 in blood sugar that occurred with the placebo.

15 Now, some might say that -- now, the
16 question is, well, why did the blood sugar go up in
17 the placebo patients, and I think one might look at
18 this and say, well, this is the natural history of
19 diabetes. In this particular incidence, this was the
20 natural history of diabetes, and I have a very ready
21 explanation for this, and I will go into that in a few
22 minutes. But, let's just assume, just even for the
23 sake of discussion, that there is, this rise with the
24 placebo patients is, indeed, the natural history of
25 diabetes. To me, it still does not follow, even if

1 you accept that, that this should be the basis for
2 approvability of an agent like this, and I'll just
3 give you the reason why I think that.

4 Let's say, you know, we all treat
5 patients, I did treat patients, I don't anymore, but
6 let's say that a patient came to your office and the
7 patient's blood sugar is 200, and you decide to treat
8 this patient with this drug, and you give her to drug
9 and she comes back three months later and she's very
10 upset, and she says, well, you know, you gave me that
11 drug, it's very expensive and it isn't working.

12 And, you say, well, why isn't it working,
13 how do you know that?

14 And, she says, well, you know, three
15 months ago my blood sugar was 200, and now it's still
16 200, so the drug isn't working.

17 Now, what then are you supposed to say?
18 You are supposed to say, well, it is working perfectly
19 well. Had I given you a placebo your blood sugar
20 would have been 260. I mean, that would be the kind
21 of medicine that this kind of argument would require
22 that physicians practice, and I think very few
23 patients would actually accept that kind of
24 explanation, nor should they, because all of the drugs
25 that we have on the market today actually do lower the

1 blood sugar, not versus placebo, but actually do lower
2 the blood sugar in any individual patient.

3 And, what I think we are being asked by
4 industry to consider is to abandon that standard, and
5 to say that new drugs that are approved for the
6 treatment of diabetes do not have to actually lower
7 the blood sugar, and it seems to me that this type of
8 argument, although it has some theoretic validity,
9 perhaps, in practice, really would lead to
10 consequences that are very, very undesirable.

11 Now, let me expand a little bit on the
12 natural history of diabetes. Many people, I think,
13 will recognize this slide, this is from the UGDP
14 study, this is data which is now almost 30 years old,
15 it's actually hard to believe, but I remember when
16 this was first presented, which was almost 30 years
17 ago, actually. And, of course, the UGDP study is most
18 known for the demonstrating or, perhaps, demonstrating
19 the effects of tolbutamide on cardiovascular
20 mortality. But, it actually, I think, taught us quite
21 a lot about the drug treatment of type 2 diabetes and
22 how drugs should be evaluated.

23 Just to review, for people who might not
24 be familiar with it, this was a study in patients with
25 type 2 diabetes. There was a group that received a

1 placebo. There was a group that received tolbutamide,
2 which is shown here, given 500 milligrams three times
3 a time without any dose increase, and then there were
4 two insulin groups, one that received a variable
5 amount of insulin and one that received the standard
6 fixed amount of insulin.

7 And, the insulin issue here is -- the
8 insulin data is not what I want to show, it's really
9 the -- what I want to point out is something about
10 tolbutamide. And, there are several characteristics,
11 I think, that are quite important here. The first is,
12 and you will note, I should say that each one of these
13 numbers here represents a quarterly visit, so four is
14 one year, eight is two years and so on, and we had
15 data up until four and a half years, and you will note
16 that, really, all the patients did quite well during
17 the first year of the trial, the tolbutamide patients,
18 as well as the placebo patients. The placebo patients
19 went from a glucose -- this is now a postprandial
20 glucose -- the placebo patients went from around 250
21 and by six months they were down to around 200, and
22 that improvement actually continued throughout the
23 duration of the study.

24 Well, what about the natural history of
25 diabetes? I thought that diabetes always got worse,

1 and the blood sugar is always rising. This is really
2 not what happened here, and the reason that it didn't
3 happen in this early trial was that patients were
4 really given a regimentation in terms of diet and
5 exercise, and I think this was, perhaps, a surprise to
6 people, but by virtue of participating in a trial like
7 this the patients improved their diet, lost weight and
8 the consequence, their glycemic control improved even
9 though they were taking the placebo.

10 Now, I would say to you, today in the
11 studies I'm going to be showing you, we really don't
12 see this effect anymore. The baseline glucose is
13 really quite constant in most of the trials that we
14 have already seen, which I will show you some of them.
15 And, the reason for this is now nowadays we recognize
16 that drugs should be added to a good regimen of diet
17 and exercise, not substituted for, but added to a good
18 regimen, and that most trials have a run-in period
19 where patients are actually instructed about diet and
20 exercise and then the drugs are added to that based on
21 patients who have already received this instruction.
22 So, this change that occurred, dramatic change that
23 occurred in the UGDP patients we really don't see this
24 very much anymore.

25 But, let's look at it from the other point

1 of view. I think the point here is that dietary
2 management is really very important, in addition to
3 drug management. Let's say that a trial were done in
4 which, instead of being regimented about the
5 importance of diet, perhaps, the patients would get
6 the opposite message. Patients enter a trial, they
7 are given a tablet, and they say, well, you tried
8 diets, the diet didn't really work for you, here's a
9 tablet, this will take care of your diabetes and
10 that's that.

11 Well, what would be the result, what would
12 be the result of this trial? Patients would actually,
13 it seems to me, be getting the message that they could
14 relax their diet and exercise regimen, and as a result
15 of that it would seem to me that probably the placebo
16 level cases would actually get worse, instead of
17 getting better they would get worse. You would see a
18 rise in the baseline.

19 Well, is that the natural history of
20 diabetes or not? Well, I don't really think it is.
21 I think this would be something which would kind of be
22 an artificial aspect, really an artifact of the way
23 the trial is done, and that's why in contrast, if you
24 look at this data, which is a lot more recent than the
25 UGDP data, this rise in baseline in the placebo is

1 really very suspicious. And, as an FDA officer
2 looking at this data, my reaction is, why is that?
3 What was going on there?

4 If the patients were having a relaxation
5 of their dietary management, this is really not a
6 valid trial, because it was done under conditions of
7 poor medical management, which is not the way we want
8 diabetes, type 2 diabetes to be treated. So, this
9 idea that we should just kind of subtract this rise in
10 baseline that occurs with the placebo I think is
11 potentially very hazardous.

12 Let me just illustrate two other points
13 here. The first is the way we calculate a treatment
14 effect would be the effect on drug, in this case a
15 tolbutamide minus the effect that was observed with
16 placebo, which would be around here, so this would be
17 the magnitude of the treatment effect.

18 Now, the effect that the patient realizes
19 is this entire thing, it's the treatment effect here,
20 plus the placebo effect, so that would be quite large.

21 In contrast to here, where the treatment
22 effect would be this magnitude, what was seen on drug
23 minus what was seen on placebo, but the patients would
24 actually see nothing because they subtract. So,
25 treating the patient here, the patient wouldn't

1 observe anything, very different from the historical
2 data with UGDP.

3 I would also point out, with respect to
4 durability, that the effects with tolbutamide really
5 lasted for about four years, so this was a fixed dose
6 of tolbutamide, they were not titrated, so this was
7 really a fairly durable response. And, I haven't
8 mentioned this, but one of the other areas of
9 contention was how long these trials should be, and
10 the draft guidance says that we would like an effect
11 to be durable for 12 months. Considering that type 2
12 diabetes is a life-long illness, that does not seem to
13 me to be extraordinarily unreasonable, particularly,
14 since we have data here with fixed dose tolbutamide
15 and, of course, we have a lot more potent drugs now,
16 but even looking at that, this effect really was
17 durable for at least four years.

18 Now, I'd just like to give some other
19 examples. I said all drugs that we have available
20 actually do lower the blood sugar, and I'm going to
21 prove that to you, if it should require proof. This
22 is data from the British study, the U.K. study that
23 has been going on for many years and was just
24 published in Adults last month, what we have here is
25 the fasting plasma glucose, and the hemoglobin A_{1c},

1 and I hope everyone can all see that, these curves
2 represent metformin, insulin and sulfonylureas, and if
3 you look at fasting plasma glucose insulin was more
4 effective than either of the two oral agents, whereas,
5 if you look at hemoglobin A_{1c} they were all roughly
6 the same. This is actually identical to the data in
7 the UGDP study. I didn't show the fasting glucose
8 levels, but actually insulin was the most effective
9 there as well. So, this is totally consistent with
10 what was observed 30 years ago.

11 But, the point I want to make is that the
12 drugs were all very effective, hemoglobin,
13 Glycohemoglobin going from 11 down to around seven,
14 and that this effect was quite durable. It lasted for
15 the six years of the study. So, again, to say that a
16 new agent should show a durable effect for 12 months,
17 I think is really not an unreasonable requirement.

18 Well, I've shown metformin and
19 sulfonylureas, and here is acarbose, and here's
20 acarbose tested against diet and acarbose tested --
21 well, sorry, these are patients who are on diet and
22 acarbose was tested against placebo. Here is patients
23 who are already on sulfonylureas and, again, acarbose
24 was tested against placebo. All these patients were
25 on high dose sulfonylurea.

1 And, the point here is, again, that there
2 is a little variation in the baseline, but this is not
3 an enormous change over the period of one year, either
4 in the diet alone patients or in the patients who were
5 on maximum dose sulfonylurea, and the drug was quite
6 effective. It lowered Glycohemoglobin in both
7 settings, roughly around .9 percent, and the effect
8 was also durable, and we can see that the effect at
9 the end of 12 months is really the same as it was at
10 the end of six months.

11 Well, I've shown metformin, and
12 sulfonylureas and acarbose, that leaves only
13 troglitazone, and this is data for troglitazone, which
14 you will recognize is the data that I showed at the
15 beginning.

16 Again, this was a placebo-controlled trial
17 at various doses of troglitazone, 100 milligrams, 200
18 milligrams, 400 and 600. And, we can see that the 600
19 milligram and 400 milligram dose were quite effective
20 versus the placebo patients. But, again, if we
21 actually ask the question, did the drug really lower
22 the blood glucose in these patients, the answer really
23 would have to be no. The only way to demonstrate this
24 effect was versus placebo, rather than versus the
25 individual patients' starting values.

1 Now, the question is, well, really why is
2 this? This is really very surprising data, and I
3 remember when I saw this I really couldn't quite
4 understand it, because I knew that troglitazone was
5 really extremely effective, say, in patients who were
6 on sulfonylureas as well as in patients who are in
7 insulin, that was data this committee had already
8 seen, so this was really very surprising.

9 But, we do have a ready explanation for
10 this, and I'm now going to show it. The explanation,
11 really, is based on what the patients had been taking
12 before they entered the study. Here we have patients
13 who were taking -- who were on diet alone before
14 entering the study, they were not on other oral
15 hypoglycemic agents, and the effect of troglitazone
16 here is really not very obvious. Placebo are the
17 small circles, and they started with a Glycohemoglobin
18 of around 8.5 and ended around 8.5, the 100 milligram
19 dose, you know, a total straight line is not effective
20 at all. The dark circle here is actually 400
21 milligrams, then the 200 milligram is the triangle,
22 neither one of these were effective, and you really
23 don't see anything at all until you get down to 600
24 milligrams, and here there was a statistically
25 significant improvement, both from the -- no matter

1 how you calculate it, really, from the baseline or
2 from versus placebo.

3 But, I would point out, just in case
4 anyone missed it, this is 200 milligrams, but here is
5 400 milligrams, 400 milligrams was totally
6 indistinguishable from placebo, so you really only
7 first see an effect at 600 milligrams, and just
8 looking at this one would have to question whether
9 troglitazone had any real activity in this setting
10 altogether.

11 I seem to be missing my best slide. I'm
12 sorry, I apologize for that, I just got them out of
13 order.

14 This is the data with troglitazone in
15 patients who had been on sulfonylureas before entering
16 the trial, and their values were, roughly,
17 Glycohemoglobin of around 8 to 8.5, and then there was
18 a one month run-in period, and then the patients were
19 randomized either to placebo or varying doses of
20 troglitazone.

21 If we look over here, we can see that in
22 this setting troglitazone was active in monotherapy.
23 The 400 and 600 milligram, and even, actually, the 200
24 milligram, were both significantly less than the value
25 with the placebo here, placebo value, Glycohemoglobin

1 almost 11, and the high-dose troglitazones down to
2 around 9.5.

3 But, let's just look a little bit at the
4 time course here. Patients started out at a
5 Glycohemoglobin of about 8.5, and the patients who
6 were taken off drug, well, they were all taken off
7 their baseline therapy and put on these various other
8 treatments, the placebo patients, in other words
9 getting no active drug, they all got worse, they went
10 from a Glycohemoglobin of 8.5 up to about nearly 11
11 after six months. But, the patients on troglitazone
12 also got worse. Now, they got less worse than the
13 patients on placebo, but they got worse nonetheless.
14 And, even patients on the highest dose of troglitazone
15 ended up at a Glycohemoglobin of 9.6, and really did
16 not achieve the values that they had at the beginning.
17 So, what good is this data? How is one going to use
18 this data?

19 It seemed to me that it really provided no
20 information at all about the approvability of
21 troglitazone for monotherapy. The only thing it did
22 tell you was that if you have patients on sulfonylurea
23 you should not stop the sulfonylurea in favor of
24 starting them on monotherapy with troglitazone, and
25 that's really the only use we put this data to in the

1 label. But, otherwise, this data was really totally
2 discarded, with respect to the justification for
3 approval of troglitazones in monotherapy.

4 But, it also raises, I think, another
5 question, even, I think, a more serious question, and
6 that is, what are the ethical implications of doing
7 this? How can one justify taking patients who are on
8 standard therapy, having hemoglobin A_{1c} of about 8.5,
9 taking them off of the standard therapy, giving them
10 a placebo, and then watching their Glycohemoglobin
11 going up to 11? I don't see how one can justify doing
12 this in today's age.

13 Now, this study was done years ago, and we
14 don't have to go through that history, but I think in
15 the present guidance I really would very much like to
16 say that we should not tolerate this, and this kind of
17 study is just not ethical, and if presented to us we
18 should just not agree to allow to have it to be done.

19 Again, I apologize if I'm saying the
20 obvious, but we do have these issues coming up all the
21 time, and I would hope that the committee members
22 would be willing to go on record to say that this type
23 of trial really should not be done.

24 Having said that, though, I think it
25 raises a question. Let us say that the guidance says

1 that we will not accept studies in which patients are
2 on active treatment and they are taken off active
3 treatment in order to be put on a placebo-controlled
4 trial. How are we actually going to enforce that?
5 How would we know, and I think it's quite clear here
6 that it's a lot easier to demonstrate the activity of
7 a drug in patients in whom the natural history of
8 diabetes has been artificially accelerated, than to
9 take patients in their normal state and demonstrate
10 that activity.

11 And so, there's kind of a -- oh, how
12 should we say, there would be, I think, an incentive
13 for physicians to, perhaps, take patients off of
14 standard treatment, refer them to investigators, and
15 then have the investigators then randomize these
16 patients in trials like this, recognizing that those
17 patients would actually be very good subjects to
18 demonstrate the effect of a drug that might not be
19 easy to demonstrate otherwise. How could we prevent
20 that? How would we know about it?

21 Well, I think the way we can prevent it is
22 to stick hard to the criteria that a new drug actually
23 does have to lower the blood sugar, and that it has to
24 do more than just be active against the placebo,
25 because if a patient were taken off of a sulfonylurea

1 and then referred to a new investigator, and the
2 investigator randomized the subject, and the subject
3 got a placebo, that patient's glycemc control would
4 decay over a period of time, and we would know that,
5 but we would say, well, that's all right, but we will
6 not accept that as a basis of approval. You actually
7 have to show that the new drug really does lower the
8 blood sugar, and that it's not adequate just to say
9 that it's active against the placebo. And, that's
10 really the reason why I feel strongly that we should
11 maintain the historic standard that diabetic drugs
12 really do lower the blood sugar.

13 Mr. Chairman, you've asked if there was a
14 time to pause for questions. I think this might be a
15 reasonable time.

16 CHAIRMAN BONE: I am sure there will be a
17 spirited discussion about this point. I would only
18 ask that the committee members, at this point, ask
19 questions related to clarification of, not concepts,
20 but, I mean, information that Doctor Misbin has
21 presented, because I know that we're going to be
22 spending a lot of time discussing this very
23 interesting perspective.

24 Okay, go ahead, Doctor Cara. Doctor Cara,
25 could you sit at the table, please, and use the

1 microphone?

2 DOCTOR CARA: In your proposal, now these
3 were patients that were already on treatment, the
4 examples that you gave.

5 DOCTOR MISBIN: Shall I put the slide up?

6 DOCTOR CARA: No, no, it's not necessary.

7 The examples that you gave included
8 patients that were already on treatment. Do your
9 recommendations also apply for patients that are newly
10 diagnosed?

11 DOCTOR MISBIN: I'm sorry, what
12 recommendations do you mean?

13 DOCTOR CARA: This whole issue of
14 comparing active drug to placebo, placebo being no
15 treatment, and the whole ethical issues around that,
16 what is your stance in terms of newly diagnosed
17 patients?

18 DOCTOR MISBIN: The draft does not make
19 that distinction.

20 CHAIRMAN BONE: Doctor Sherwin?

21 DOCTOR SHERWIN: Do we know about the
22 treatment of these patients prior then to the trial,
23 and is the criteria then that it has to be better than
24 their existing treatment? In other words, the big
25 problem with the data you showed us relates to the

1 fact that according to the criteria then we would have
2 to have a drug superior to whatever the existing
3 treatment was prior.

4 DOCTOR MISBIN: Well --

5 DOCTOR SHERWIN: And, that gets into a lot
6 of deep trouble.

7 DOCTOR MISBIN: -- I don't think that
8 would be required. I think that -- well, I think
9 there are two kinds of trials. If one had a placebo-
10 controlled trial in previously untreated patients, as
11 Doctor Cara was saying, then it would just be -- there
12 wouldn't be any comparison, we would just look at the
13 absolute change versus placebo, as well as the change
14 from baseline.

15 If one were dealing with patients who were
16 on previous treatment, such as these patients, I think
17 it would be quite reasonable testing a new agent,
18 troglitazone or any other, that instead of using a
19 placebo here to actually continue the sulfonylurea.
20 You would have another arm that would go this way.

21 Now, we would then not require that the
22 new drug meet the same, be as effective, necessarily,
23 as the old drug, although I think that would not -- we
24 get into this in the examples -- that I do not think
25 would be a requirement. There may be other things,

1 for instance, if you took patients starting here,
2 Glycohemoglobin of 8.5, not adequately controlled on
3 glyburide, a reasonable trial would be to use two
4 doses of glyburide, say, 10 and 20 milligrams, versus
5 these doses of troglitazone, and then you would
6 compare at the end both the effect on Glycohemoglobin
7 as well as hypoglycemia.

8 Now, if you push glyburide, you probably
9 will have a very good effect, but you'll also have a
10 lot of hypoglycemia, which you wouldn't have, say, if
11 you did this with a troglitazone, a metformin or
12 whatever. And so, at the end of the study we would be
13 looking at both the improvement in Glycohemoglobin, as
14 well as differences in hypoglycemia. And, a new agent
15 would be approvable, really, based on a composite of
16 those endpoints.

17 DOCTOR SHERWIN: So, if they were
18 equivalent, in effect, the two drugs, the new drug
19 would be approved, is that right?

20 DOCTOR MISBIN: If it was equivalent, but
21 it doesn't even have to be equivalent. I could easily
22 see a situation where the change in Glycohemoglobin
23 was less with the new drug, but the side effect
24 profile was better, and that would be approvable.

25 DOCTOR SHERWIN: But, the hard part is

1 going to be trying to figure out what the diff --
2 well, for example, let's say you have a certain effect
3 of a sulfonyleurea, how much worse will a drug have to
4 be than the sulfonyleurea to get approved, and then you
5 have -- I mean, in other words, we are going around --
6 it's going to be extremely difficult to know how much
7 worse an effective drug would have to be to be
8 approved. And, that's, I think, the dilemma that we
9 are going to face.

10 DOCTOR MISBIN: Well, I think it would
11 still -- I think, again, here we are talking about the
12 last phase, the final pivotal study, say, we would
13 have earlier data, say, against a placebo in short-
14 term trials, or in milder patients, and we would have
15 demonstrated -- I mean, this is a hypothetical
16 example, obviously, it's better if you actually have
17 something in front of you, but we could have had data
18 demonstrating efficacy and reduction in baseline, say,
19 over 12 weeks with hemoglobin A_{1c}, and then let's say
20 a reduction of one percent. Let's say that the same
21 thing then is done in a large 12-month trial versus
22 glyburide, and you still get a reduction with that new
23 drug of one percent, well, that's an active drug.
24 That definitely is active in that setting.

25 Now, glyburide on that setting might get

1 you down to 1.5, so the new drug is not as good as
2 glyburide, but still is an active drug, and I would
3 say we should still be able to approve that drug.

4 DOCTOR SHERWIN: With who are you --

5 CHAIRMAN BONE: Excuse me -- Doctor
6 Davidson -- we have several questions. Doctor
7 Davidson?

8 DOCTOR DAVIDSON: Well, you know, if you
9 look at that study, and based on your recommendations,
10 that study will have been terminated in about six
11 weeks, because there's a significant increase from
12 baseline, you know, and if we see a deterioration, you
13 know, of the hemoglobin and the glucose levels, that
14 patient should be placed on active drug.

15 DOCTOR MISBIN: Absolutely.

16 DOCTOR DAVIDSON: Which I think is fair,
17 you know, based on the deterioration of the patients.

18 And, I want to make a couple of points to
19 illustrate your message. If you look at the study
20 that you show us on troglitazone, you know, naive
21 patients, okay, it looks like these patients were
22 previously treated because there is a deterioration,
23 you know, from minus one to one. No, in the blood
24 sugars, that's A_{1c}. If you look at the blood sugars
25 of minus one to one, you know, the average increase is

1 about 40 to 50 milligrams per deciliter. You know,
2 very rarely we will see in 30 days such a
3 deterioration, which means that you are right, some of
4 these patients probably were referred to the
5 investigator, you know, and they were still, you know,
6 on the original drug. They appear to be naive, but
7 they deteriorate, and that's a very important point.

8 And, the final point I want to make is
9 that, in spite that in 12 months in some of the
10 studies there's not a significant increase in the
11 glucose levels, you know, I think the first study to
12 show that there is a natural history of the
13 progression of hypoglycemia in diabetes is the UGDP,
14 because after 12 months, even though they don't go
15 back to placebo, there is a significant increase in
16 glucose levels and that has been demonstrated in all
17 the studies including the UKPDS.

18 CHAIRMAN BONE: Doctor Misbin, I have just
19 one or two points of clarification, then Doctor Cara
20 has a question.

21 Do I understand you to say that you would
22 only evaluate monotherapy in previously untreated
23 patients?

24 DOCTOR MISBIN: No, I didn't say that.

25 CHAIRMAN BONE: Well then, I'm having

1 trouble putting all of these items together.

2 If you are going to evaluate monotherapy
3 in a previously treated patient, you will have to
4 withdraw that patient from treatment with the prior
5 agent.

6 DOCTOR MISBIN: Yes.

7 CHAIRMAN BONE: At which point,
8 presumably, the blood sugar and glycosylated
9 hemoglobin levels will rise.

10 DOCTOR MISBIN: Well, no, not if the agent
11 is active. What I'm proposing --

12 CHAIRMAN BONE: No, no, no, no, no, are
13 you talking about not having a wash-out period?

14 DOCTOR MISBIN: -- well, why is that so
15 unreasonable?

16 CHAIRMAN BONE: Well, it's a pretty
17 substantial confounder.

18 DOCTOR MISBIN: Well, I don't know, 12
19 month of a trial is enough to wash out pretty much
20 drug.

21 CHAIRMAN BONE: So, you are saying that
22 the patients -- I'm asking you explicitly, are you
23 saying that that's what you are expecting to require
24 people to do?

25 DOCTOR MISBIN: No, no, I'm saying that

1 that is a possibility.

2 CHAIRMAN BONE: Well, there are only two
3 possibilities, either you wash them out or you don't.

4 DOCTOR MISBIN: Oh, let's rephrase the
5 question. I'm not saying that one necessarily has to
6 do one way or another, what I'm --

7 CHAIRMAN BONE: Well, there are two
8 possibilities, if you wash the patients out, which
9 would be the way we'd always do drug trials, is to
10 stop the drug that we are not testing, then the blood
11 sugar presumably will rise substantially throughout
12 the wash-out period, which looks like three to four
13 months here, which is quite a bit longer than we
14 usually use, all right, at which point the blood
15 sugars will all have gone up and the glycosylated
16 hemoglobin levels will have gone up. So, in that
17 case, do you then propose that in order to be
18 efficacious the drug would not only have to be more
19 effective than placebo in lowering the blood sugar,
20 but it would actually have to take the patient back to
21 below their pre-wash-out baseline?

22 DOCTOR MISBIN: Okay, I misunderstood what
23 you meant by the wash -- I was confusing wash-out and
24 run-in.

25 CHAIRMAN BONE: Well, it's the same thing,

1 usually.

2 DOCTOR MISBIN: Well, a run-in could be a
3 patient who was not treated otherwise, I mean, that
4 would be a --

5 CHAIRMAN BONE: But, we are not talking
6 about that. We are talking about patients who are
7 being withdrawn from therapy.

8 DOCTOR MISBIN: Yes, let's just talk about
9 the same thing, and I was confused by your question,
10 I apologize.

11 CHAIRMAN BONE: All right.

12 DOCTOR MISBIN: What I'm saying is this,
13 if one looked at trial of this nature, I would say
14 that it is far preferable to continuing to, even
15 without a wash, and I'm not sure why a wash-out is
16 actually necessary, if the patient is on sulfonylureas
17 one could just continue this dose of sulfonylureas and
18 in the experimental group just switch them directly to
19 the experimental drug.

20 CHAIRMAN BONE: Well, is that your
21 guidance recommendation, to not have a wash-out period
22 in that, or a run-in period?

23 DOCTOR MISBIN: The recommendation doesn't
24 specifically say that, though I think --

25 CHAIRMAN BONE: Well, okay, but let's talk

1 about, there are two possibilities, okay, one is that
2 you do and the other is that you don't.

3 DOCTOR MISBIN: Yes, in the --

4 CHAIRMAN BONE: All right. Let's talk
5 about first that you have the standard wash-out/run-in
6 period, where the patient is given a sufficiently long
7 period off the prior treatment that you are satisfied
8 that drug is no longer affecting, which looks like
9 three or four months in the example you give here.

10 DOCTOR MISBIN: Right, I'm proposing that
11 the way you are presenting it, that we do not do that.

12 CHAIRMAN BONE: Okay. So, at least we now
13 clearly --

14 DOCTOR MISBIN: The reason I'm saying that
15 is that I have a tremendous ethical issue of taking
16 patients who are on active drug and stopping that for
17 the purposes of including them in a placebo-controlled
18 group.

19 CHAIRMAN BONE: Well, okay, then I
20 understand your point, but I want you to be clear
21 about it. Okay. So, you are saying that the proposed
22 guidance document from the FDA would say that we
23 would, to evaluate monotherapy we would not withdraw
24 a patient from prior treatment for a period of time to
25 establish a new baseline.

1 DOCTOR MISBIN: Yes, in a --

2 CHAIRMAN BONE: That's what you are
3 saying.

4 DOCTOR MISBIN: -- trial of that design.
5 There are other potential designs, but in that design
6 that would be what we'd say.

7 CHAIRMAN BONE: You would say that that's
8 the -- so, then that's the position of the Division at
9 this moment.

10 DOCTOR MISBIN: That's correct.

11 CHAIRMAN BONE: Okay.

12 DOCTOR MISBIN: Unless Doctor Sobel --

13 CHAIRMAN BONE: Who was unfortunately not
14 able to be here. I want to be clear. Okay.

15 So then, let me just pursue this for a
16 second, I want to be clear, because I think this is
17 really crucial to the whole question. It's a
18 different question altogether if we are talking about
19 adding the therapy. So, you are suggesting that the
20 only acceptable trial design under the guidance
21 document would be, for evaluation of monotherapy in
22 previously treated patients, would be that one arm of
23 the study would continue their prior treatment, or one
24 or more arms of the study would continue their prior
25 treatment, and the experimental arm, if you will, of

1 the study would be switched directly from prior
2 treatment one day to their new treatment the next day,
3 and then you would evaluate the effect on blood sugar
4 over the ensuing year, and primarily on glycosylated
5 hemoglobin, and that that's the only acceptable way to
6 do this, as far as you are concerned.

7 DOCTOR MISBIN: Okay, I'm not happy with
8 saying it's the only acceptable way, because somebody
9 may come up with some other way that I haven't thought
10 of.

11 CHAIRMAN BONE: Well --

12 DOCTOR MISBIN: But, the way you have said
13 it is an acceptable way, what is not an acceptable way
14 is to take the patients off of the prior drug.

15 Now, somebody may have some other design
16 neither one of us have thought of.

17 CHAIRMAN BONE: Okay, but those are you
18 either have a wash-out or you don't.

19 DOCTOR MISBIN: Yes.

20 CHAIRMAN BONE: So, you are saying you
21 would forbid the wash-out period for previously
22 treated patients.

23 DOCTOR MISBIN: Yes, that's what I'm
24 saying.

25 CHAIRMAN BONE: Okay. I just want you to

1 be clear about it. I'm not arguing about it, I just
2 want you to be absolutely clear about what we are
3 talking about here.

4 And, do you think there would be any kind
5 of founding effects during the first few months on
6 treatment, in terms of being able to analyze what's
7 happening?

8 DOCTOR MISBIN: Well, that will depend on
9 the nature of the drugs. Each drugs are going to be
10 different, but, again, I just want to stress that we
11 are talking about the last, the phase III trial of a
12 year's data, so what happens during the first weeks is
13 not really going to be relevant to what happens at the
14 end.

15 We will already, before doing this trial,
16 have a lot of data on this drug based on earlier
17 studies.

18 CHAIRMAN BONE: That does bring up a point
19 that the document in its current draft form doesn't
20 actually discuss the separate phases of phase I, phase
21 II and phase III of developing, or indicate what the
22 appropriate trial designs, or acceptable trial
23 designs, might be at different phases of development,
24 and I suspect that that would be enormously clarifying
25 when it's developed further to discuss those points.

1 DOCTOR MISBIN: Well, actually, in the
2 example that's given, there is a discussion of earlier
3 trials versus later trials.

4 CHAIRMAN BONE: Yes, I think, though, that
5 what we are talking about here would be helpful to
6 have clarified as far as what phase we are in, because
7 I do think what you are saying then is, if I
8 understand correctly, that you would accept withdrawal
9 of the patients in phase II for smaller-scale studies,
10 do I understand that correctly, that a wash-out period
11 would be acceptable for a phase II study but would not
12 be acceptable for a phase III study?

13 DOCTOR MISBIN: It would -- I don't think
14 we addressed that issue specifically in the guidance.

15 CHAIRMAN BONE: Well, clearly not, I mean,
16 there's no real discussion of the difference between
17 phase II and phase III, so is there an opinion on
18 this, whether a wash-out period using stabilized
19 patients off treatment for monotherapy, would be
20 acceptable?

21 DOCTOR MISBIN: Well, I would like the
22 input from this committee about that. I mean, I
23 personally would not have difficulty with taking
24 patients off of an active drug for a week, I mean,
25 that --

1 CHAIRMAN BONE: But, you've demonstrated
2 they have to go off for three or four months.

3 DOCTOR MISBIN: Yes, well, that's why I'm
4 asking input. I mean, you are asking me a question I
5 can't answer off the top of my head.

6 CHAIRMAN BONE: Okay.

7 DOCTOR MISBIN: I mean, we would need, I
8 think, input from the group, but I think what I do not
9 want to see happen is patients coming off active
10 therapy and being off for a long period of time.

11 CHAIRMAN BONE: And, you would have no
12 placebo group then, as you describe it, in a phase III
13 trial of monotherapy.

14 DOCTOR MISBIN: In this type of design.

15 CHAIRMAN BONE: Well, I mean, that's the
16 only type of design you are saying you are going to
17 permit.

18 DOCTOR MISBIN: No, I didn't say that. We
19 can still have placebo-controlled trials in patients
20 who have not been on previous therapy. I mean, we do
21 actually generally require two different trials.

22 CHAIRMAN BONE: Right, okay.

23 I think Doctor Molitch and then Doctor
24 Cara, and I'm sure other people have questions. I'm
25 sorry I took so many questions, but it was a little

1 hard to get -- apparently, I had to clarify what I was
2 asking.

3 Doctor Molitch?

4 DOCTOR MOLITCH: Just in sticking with
5 this particular design, it would seem that if you do
6 not have a placebo control at that last step you would
7 have no way of knowing whatsoever whether the active
8 drug was active at all, since you would have no
9 comparator to placebo.

10 If glyburide, which was the initial drug,
11 for example, they stayed flat, and then you had a rise
12 of troglitazone, is clearly less than with placebo, as
13 you have shown here, then you would have no way of
14 knowing whether that has an effect with any kind of
15 placebo control.

16 DOCTOR MISBIN: In this setting, that's
17 true. Now, we would have, and that's, I think, a very
18 reasonable question, I would just answer it by saying
19 that -- I would answer it in several ways. First,
20 again, I'm stressing repeatedly, that we are talking
21 about the last trial, and which we had many other
22 trials, so before one even gets to that point we would
23 have demonstrated that the new drug was active against
24 placebo in shorter trials.

25 Secondly, we do know that glyburide is an

1 active drug, and that trial design that you are
2 mentioning clearly has faults, but this actually was,
3 for instance, what the committee saw in the
4 repaglinide study, were those comparators. So, I
5 think there is -- this is not breaking new ground, and
6 you've already seen that kind of study.

7 And, it is, your point is well taken, I
8 mean, there is a tradeoff by saying that you are not
9 going to have a placebo but just assuming that a
10 baseline continuation of the glyburide is going to be
11 adequate and that it still is doing something. That
12 certainly is an assumption, but I think it's far
13 better to make that assumption than to actually take
14 patients off of the glyburide and demonstrate that you
15 can get the hemoglobin up to 11. That clearly is, I
16 think, an unethical alternative.

17 If I could just -- I do have a lot of
18 other things to say.

19 CHAIRMAN BONE: Doctor Cara has -- just a
20 moment, Doctor Cara has another question.

21 DOCTOR CARA: I mean, along the same lines
22 as Doctor Molitch's question, it seems to me, if I'm
23 understanding you correctly, is that you are proposing
24 only comparator studies for the evaluation of drugs
25 for diabetes.

1 DOCTOR MISBIN: No, I didn't say that.

2 DOCTOR CARA: Well, can you envision a
3 study that, in fact, will involve a placebo?

4 DOCTOR MISBIN: Yes.

5 DOCTOR CARA: Which one?

6 DOCTOR MISBIN: I would have no problem
7 with taking patients, previously untreated patients,
8 whose Glycohemoglobin, say, was eight when they are
9 coming in to the trial, and doing placebo-controlled
10 trials using those patients.

11 DOCTOR CARA: When I asked you previously,
12 though, you had said that even for newly diagnosed
13 patients you would not accept a placebo arm.

14 DOCTOR MISBIN: I would not have accepted
15 a placebo arm if the patients had a Glycohemoglobin,
16 say, of ten. I mean, I can't see how we could take
17 patients like that and commit them to a long-term
18 placebo.

19 Now, there might be a way of doing it with
20 an early dropout. I mean, you might say after two
21 weeks, or a month, or we would need really input from
22 this committee as to what would be reasonable, but I'm
23 really unwilling to say that we should have patients
24 admitted to a trial starting with a Glycohemoglobin of
25 ten, or nine, whatever, which is the average we see,

1 and letting them go untreated for a period of a year.
2 Again, I don't think that that's an acceptable design.

3 If the Glycohemoglobin coming into the
4 trial is eight, then I see no difficulty, then there
5 would be no problem there using a placebo-controlled
6 trial.

7 And, I would say that for most new agents
8 we would want really data of both types.

9 CHAIRMAN BONE: Doctor Sherwin?

10 DOCTOR SHERWIN: You said that you would
11 accept short-term studies, phase II, if there is a
12 placebo-controlled trial, and that long term that
13 would be less acceptable. And, there are a lot of
14 ethical issues, it's a very tough problem, but one
15 problem is that a drug can work short term and not
16 long term, and this is one of the reasons why we want
17 to do long-term studies, and if a drug is less
18 effective than another drug long term, it's going to
19 be very hard for this committee to know whether it has
20 had a short-term effect and then not a long-term
21 effect.

22 So, it's going to be much harder for us to
23 assess long-term effects and make decisions as to
24 whether the treatment is really effective or not. So,
25 I think it makes the committee's decision very

1 difficult in comparative studies.

2 And, the other concern I would have about
3 the comparative studies is, you would also probably
4 have to randomize according to the specific drug, the
5 specific dosage, because, obviously, if you had -- you
6 have a lot of confounders with treatment if you have
7 your placebo group has four people on glyburide, 15
8 milligrams, and you could end up with one group of
9 drugs, but many different doses, many different drugs,
10 and it could get very difficult.

11 DOCTOR MISBIN: Well, this has, actually,
12 been done before. I mean, there are many trials where,
13 say, combination with sulfonylurea, where patients
14 come in on various sulfonylureas, various doses, and
15 this has been -- with acarbose in several different
16 trials. Sometimes those sulfonylureas were just
17 continued, whatever they are, patients just continued
18 on baseline treatment. In other designs, they were
19 switched over to glyburide, in a roughly equivalent
20 way.

21 So, this can be done, but the problem of
22 stratifying different patients based on their previous
23 history is true of all trials. I mean, that's just
24 part of the heterogeneity of the disease.

25 CHAIRMAN BONE: Yes, but we usually take

1 the people off the drugs that they were on, so that
2 makes it -- that complexity persists, rather than
3 being removed.

4 Doctor Cara?

5 DOCTOR CARA: How would you then evaluate
6 a drug that is partially active, not as active as the
7 drug that you chose, say, as a comparator drug, but
8 still is active, but maybe not as active?

9 DOCTOR MISBIN: Well, that would be a
10 decision that would have to be made in consultation
11 with this committee, because a drug, and I do have
12 some other points which are relevant to this that I
13 would like to present, in fact, one is coming up right
14 now, which I think partially addresses your question,
15 because the issue comes up, if a drug has a minimal
16 activity versus a placebo, say, a Glycohemoglobin of
17 .3 reduction, something like that, over a period of
18 time, say, let's say a year, and it's put up against
19 various comparators and really is not as good as any
20 of those comparators, the question that would have to
21 be answered, and I think this committee would have to
22 answer it, is why should we go ahead and approve that
23 drug if it's not as good as anything that's on the
24 market, and we haven't even discussed safety issues.
25 But, I think that would be something that this

1 committee would have to debate.

2 It's not clear to me that the criteria for
3 approval should be so low that we allow virtually
4 anything on the market, even though it may not be very
5 useful, but that's something which I think this
6 committee would have to discuss.

7 CHAIRMAN BONE: Yes. Well, I think
8 writing a guidance document, though, we are not -- I
9 don't think in your guidance document, when it does
10 reach its final form, you'd want to say that each
11 individual problem will have to be resolved by the
12 committee. I think you'd like to be able to give the
13 sponsors the sufficient guidance that they could, at
14 least in the early stages of a project, have an idea
15 of what they might be required to do.

16 I think I'd share Doctor Cara's question
17 about, and it goes back to something you said earlier
18 about a compound might be efficacious, perhaps,
19 somewhat less efficacious than the positive control
20 but, nevertheless, useful, sufficient to warrant
21 approval by the criteria that are discussed elsewhere
22 in here, and, nevertheless, as Doctor Sherwin has
23 pointed out, you might have a very hard time telling
24 whether it was having that effect or not because you
25 wouldn't have the placebo group against which you

1 would compare it. So, you wouldn't know how much
2 relative reduction of Glycohemoglobin was occurring
3 without that comparison.

4 I understand quite well your concern about
5 the problem of allowing patients' Glycohemoglobin
6 levels to rise, but as you can see there is certainly
7 -- it does leave a problem because of the precise
8 number that you are referring to, for example, a one
9 percent reduction of Glycohemoglobin would, under
10 those circumstances, I think be impossible to
11 calculate.

12 DOCTOR MISBIN: Well, again, I'm not
13 saying that we get right of placebo-controlled trials,
14 what I'm saying is, is that there's a place for them,
15 and I think the place really is in patients who do not
16 have severe hypoglycemia, and also in the setting of
17 trials of more limited duration.

18 CHAIRMAN BONE: Well, it's rather
19 challenging if we have an entry criterion that
20 Glycohemoglobin levels must not exceed eight, to have
21 a one percent reduction in Glycohemoglobin is the
22 threshold for efficacy. That's pretty challenging.

23 And, that brings up one other question I
24 had, and then we'll go on, I think, maybe unless there
25 are other questions from the committee, and I think

1 Doctor Fleming has a comment --

2 DOCTOR MISBIN: Can I ask you, why is that
3 so challenging? All the oral agents we have, acarbose
4 would be around .9, so --

5 CHAIRMAN BONE: Well, I mean, you said one
6 percent, and I just want to make sure that we
7 understand that without the placebo.

8 Let me just one second, are you talking
9 here, the other question that I know is one that
10 everybody in the room practically wants to know the
11 answer to, is that if your primary endpoint is the
12 reduction in Glycohemoglobin, are you talking about
13 having a percentage reduction or an absolute
14 reduction? In other words, is the reduction from a
15 starting Glycohemoglobin of 14 percent, should that be
16 the same reduction as one that starts at eight
17 percent?

18 DOCTOR MISBIN: The guidance does not
19 address that specifically, and that would be an area
20 where I think we would want to discuss that and get it
21 from the committee.

22 CHAIRMAN BONE: It does actually appear
23 to, so that was the question.

24 DOCTOR MISBIN: Well, I don't really think
25 so.

1 CHAIRMAN BONE: I think some people may
2 have had the impression that you used a fixed number
3 of .7 percent.

4 DOCTOR MISBIN: Well, I think if we would
5 take out the actual guidance and read it, it says that
6 in the past we have accepted, it just gives a
7 precedent, and the precedent really is acarbose, and
8 says that in a drug which we believe to be extremely
9 safe, but which is not very potent, that drug had a
10 kind of, in various studies, a minimal effect of .7,
11 and so this is what we have done in the past.

12 Now, I would also say that when acarbose
13 was first put up it was actually rejected, because the
14 feeling was that its efficacy was too low, so this is
15 kind of on a threshold.

16 CHAIRMAN BONE: So, the current draft
17 guidance doesn't actually address this issue at all?

18 DOCTOR MISBIN: The current draft guidance
19 says, in the past --

20 CHAIRMAN BONE: Yes, I know what it says.

21 DOCTOR MISBIN: -- yes, that's all that it
22 says.

23 CHAIRMAN BONE: But, it doesn't actually
24 make a specific recommendation.

25 DOCTOR MISBIN: That's correct.

1 CHAIRMAN BONE: I think we have Doctor
2 Hirsch, and then Doctor Fleming, and then Doctor
3 Davidson.

4 DOCTOR HIRSCH: We're just slipping into
5 getting clarification, but beginning to express some
6 opinions. There will be an opportunity later, won't
7 there, because I have a very strong opinion about it,
8 but I don't want to get into it now.

9 CHAIRMAN BONE: We're just trying to find
10 -- I think what we are trying to find out now is what
11 is being said, and then we are going to talk later
12 about what we think about it.

13 Okay, although, you are right, and the
14 Chair accepts responsibility for having fallen into
15 the trap against which we warned everyone else. Okay.

16 Doctor Fleming?

17 DOCTOR FLEMING: Just a general
18 clarification. This is, obviously, an extremely
19 useful discussion, and we are getting off into some
20 fairly complex issues, particularly, the idea of
21 comparative efficacy, and we'll need to address that
22 specifically later.

23 I do think it's important to understand,
24 or at least, number one, why we are here, and that's
25 mainly to get your input, and not so much to suggest

1 that we have a particular line that we are asking you
2 to adopt. And also, that this guideline, or draft
3 guidance, is one that has been under works for a
4 while, but I would not represent it as being an Agency
5 view, or a Division view.

6 I think the approach that Doctor Sobel and
7 I have taken in our involvement is to encourage Doctor
8 Misbin to proceed in the way he has, and to put down
9 on paper what seems to be at least a reasonable
10 starting point, but let us not ascribe this, or
11 ascribe a Division imprimatur to that.

12 CHAIRMAN BONE: Fair enough, that's what
13 I was trying to inquire about, and Doctor Davidson,
14 and then we'll go on with Doctor Misbin.

15 DOCTOR DAVIDSON: Well, you know, I think
16 the ethical issue is very important. I believe
17 strongly that the first thing that we need to do in a
18 trial is no harm, you know, and I believe strongly
19 that that should be part of this committee's
20 responsibility.

21 And, the second thing is that, you know,
22 in previous trials it is not the absolute A_{1c}
23 reduction per patient, but it is the average reduction
24 in the trial.

25 CHAIRMAN BONE: Okay, thank you.

1 Doctor Misbin.

2 DOCTOR MISBIN: Well, I just want to get
3 back, really, to kind of the exposition, really, of my
4 point.

5 I think Doctor Cara raised the question,
6 several people raised the question of durability, and
7 as I indicated previously all the drugs that are
8 presently available we have long-term data on. In the
9 controlled trials that led to that we have generally
10 12 months, and we have even data beyond that.

11 But, I think it's fair for you to say,
12 well, to challenge me to say, well, do I have -- are
13 there examples of drugs that appeared to be active
14 early in the development in the trial, but then later
15 turned out not to have persistent activity.

16 I'll just show you this example. Here we
17 have data from patients, again, patients with type 2
18 diabetes, and at 13 weeks -- and this is all expressed
19 as a change in hemoglobin A_{1c} from baseline, and at
20 the end of 13 weeks you can see in this particular
21 case that there was a fall, both in the placebo
22 patients and in the drug patients. The placebo
23 patients fell by .54, the drug by .94, so that would
24 be, say, a value of collected hemoglobin of nine down
25 to 8.5 or thereabouts.

1 Now, over the period of 13 weeks, given
2 the fact that Glycohemoglobin is a lagging indicator,
3 that this of itself is not really bad, and I think
4 looking at that you might say that, indeed, there may
5 be something here, and it was a highly significant
6 fall. And, the difference, the drug effect, the
7 treatment effect of the drug from placebo here is a
8 difference of .4.

9 If one goes on, say, to 26 weeks, then the
10 situation becomes a little bit unsettled. We see that
11 the placebo patients are beginning to revert back
12 toward baseline, it's not exactly clear, and the drug
13 patients also are beginning to revert back toward
14 baseline, but it's not terribly different from 13
15 weeks.

16 The treatment effect, the drug effect of
17 .42 now is the same as it was at 13 weeks, but because
18 of the variability in our individual response we are
19 really beginning to lose our statistical significance
20 in this trial.

21 But then, if we go to 52 weeks, I think
22 the pattern really is fairly clear, but the placebo
23 again is going back toward baseline, initially there
24 was a drop of .54 and now it's only .2. The drug is
25 going back toward baseline as well, initially it was

1 .94 and now it's only .47, and by 52 weeks there
2 really is no difference statistically between the
3 treatment and the placebo.

4 Now, had you just looked earlier, you
5 would have said that this looked like an active,
6 positive trial, even at 26 weeks it's kind of a
7 marginal call here. But, by requiring that we
8 actually go to 52 weeks, I think it would be clear,
9 really, this drug does not have a durable effect,
10 which we would not have known if we had only required
11 earlier trial.

12 So, again, I think that the requirement of
13 the 52 weeks of a controlled observation, I think is
14 something that we should maintain.

15 I would add that that requirement, I think
16 is particularly important with drugs that are not
17 very, very effective. If this were glyburide we'd see
18 a major, enormous effect in comparison to what we see
19 here, but since we are really talking about drugs
20 where the effect is really rather small, I think it's
21 quite clear that if you really don't wait long enough
22 that very small effect might actually disappear
23 altogether.

24 For comparison, though, we do have drugs
25 that are maybe not terribly potent, but which do have

1 durability, and I'll just show the data on miglitol.
2 Miglitol is similar to acarbose. It's actually
3 approved for use in the United States, but has never
4 been marketed here. But, the point I want to make is
5 that it's not an enormously effective drug. This is
6 a time course, here we have placebo, and here we have
7 miglitol, and at the end of the year it really only
8 reduced Glycohemoglobin of about one percent, barely
9 that, but even though the effect was small it was
10 really quite durable. If anything, it seems to be
11 getting better at the end of the trial.

12 This study of miglitol was actually done
13 in African-American patients, and this little insert
14 is actually different data, this was done in Latino-
15 American patients, both showing, roughly, both two
16 groups with high risk of diabetes, both showing,
17 roughly, the same kinds of data. So, even though we
18 have drugs that are not terribly potent, like
19 miglitol, very, very safe and does appear to be
20 durable.

21 Well, I'd like now to enter into, really,
22 the most difficult question. Doctor Bone is telling
23 me to hurry up. The question I think the most
24 important question, really, is what constitutes a
25 clinically-significant change, .7, .3, how do we

1 actually determine that?

2 And, this is data, let's look at this as
3 hypothetical data in patients with type 1 diabetes,
4 and, again, it's a time course starting at a
5 hemoglobin of around nine, but the data here is
6 expressed as a delta effect, a reduction from
7 baseline. And, you can see over 52 weeks that
8 patients here who received placebo really did not have
9 very much effect at all, this was a pretty constant
10 baseline. The patients who received this hypothetical
11 drug did show improvement. There was a treatment
12 effect here, but I'm not certain that it was
13 statistically significant at 52 weeks, although, this
14 seems to be a trend that, perhaps, it's not going to
15 be durable beyond that, but let's just, for the sake
16 of discussion, say that this is where we ended and
17 this is where we have to make a decision.

18 Well, the treatment effect here is about
19 .3, over here it was a little greater, the question
20 is, really, is this a clinically significant change,
21 that's, I think, the most important and most difficult
22 question, and I think there are really two ways of
23 looking at this.

24 It's certainly clear that we don't
25 recognize a threshold for the development of vascular

1 complications of diabetes based on any specific level
2 of Glycohemoglobin, and there's no doubt that I think
3 a patient is better off if they have a hemoglobin of
4 -- Glycohemoglobin of 8.5 than if they have a
5 Glycohemoglobin of 8.8. I'm certainly willing to
6 concede that.

7 And, if one looks at that phase of the
8 argument in that way, then one would say, yes, this is
9 a clinically significant change. But, I would really
10 challenge people to look at it in a different way, and
11 the way I would -- the reason I say that is this, it's
12 true that 8.8 is less than 8.5, and that it's better
13 to be at 8.5 than at 8.8, but, in fact, neither one of
14 them are very good, and the ADA recommendations are
15 that, really, what we should strive to get patients
16 down to a Glycohemoglobin of seven, that's not always
17 possible, of course, but that really we should not
18 really be complacent until we get them down to a value
19 of eight or less. And so, if one accepts that, then
20 patients with a Glycohemoglobin of 8.5 over here
21 really still has to be offered some other kind of
22 therapy.

23 What other kind of therapies are there?
24 Well, there any number, more insulin, troglitazone,
25 whatever, but whatever a physician wanted to do in

1 that patient at this point he could have also done it
2 up here at the beginning of the trial. So, if you say
3 that, well then, what is the purpose of using this
4 drug in this setting, if the options we have at the
5 end are the same as the options we have at the
6 beginning, and the patient still needs to be treated
7 further?

8 It seems to me that this is really more
9 like a detour than actual effect of treatment. And,
10 just to illustrate what I mean, I replotted that data
11 shown up here, and also to scale showed the change in
12 glycosylated hemoglobin in the intensively treated arm
13 in the DCCT studies, and you can see that the effects
14 of this hypothetical drug here are very, very much
15 less than what one sees with intensive insulin
16 treatment. And also, one has to again bring up the
17 time point, the duration of effect, but we know from
18 the DCCT trial this really goes on to nine years, I
19 imagine we could have data beyond that, I didn't plot
20 it more than two years, and with this hypothetical
21 drug, if one just kind of extends the values here it
22 looks to me like even if one took this as a clinically
23 significant effect it probably wouldn't really last
24 more than about two years.

25 Now, what do we know about Glycohemoglobin

1 and microvascular disease? Well, it seems to me it's
2 not just the absolute level, but it's really the total
3 exposure and the duration of that exposure is just as
4 important as the actual level itself.

5 And so, if one takes that argument,
6 really, what is actually accomplished by using a drug
7 like this, when one can do something like this. My
8 point is that to actually treat a patient with a drug
9 like this, given this data, I don't think is actually
10 neutral, I think it's actually perpetuating a bad
11 situation, and, therefore, to me it's hard to say that
12 it's clinically significant benefit. To me, it just
13 looks like one is just kind of doing something in lieu
14 of actually taking a definitive action.

15 And, if you accept that kind of reasoning,
16 though, then I think something else follows, and I do
17 want to make something -- I may have misspoken, I want
18 to make something clear, I'm not saying based on this
19 that I would say that this drug really is not useful
20 in this setting. What I'm saying is that we really
21 haven't -- that it hasn't been demonstrated in an
22 appropriate setting, and the appropriate setting
23 really to study this, a drug of this nature, would be
24 not to do it in conventional treated patients where
25 the hemoglobin A_{1c} is kept constant, but actually to

1 combine it with more intensive insulin treatment, so
2 one would have an arm like this, and then an arm with
3 the drug, and at the end of the 12 months one would
4 say, did that drug actually make a difference in
5 addition to insulin, both with respect to the level of
6 Glycohemoglobin that one could achieve, and also with
7 respect to the incidence of hypoglycemic episodes.

8 Now, a reduction of .3 may not be large in
9 itself, particularly in this setting, but if one could
10 see a reduction of Glycohemoglobin of .3 and in
11 addition to that have a reduction in hypoglycemic
12 episodes that I would think would be a very important
13 and very clinically significant effect. But, in order
14 to actually demonstrate that you really do have to do
15 the right study, and the way this was done, really, is
16 not a definitive study.

17 And finally, I will just -- and this is my
18 last slide before I lose my voice entirely, and that
19 is, I think when evaluating drugs in the future, I
20 think we really should recognize that it's not the
21 absolute level of Glycohemoglobin that we should be
22 looking at, but really the relationship between
23 Glycohemoglobin and hypoglycemic episodes.

24 And, using the drug that I have just
25 demonstrated, if that drug could show that there was

1 a change in this relationship, if, for instance, you
2 had a curve down here, where at a Glycohemoglobin of
3 .7 using a new drug, you only got 15 hypoglycemic
4 episodes per year, whereas in the absence of that new
5 drug with the controlled population you would get 100,
6 then that, I think, would be an extremely important
7 clinically significant event, because then you really
8 do something to those patients that you cannot be
9 doing now, do now with insulin alone, and would be, I
10 think, potentially making a major difference.

11 So, anyway, I think just in summary, I
12 would, myself, being shown this data would really not
13 affect this as being a clinically significant result,
14 it seems to me that at the very best it's actually
15 just chipping away at control, and looking at it in,
16 I think, a more realistic situation, if anything, I
17 think it's perpetuating the situation of poor control,
18 and that's why I say that when given data of this type
19 I, myself, would not accept it as being a basis for
20 approval.

21 Thank you.

22 CHAIRMAN BONE: Okay.

23 Doctor Misbin, were you planning to
24 present the remainder of the guidance document?

25 DOCTOR MISBIN: Not at this moment.

1 CHAIRMAN BONE: Good.

2 All right. I guess if there are any
3 questions for clarification of this partial exposition
4 of the guidance document, I think Doctor Molitch had
5 a question for Doctor Misbin.

6 DOCTOR MOLITCH: It just seems that in
7 this capacity, you just maybe sort of comparing
8 apples, oranges and pears all together here, with some
9 difficulty.

10 I think the last thing that you mentioned,
11 actually, has some relevance, about the chipping away,
12 and I think that we've entered into an era of
13 polypharmacy of using more than one oral agent
14 together with the realization that no one of them is
15 going to be a single agent that will get a normal
16 Glycohemoglobin for many patients, or even for most
17 patients, and so the idea of showing partial efficacy
18 in reducing Glycohemoglobin we can pick a level,
19 whichever we like, that it can then be added to
20 another oral agent, perhaps, with a different
21 mechanism of action. It can be a very useful addition
22 of treatments, and not necessarily have to be added to
23 insulin.

24 So, the fact that you have made a
25 substantial reduction, although, not down to normal

1 with a single drug, does not necessarily preclude its
2 efficacy.

3 DOCTOR MISBIN: Yes, I agree with that.

4 CHAIRMAN BONE: Doctor Cara?

5 DOCTOR CARA: You talked a lot in the last
6 segment of your presentation on what you would not
7 consider an appropriate efficacy or efficacious
8 regimen, but I didn't quite catch what your
9 conclusions were regarding minimal standards of
10 efficacy. Have you developed those?

11 DOCTOR MISBIN: I think I'll go back to my
12 chair.

13 CHAIRMAN BONE: Well, it might be helpful
14 if you would -- maybe somebody will want to see one of
15 your slides.

16 DOCTOR MISBIN: Oh, all right.

17 Well, we don't have, again, in the draft
18 as it is, we don't have a statement about what is a
19 minimal criterion. I mean, I think anything that we
20 said would be open to attack and would be arbitrary.

21 I think the way it's stated in the draft
22 is just stating the fact that in the past, given a
23 treatment which we thought was very safe, namely
24 acarbose, although not terribly effective with a
25 Glycohemoglobin reduction of about .7, we did, in

1 fact, approve that.

2 Now, something -- if we were faced with an
3 agent that was less effective than acarbose, and did
4 not have the good safety profile that acarbose had, I
5 would not see any reason why we ought to approve it.
6 What would be the reason to approve that? And,
7 perhaps, people on the committee feel differently.

8 I think that's really -- since we are
9 talking about various types of drugs, both type 1 and
10 type 2 diabetes, drugs used in combination, I don't
11 really see any way of setting an arbitrary level,
12 unless the committee feels otherwise.

13 CHAIRMAN BONE: Well, I guess what -- just
14 one moment, and then Doctor Marcus -- I guess what
15 several members of the committee, I think, are kind of
16 working toward here is a question for you, based on
17 how the document that we've had a look at, and in this
18 discussion of some elements of the document that
19 you've given us, how is industry to be guided here?
20 I mean, if the intention is to guide industry in the
21 design and execution of trials, I think we have gained
22 some interesting insight into how you might review the
23 results after they are completed, but I'm not quite
24 sure if I were a sponsor right now if I'd know what I
25 needed to know to plan the development program, which

1 is, of course, when the guidance would be most
2 informative.

3 DOCTOR MISBIN: Well, again, I think
4 industry can be guided that we are likely to do in the
5 future pretty much using the same reasoning that we
6 have in the past, that in the past we approved a drug
7 that we thought was very safe based on a
8 Glycohemoglobin reduction of about .7, perhaps, a
9 little bit greater. So, that would be the guidance
10 that I would give to industry, that if the product
11 they are then thinking about is likely to be less
12 efficacious than that, then I think they should not
13 assume that it would be approved.

14 On the other hand, if the product were
15 more efficacious than that, we have approved a product
16 like that, with that degree of efficacy before,
17 barring any significant safety issues it's likely that
18 we would approve it again. I wouldn't see any reason
19 why not.

20 CHAIRMAN BONE: Doctor Marcus, and then
21 several others.

22 DOCTOR MARCUS: Let's assume for the
23 moment that in the early phase of drug development a
24 manufacturer becomes convinced that drug A is not
25 particularly potent on its own, but has a remarkable

1 capacity to enhance some other drug, are you going to
2 hold still, hold firm to the view of having to do a
3 certain number of trials that are versus placebo, or
4 can the manufacturer just focus on this use as the use
5 of this drug as an insulin enhancer, let us say, and
6 have all the trials that would come to the Agency be
7 in its use as an enhancer?

8 DOCTOR MISBIN: We haven't faced this yet,
9 but posing it the way you do, my reaction would be
10 that it should be used the way they intend, so there
11 it would be used as --

12 DOCTOR MARCUS: Is there a precedent for
13 anything like that, that you are aware of?

14 DOCTOR MISBIN: I'm not aware of anything
15 like that. I mean, troglitazone, of course, is an
16 insulin sensitizer, and we approved it initially, as
17 this committee knows, based on data used concomitantly
18 with insulin, and so actually that data that led to
19 that approval was, I think, entirely based on its data
20 used in insulin treated patients, although there was
21 a body of data used in placebo and so on.

22 But, I think -- I suppose it's
23 theoretically possible that a new compound would do
24 nothing by itself, but can only be used in association
25 with something else, and then I would say that,

1 really, I think we'd be looking at the drug product,
2 really, as a kind of a package. You know, it wouldn't
3 make any sense to test something under conditions in
4 which it would not be used, but that's kind of an off-
5 the-cuff reaction.

6 CHAIRMAN BONE: Doctor Molitch, Doctor
7 Zawadzki and Doctor Hirsch.

8 DOCTOR MOLITCH: I have a fundamental
9 philosophical question about the role of this
10 committee and, perhaps, the Agency. If a drug is shown
11 to have some efficacy, perhaps, less than other drugs,
12 but still efficacious with a very favorable safety
13 profile, it seems to me that our role in looking at
14 this would be to exactly state that, and that, to me
15 at least, would seem a reason for approval.

16 If the drug was really ultimately
17 minimally efficacious, but still efficacious, then it
18 may not actually do very well in the marketplace, and
19 the marketplace would actually satisfy that and nobody
20 would use the drug, and the drug company would
21 probably realize this as it was developing the drug,
22 and realize that this is something that probably is
23 not going to make it. Where, if they decide to market
24 it anyway and it doesn't go, then that's their
25 problem.

1 So, it really depends upon what exactly is
2 our role here in trying to decide these things, and
3 maybe we can clarify that.

4 CHAIRMAN BONE: Perhaps, that's a subject
5 to discuss in more detail in the afternoon.

6 Yes, briefly, please, because we're --

7 DOCTOR FLEMING: Well, I think that is a
8 very critical point, and it really is very close to my
9 particular opinion, as to how we should view the drug
10 approval process. And, I do have a different
11 perspective from Doctor Misbin on this very point, in
12 that, deciding what is clinically significant is very
13 difficult and, in fact, we have data from the DCCT and
14 other studies that show that small differences in
15 approved glycemc control can make a difference.

16 I think we've got to emphasize that it's
17 not only the effect, but it's the cost, in terms of
18 safety and other considerations, for us to make the
19 risk benefit determination. That, ultimately, is the
20 basis of how we decide whether to approve the drug or
21 not.

22 It's conceivable that we could approve a
23 drug with an effect of .2 hemoglobin percent units, if
24 it has minimal risk, say, taking two Vitamin C tablets
25 a week can bring about that improvement, I would think

1 that would be approvable.

2 CHAIRMAN BONE: Thank you, Doctor Fleming.

3 Doctor Zawadzki and then Doctor Hirsch.

4 DOCTOR ZAWADZKI: I would just like to
5 request a clarification that applies to the next to
6 the last slide that you had shown, which showed that
7 the hemoglobin A_{1c} had decreased and then gone back up
8 again in the one group, and the comparison was with
9 the hemoglobin A_{1c} going down and staying sustained in
10 a sustained decreased amount. Are those populations
11 the same?

12 DOCTOR MISBIN: I was showing that,
13 really, for the purposes of comparison. They are --
14 these were not the trials that were done
15 concomitantly, the DCCT trial, of course, was
16 different from the hypothetical trial that I showed.
17 Of course, it was both in type 1 patients, and the
18 starting glycosylated hemoglobin was actually the
19 same, and the baseline data were the same. So, I
20 think one can look at that in a gross sense as to what
21 one can do in this type of patient, but they were
22 certainly not exactly comparable, I've certainly not
23 done that kind of analysis.

24 DOCTOR ZAWADZKI: That clarification is
25 helpful to me personally, because my impression was

1 that the first set of data were really from a type 2
2 diabetes population.

3 DOCTOR MISBIN: It was type 1.

4 DOCTOR ZAWADZKI: And, that's helpful.

5 One thing that hasn't been very clear to
6 me in reading the draft guidance, and in some of the
7 discussion points so far, has been a distinction
8 between type 1 and type 2 diabetes, and I think there
9 is a significant difference in the two, especially
10 when we start discussing the importance of
11 hypoglycemia in the adjustment of therapy. I would
12 just -- I would recommend that we think a little bit
13 more specifically versus type 1 or type 2 diabetes, or
14 apply to both if it is, indeed, applicable to both
15 types of pathophysiologies.

16 CHAIRMAN BONE: Thank you.

17 Doctor Hirsch, and then I think Doctor
18 Sherwin, and then as soon as we wrap up the comments
19 and questions concerning Doctor Misbin's specific
20 presentation we'll go to the industry comments.

21 DOCTOR HIRSCH: I just wanted to make a
22 little point about what I understood to be the
23 exchange of Doctor Marcus and Doctor Misbin, namely,
24 the precedent for having a complex mixture of drugs as
25 a placebo versus -- well, that happens in oncology all

1 the time, thank the Lord, namely, a child with acute
2 lymphocytic leukemia is not allowed to go or wash-out
3 or whatever, you do treatment A versus treatment B,
4 and all of the innumerable cooperative studies have
5 always used that paradigm of necessity in that extreme
6 case. I don't see why it's different here, and I'll
7 expand on that later, if I may.

8 CHAIRMAN BONE: Doctor Sherwin?

9 DOCTOR SHERWIN: Just to add on to that,
10 and just to make a small point, in terms of the
11 varying Glycohemoglobin. One of the problems is that
12 measurement is affected by three months of -- two or
13 three months results, and so that the baseline value
14 during the withdrawal period is generally under
15 estimated compared to the time when the drug is
16 stopped.

17 So, often, if you use a change in
18 Glycohemoglobin as your measurement, you are
19 confounded by the fact that you are under estimating,
20 during a withdrawal phase, the actual baseline value,
21 which complicates an assessment even further.

22 So, I mean, that's one of the problems
23 during that withdrawal phase that needs to be taken
24 into account, unless you have a long withdrawal phase
25 you are going to under estimate the Glycohemoglobin at

1 baseline.

2 CHAIRMAN BONE: And, for example, Doctor
3 Misbin's set occurs from troglitazone if you looked at
4 the baseline.

5 DOCTOR SHERWIN: That's why I was making
6 that point.

7 CHAIRMAN BONE: You would have seen a
8 placebo effect, a nice dose response group.

9 We have -- are there further comments of
10 questions specific to Doctor Misbin's presentation?

11 Doctor Davidson?

12 DOCTOR DAVIDSON: You know, two points,
13 you know, always we need to give reduction in A_{1c} ,
14 but, you know, drugs have beneficial and deleterious
15 side effects, and one of the drugs could have a very
16 good effect on lowering blood pressure with an A_{1c}
17 only of -.3 percent, or a significant decrease in one
18 of the lipid parameters, then I think that we can, you
19 know, take exceptions to the rule, you know, based on
20 the profile of the drug, which I think we always do.

21 And, you know, in your document, you know,
22 one of my few concerns, you know, even though we still
23 have many questions is, you know, a parameter for, you
24 know, that you consider a positive is a reduction in
25 the need for frequent injections in patients with type

1 2 diabetes, and I want to delete that, you know,
2 because a decrease in the number of injections, you
3 know, for me is not a parameter of improvement, you
4 know, and actually may send the wrong, you know, idea
5 to physicians in practice that, you know, multiple
6 injections are not the way to go. And, I think that
7 in 1998 that's the therapy of choice in patients with
8 type 1 and type 2 diabetes until proven otherwise.

9 CHAIRMAN BONE: Thank you.

10 We now have a series of presentations on
11 behalf of various interested sponsors. Some of these
12 will, undoubtedly, relate to the topics exposed by
13 Doctor Misbin. We had anticipated -- well, Doctor
14 Misbin decided to really provide the rationale for
15 some of the more challenging parts of the document,
16 rather than to go through the entire guidance, which
17 may mean that some of these industry comments will
18 pertain to other areas of the guidance draft, I
19 suspect, than those already discussed, and then we
20 will be discussing material that has not been
21 presented.

22 Presumably, everyone has had access to the
23 draft guidance document, because that's, obviously,
24 presupposed, the committee has -- pardon me?

25 DOCTOR CARA: Can we take a break?

1 CHAIRMAN BONE: We will take a break, do
2 you mean now? I guess we had already scheduled one
3 for half past ten, but we can -- if you'd like to,
4 that would mean moving the break up before the
5 industry comments section. I'd kind of like to get
6 through that and then take the break, I think that's
7 logical, if you can manage. Okay.

8 The first speaker scheduled is Doctor
9 Orville Kolterman from Amylin Pharmaceuticals, who
10 wishes to comment on a number of points in the
11 guidance document.

12 We are going to be asking each speaker to
13 stay within about five or six minutes, in order to
14 complete this in the allotted amount of time, and I'll
15 give you a signal with about a minute or so to go.

16 DOCTOR KOLTERMAN: Mr. Chairman, allow me
17 to begin by thanking the Advisory Panel, as well as
18 the Agency, for the opportunity to address these
19 important issues. It's obvious that a fair amount of
20 work has gone into the preparation of this document,
21 and that we now have an open forum for discussion.

22 In the time allotted, I'd like to touch
23 briefly upon four issues. First, diabetes is a
24 multifaceted disease, some comments about assessments
25 of reduction in hemoglobin A_{1c}, mean reductions, post

1 alternative assessments, a couple comments about
2 hypoglycemia, and then some comments about evaluation
3 of new agents in patients who are using insulin
4 therapy.

5 As you all are aware, diabetes is a
6 multifaceted disease, it's not only a disorder of
7 glucose metabolism, metabolism of carbohydrate,
8 protein and fat are altered in this disease. In fact,
9 the leading cause of death in patients with diabetes
10 is due to microvascular events. Therefore, risk
11 factor reduction in that area, I believe, is agreed to
12 be mandatory.

13 And, in that area, the role of
14 hypoglycemia remains debated and unclear at the
15 present time. Clearly, glycemia control was important
16 because the relationship between microvascular disease
17 and hypoglycemia has been clearly established by the
18 diabetes control and complications trial.

19 We would suggest that in terms of
20 assessments of new therapeutic agents that the entire
21 metabolic profile of a patient be evaluated in terms
22 of both microvascular and microvascular risk. You
23 know, improvements in hemoglobin A_{1c}, without an
24 increase or a reduction in hypoglycemia, are important
25 in terms of addressing the microvascular risk profile.

1 In terms of microvascular risk, it's
2 important to pay attention to plasma lipids, both
3 concentrations and composition amongst the sub-
4 fractions, body weight, blood pressure.

5 While the focus of the discussion this
6 morning has been predominantly on improvement in
7 glycemia control, would argue that a blend of these
8 parameters that on this overhead could actually serve
9 as the basis for the approval of an agent, that is, an
10 agent that brings some improvement in glycemia
11 control, but has favorable impact in terms of the
12 microvascular risk, I would argue should be viewed
13 with some favor, at least given credit for the impact
14 upon the microvascular risk profile.

15 Moving on, in the interest of time, to
16 talk about hemoglobin A_{1c} assessments, I'd just like
17 to point out that I think that there are some
18 limitations in employing mean reduction in hemoglobin
19 A_{1c} as a sole assessment. The clinical impact of a
20 given mean reduction is critically dependent upon the
21 baseline from which the patient begins, as has been
22 alluded to by some panel members this morning.

23 In addition, the feasibility in the clinic
24 of achieving any given mean reduction in hemoglobin
25 A_{1c} varies based upon the baseline from which the

1 patients begin. It's much more difficult to get a
2 reduction of one percent if the patient begins with a
3 baseline of 7.5, compared to a patient that begins
4 with a baseline of ten or 11 percent.

5 Furthermore, the mean reduction as a point
6 estimate provides limited insight into the pattern of
7 response throughout the population studied, throughout
8 the cohort study.

9 You could come to the same mean reduction
10 in hemoglobin A_{1c} by having a relatively constant
11 reduction across the study cohort, as opposed to
12 having a study population that is composed of some
13 patients that have, you know, an extremely good
14 response, but is then blunted somewhat by patients who
15 are somewhat unresponsive, or appear to be
16 unresponsive to the drug, and that should not be
17 surprising given the known heterogeneity of diabetes.

18 Well, in terms of alternative assessments
19 we think should be considered, utilization of the
20 relative proportionate reduction from baseline as it
21 has been shown, based upon the DCCT data set, to
22 provide a uniform assessment of microvascular risk
23 reduction. Alternatively, the number or the
24 proportion of patients achieving and maintaining
25 meaningful -- clinically meaningful targets, such as

1 less than eight percent or less than seven percent,
2 could also be employed as appropriate endpoints.

3 In terms of hypoglycemia, as I read the
4 draft guidance, it may be a bit -- it's not completely
5 clear to me, and we just want to make clear that any
6 event that requires the assistance of another
7 individual into neurologic impairment should be
8 considered as a severe episode.

9 Also, I would argue that instead of 50
10 milligrams per deciliter, as suggested by the current
11 version of the draft guidance, that 60 milligrams per
12 deciliter should be considered as studies in the
13 literature document that as being the threshold for
14 the initiation of glucose counter-regulatory
15 processes.

16 Risk reduction for hypoglycemia, due to
17 the severity of this -- or the threat that this
18 conveys to the patient, should also be considered. We
19 reduce frequency of hypoglycemia while maintaining the
20 same hemoglobin A_{1c}, reduction in nocturnal
21 hypoglycemia, or a reduction or a reversal of
22 hypoglycemia unawareness should also be given
23 consideration.

24 I'll now turn to the final point in the
25 evaluation of new agents in patients who are using

1 insulin. We do not feel that this issue is adequately
2 addressed in the present draft of the draft guidance
3 document. The statement is sometimes made that any
4 improvement in glucose control in patients -- any
5 desired improvement in glucose control in patients
6 using insulin can be achieved by just simply
7 increasing the insulin dose. Clinical experience
8 shows that that, apparently, is not the case, because
9 both providers and patients are frequently resistant
10 to the concept of increasing insulin doses, and the
11 side effects of insulin therapy themselves, two major
12 side effects being hypoglycemia and weight gain,
13 convey increased risk of another type, of another sort
14 to the patient.

15 Finally, the metabolic benefit of reducing
16 insulin dosage, while it remains a topic for
17 interesting debate, remains unproven at the present
18 time.

19 So, when evaluating agents in patients
20 using insulin, it seems that agents which achieve
21 equivalent degrees of glycemic control, without
22 increased hypoglycemia or weight gain have merit, and
23 in terms of quantitation of magnitude of drug effect
24 requires that major changes in insulin regimens not be
25 allowed during the trial. Increases in the total

1 daily insulin dose of the patients makes the data
2 uninterpretable and decreases in total daily insulin
3 use in the active arms can deminimize the drug effect.

4 So, in conclusion I'd offer four
5 recommendations. One is that the panel consider the
6 assessment of the patient's entire metabolic profile
7 when evaluating new therapeutic agents, that we employ
8 the relative proportionate reduction in hemoglobin A_{1c}
9 from baseline as a uniform assessment of microvascular
10 risk, expand upon the hypoglycemia endpoints, as I
11 touched upon, and finally, address the unique aspects
12 of evaluating a drug in patients using insulin.

13 Thank you for your attention.

14 CHAIRMAN BONE: Thank you.

15 Yes, please. This is Doctor Marcus
16 speaking.

17 DOCTOR MARCUS: Yes.

18 Orville, can you -- when you said 60, are
19 you talking plasma glucose or whole blood glucose?

20 DOCTOR KOLTERMAN: Plasma glucose.

21 DOCTOR MARCUS: Thank you.

22 CHAIRMAN BONE: Okay.

23 The next speaker on the agenda will be a
24 representative of Bayer Pharmaceuticals.

25 DOCTOR MAGNER: My name is James Magner,

1 and I'm an Associate Director of the Metabolics. I
2 had some comments to make about A_{1c}, but I'd actually,
3 in the interest of time and because we've sort of been
4 over that just restrict it to some statistical issues.

5 First, I'd like to make a preliminary
6 comment that I think in the long-range development of
7 therapies for diabetes, if you take a long-range
8 approach from 1921 to the present this is certainly,
9 in 1998, an appropriate time to rethink and really
10 look to see the way the drug development should be
11 pursued. And so, we do feel that it is not just a
12 creative academic exercise, but it is an appropriate
13 exercise to go through, in spite of the very thorny
14 problems that, you know, have already been expressed
15 on exactly how to do this, but the exercise itself, I
16 think, is a very commendable one.

17 I should also briefly express our
18 surprise, both pleasant and unpleasant, by the
19 prominent mention of our drug acarbose in the proposed
20 guidelines. I could make the tongue and cheek comment
21 that rather than being described as the possible
22 placebo-like drug that when the final draft guidelines
23 are published we'd like it referred to as the gold
24 standard for the comparison to diabetes.

25 On a more serious note, I should mention

1 that actually within the medical branches of the Bayer
2 Corporation we actually have no objection to using
3 acarbose as a comparator, since, as Doctor Misbin has
4 already explained, it sort of has the minimal degree
5 of efficacy that a clinician would generally accept in
6 clinical practice and, perhaps, is acceptable with
7 that minimal degree of efficacy because of its well-
8 known safety.

9 And, I think from the medical community
10 within our Bayer Corporation, we have no opposition if
11 that's written into the guidelines. It's probably my
12 responsibility to report here that within our internal
13 discussions some of our marketing people expressed
14 some concern and weren't so sure whether or not we
15 should, you know, accept this or oppose it, because,
16 presumably, there would be a lot of future
17 publications, you know, in the next few years, almost
18 every one showing that the new drug was slightly
19 better than acarbose. My argument is that, yes, but
20 we would have almost the same efficacy but with very
21 good safety.

22 But, I think the overall message here is
23 that I guess our company would not oppose, if that's
24 the way these published guidelines would come out.

25 Very briefly in closing, I wanted to raise

1 two issues that I've been given by a very bright
2 statistician, Alice Croel, who works in our company,
3 and she wanted me to mention two points. If you have
4 a comparator drug versus a new drug, what's critical
5 in the design of a 12-month study is to specify in
6 advance the maximum allowable difference that you
7 would accept at the end of the trial as being a
8 positive result. And, you need to specify that in
9 advance in order to properly calculate the sample size
10 and to specify in advance in the protocol the proper
11 way that the treatment would be evaluated.

12 And, it's possible that the maximum
13 allowable difference might be different depending on
14 what the comparator is, whether it's an SFU, or
15 troglitazone, or acarbose, or whatever, but that we
16 had actually been thinking in terms of superiority,
17 proof of superiority, versus non-inferiority, and
18 that, apparently, I mean, statisticians make fine
19 distinctions like this, but actually that they make
20 the point that in non-inferiority trials the sample
21 sizes are much larger, and she went through some
22 calculations which actually we'll submit to the
23 committee in written form in the future, and I won't
24 go into any detail here, but that's sometimes -- to
25 prove a superiority of .5 percent of A_{1c} in a two-arm

1 study, in a conventional manner, might take 50
2 patients per treatment arm, but if you say that we
3 might approve a drug that was not inferior by more
4 than .2 of an A_{1c} unit, you might need 400 patients
5 per treatment arm to show that concept.

6 And so, certainly, there would be major
7 implications for the sponsors if we would have to
8 triple, let's say, the size of some of our 12-month
9 studies.

10 Any other comments? Okay, that's all I
11 have to say. Thank you.

12 CHAIRMAN BONE: Thank you very much,
13 Doctor Magner.

14 I'll just mention, as Doctor Wishner from
15 Eli Lilly & Company is coming up to the microphone,
16 that the committee has been provided with some written
17 materials by a number of the speakers, and that we, in
18 addition, have written comments from the Robert Wood
19 Johnson Foundation and from Doctor Illingworth who,
20 unfortunately, is not able to be here today, although,
21 he's a member of the committee.

22 This is Doctor Wishner, I believe?

23 DOCTOR WISHNER: Yes, is this on?

24 CHAIRMAN BONE: Yes.

25 DOCTOR WISHNER: With apologies to my

1 Bayer colleague, I would suggest that using acarbose,
2 perhaps, would unblind the studies.

3 CHAIRMAN BONE: That's referred to as an
4 inside joke.

5 DOCTOR WISHNER: We, too, appreciate the
6 opportunity of addressing both the FDA and the
7 Advisory Committee.

8 I think that the discussion has so far
9 shown that this is a very complex issue. It's very
10 difficult to design studies to prove the points which
11 have been mentioned.

12 We would like to suggest that this
13 document be divided by type of diabetes being treated.
14 I think that most of the guidance that has been given
15 has been for type 2, and type 1 and type 2 require
16 very different designs for the studies.

17 We have several comments to make, many of
18 which have already been addressed in the discussion so
19 far. First, we would like to address the endpoints,
20 both the hemoglobin A_{1c} endpoint, as well as
21 hypoglycemia.

22 It has been stated in the guidance that a
23 mean treatment effect of approximately .7 percent
24 hemoglobin A_{1c} reduction for the final six months of
25 a 12-month study is suggested as acceptable for

1 clinical significance, and, furthermore, to be
2 acceptable that that difference must be sustained over
3 the 12 months and also that there be a decrease from
4 baseline in the study drug.

5 We believe that for most of the
6 antidiabetic agents a six-month trial is adequate to
7 establish efficacy, and, furthermore, to predict
8 chronic efficacy. An exception, of course, would be
9 those drugs that primarily affect weight loss, and I
10 think that it's been suggested that this would be,
11 perhaps, a point of negotiation with the FDA in the
12 design of the trials at the outset.

13 With respect to the decrease of hemoglobin
14 A_{1c} from baseline, it has already been pointed out
15 that responses to any class of drug over time will
16 vary significantly depending on a number of factors,
17 including those that we have listed, the population
18 under study, the national history of the disease with
19 the expectation of declining glycemic control, the
20 baseline hemoglobin A_{1c}, obviously, starting at a
21 higher baseline is going to be easier to demonstrate
22 efficacy, if you will, and the mechanism of action of
23 the drug, so that we must take into account all of
24 these factors and I think it's difficult to establish
25 a single recommendation in this case. I also believe

1 that to demand a change from baseline is unreasonable.

2 If we have a drug, for instance, in which
3 the placebo control increases -- or the decline in the
4 hemoglobin A_{1c} is from, perhaps, eight, and it
5 declines to nine, and the study drug, on the other
6 hand, shows a decrease of about .1, is this drug -- an
7 increase, I said -- is this drug not going to be
8 acceptable because there was no decline? I would
9 suggest that, in fact, this drug is efficacious. So,
10 I think that we have to rethink whether a demand for
11 decrease from baseline is necessary.

12 We've had a lot of discussion regarding
13 placebo control. We believe it's the gold standard,
14 and, obviously, ethics do come into the picture in
15 selecting those patients. Early on in the course of
16 the disease, this is certainly ethical, and, again, a
17 six-month trial, again, in the early stage of the
18 disease with a placebo control, is not unreasonable.

19 I think that the evidence that an agent
20 improves the primary endpoint compared to placebo
21 establishes efficacy, and, again, even if that
22 baseline is held constant or, perhaps, slips by a
23 small amount, so that we need to, again, make that
24 point clear, and I think that it has been, obviously,
25 brought up and discussed.

1 Turning to hypoglycemia, we believe that
2 any hypoglycemia, not only severe hypoglycemia, is a
3 deterrent to effective glycemetic control. Furthermore,
4 in type 2 patients, again, which this document
5 addresses, severe hypoglycemia, as it's defined by the
6 document, is extremely rare, occurring in less than
7 three percent of the patients per year. So, I believe
8 it would be difficult to, in fact, maybe nearly
9 impossible, to demonstrate a statistically significant
10 change in this endpoint, that is, severe hypoglycemia.

11 Therefore, we would suggest that a
12 definition be established for hypoglycemia as an
13 endpoint which would include the development of a
14 constellation of symptoms, which are reversed by the
15 administration of carbohydrate or glucagon.

16 I know that it's very difficult to define
17 this constellation of symptoms, but, perhaps, one or
18 more, including diaphoresis, tachycardia, tremor, a
19 change in -- any change in normal CNS function which
20 would be clinically significant. Orville offered one
21 suggestion, and that would be requiring assistance.
22 We also feel that a self-monitored blood glucose of
23 less than 54 milligrams per deciliter, irrespective of
24 symptoms, be included as a definition.

25 One comment on antiobesity antidiabetic

1 therapy, we all agree that weight control is the
2 cornerstone in the treatment of type 2 diabetes. Any
3 agent that demonstrates effective lowering of blood
4 sugar should be considered an effective therapy for
5 diabetes and, therefore, approvable, irrespective of
6 its mechanism of action, and especially in those with
7 type 2 diabetes where obesity accounts for 80 percent
8 of the population, and we recognize that a small
9 decrease in weight is critical or at least is a part
10 of management.

11 These drugs often affect cardiovascular
12 risk and other co-morbidities, and may result in
13 favorable risk benefit analysis. We believe that,
14 without specific scientific rationale, compared to
15 agents which directly lower blood sugar, there should
16 be no greater concern for safety. And so, evaluation
17 of safety in these agents should be the same as those
18 for other antidiabetic agents and the further
19 restrictions for antiobesity agents not be applied.

20 CHAIRMAN BONE: Thank you very much.

21 The next speaker for Glaxo Wellcome is
22 Doctor Fred Fiedorek, if I'm pronouncing that
23 correctly.

24 DOCTOR FIEDOREK: Fiedorek.

25 CHAIRMAN BONE: Fiedorek, sorry.

1 DOCTOR FIEDOREK: We at Glaxo Wellcome
2 welcome the opportunity to participate and listen to
3 the discussions. I was going to say that I would look
4 forward to the discussion to follow, but I actually
5 have already enjoyed the debate thus far.

6 And, my comments right now, really, you
7 have to understand that you all have copies of our
8 comments, and they really center on three of the
9 points within the draft guidance, and I have four
10 major points to raise.

11 The first one actually refers to the
12 development of surrogates, and I sort of welcome the
13 opportunity to hear how the committee members view
14 surrogates and identify sort of intermediate
15 endpoints, especially in relationship to end organ
16 damage, and this important concern in type 2 diabetes
17 patients. So, we certainly welcome advice and input
18 on this.

19 The next two points relate to
20 clarification of secondary outcome measures in
21 diabetes, and the first one, actually, is in response
22 to a quote within the guidance regarding insulin
23 therapy and reduction in insulin therapy.

24 The guidance currently states that, "A
25 reduction in insulin dose itself is not considered a

1 measure of efficacy unless accompanied by improvements
2 in hemoglobin A_{1c}." And, recognize that, again, we
3 are striving in treating type 2 diabetes patients to
4 improve their glycemic state, but I think that as
5 Doctor Kolterman actually mentioned as well, this
6 measure, or this assessment, is important for the
7 patient as well as the doctor, and so any kind of
8 assessment of this I would advocate should be used in
9 terms of categories wherein patients remain within a
10 hemoglobin A_{1c} bracket, and sort of use categorical
11 types of definitions, and not require necessarily an
12 improvement of the degree in hemoglobin A_{1c} like .7
13 percent, which has been advocated to show superiority.

14 The second comment on these issues, in
15 terms of secondary outcome measures, again I'll quote
16 the guidance document, it states now that, "Weight
17 loss, improvements in hypertension, and improvements
18 in serum lipid profile are also desirable, but need to
19 be accompanied by improvements in glycemic control in
20 order to be considered effective for the treatment of
21 diabetes." We also agree with this, but also would
22 welcome advice and insight from the committee members
23 on how exactly this can be, especially recognizing the
24 fact that in type 2 diabetes many of these parameters
25 are improved with improvement of glycemic control

1 itself. And so, we think that there should be some
2 sort of relative assessment relative to glycemic
3 control when you are trying to advise regarding lipid
4 improvements, weight improvement and the like.

5 Finally, the point I want to make is about
6 combination therapy, and the future of treatment for
7 diabetes is what we look at it, and this sort of
8 harkens back to Doctor Molitch's comments regarding,
9 you know, the future and the use of multiple agents in
10 combination.

11 Currently, the draft guidance states, "We
12 are not willing to allow two investigational drugs to
13 be used simultaneously, even if they have different
14 mechanisms of action." We just welcome insight and
15 advice from the committee members about how this might
16 be addressed in terms of using two investigational
17 compounds in combination, assuming that the
18 appropriately defined safety and safety pharmacology
19 and toxicology programs are shown and developed, both
20 as single agents, as well as in combination.

21 Thank you.

22 CHAIRMAN BONE: Thank you very much.

23 The next speaker is Doctor Rosskamp from
24 Hoechst Marion Roussel.

25 DOCTOR ROSSKAMP: Mr. Chairman, we very

1 much appreciate the opportunity to comment on these
2 guidelines and appreciate very much the efforts of the
3 FDA setting up these guidelines, and feel if they will
4 be left, not only its words, but by its spirit, will
5 help us very much.

6 With respect to hypoglycemia, we agree
7 that severe episodes of hypoglycemia present the
8 biggest problem for diabetic patients trying to
9 implement an intensive glucose control program.

10 According to literature estimates,
11 approximately 50 percent of all hypoglycemic episodes
12 occur during the night, and these episodes often
13 remain undetected. An unexplained rise in fasting
14 blood glucose is often the only change indicating a
15 nocturnal hypoglycemia episode has occurred.

16 A blood glucose lowering agent, which
17 reduces the likelihood of nocturnal hypoglycemia, as
18 a result of its pharmacokinetic dynamic profile, might
19 not be adequately studied in long-term trials, due to
20 general under-reporting of such events.

21 Our proposal is, therefore, that short-
22 term studies designed to adequately measure blood
23 glucose occurrences during the night should be
24 considered as a surrogate for a reduction of nocturnal
25 hypoglycemia.

1 With respect to insulin and insulin
2 analogs, the draft guidance points out that the
3 demonstration of a therapeutic equivalent with
4 existing insulin products may be adequate for insulin
5 products which have been used safely elsewhere in the
6 world. Therapeutic equivalence might imply longer-
7 term comparisons of treatments in diabetic patients.
8 We, therefore, suggest that in the case of human
9 insulin, which can well be characterized with
10 physical, chemical and biological methods, a
11 comparative bioavailability study with a marketed
12 insulin in healthy volunteers might be sufficient for
13 approval.

14 According to this guidance, the sponsor
15 should adequately investigate the pharmacokinetic
16 properties of insulin analogs. Due to difficulties in
17 generating specific insulin antibodies from insulin
18 analog, these data might not reflect the
19 characteristics of the drug, as well as
20 pharmacodynamic data do.

21 We, therefore, ask the Agency whether they
22 would accept pharmacodynamic data as the primary
23 variable in those studies, instead of pharmacokinetic
24 data.

25 With respect to the recent changes in the

1 diagnostic criteria for diabetes, the FDA guidance
2 states that the treatment of mildly diabetic patients
3 with insulin or certain oral agents will undoubtedly
4 cause serious hypoglycemia. We propose this statement
5 be omitted from the guidance based on the following.
6 Hypoglycemia, regardless of the treatment used, is
7 related to the dose of the treatment being
8 administered. Insulin and, for example,
9 sulfonylureas, given at adequate low doses would not
10 result in serious hypoglycemia. In addition, in
11 patients with impaired glucose tolerance sulfonylureas
12 have been shown to prevent the progression to manifest
13 diabetes as shown by Melander and published in
14 Diabetes.

15 Sponsors of any existing antidiabetic drug
16 would have to demonstrate the safety and efficacy of
17 their product in this indication.

18 Thank you very much.

19 CHAIRMAN BONE: Thank you very much,
20 Doctor Rosskamp.

21 The next institution listed on the program
22 is the Robert Wood Johnson Foundation. As I
23 mentioned, a document has been submitted for the
24 committee to review, but no presentation is to be made
25 today.

1 Next is Doctor Tim Seaton from Knoll
2 Pharmaceuticals.

3 DOCTOR SEATON: Thank you.

4 I'd like to thank Doctor Bone, the members
5 of the committee, Doctor Misbin, Doctor Sobel who is
6 not here, Doctor Fleming, Doctor Bildstein.

7 I have two comments I would like to make
8 today. One is on the use of hemoglobin A_{1c} in
9 placebo-controlled trials and the other is on weight
10 loss.

11 My comments really have to do, since so
12 much has been done with acarbose, even though I'm not
13 working on acarbose at this point, I spent four and a
14 half years of my life working with that product, and
15 I would like to make a comment.

16 If you look at one of the studies that
17 were done with acarbose, seen in the top graph here,
18 you can see that the placebo group, the changes in
19 hemoglobin A_{1c} in the placebo group was relatively
20 normal, it reduced with acarbose treatment. If you
21 look at some of the other studies, however, if we take
22 a second study, which was a dose ranging study, and
23 you can see in the white bars that the hemoglobin A_{1c}
24 actually went up about .25 to three percentage points,
25 and if you look at the 100 milligram dose, which is

1 shown in the half bars, which is the maximal approval
2 dose, so that there was a reduction, and so if you
3 look at this, I mean, if you just look at the range
4 from baseline and you say, well, this drug is not
5 terribly effective, and yet, the placebo subtract
6 effect is around .7, .8.

7 And, what is consistent is when you look
8 at all the trials with acarbose, and you look at all
9 the trials with miglitol, the consistency of placebo
10 subtract effect is there, and I would argue that if
11 you are trying to assess drugs that this is what you
12 really have to look at, the placebo subtracted effect,
13 to look at the effect of the drug. This is not the
14 way drugs are used in clinical trials. In clinical
15 trials, you do want to look at what is the response
16 from the patient's baseline, but when you are trying
17 to assess drugs you have to look at placebo subtract
18 effects, otherwise you don't really know how they
19 work, and that's my comment on the endpoints.

20 The other comments I would like to make
21 really has to do with, should weight loss agents be
22 indicated for approval of type 2 diabetes. I share
23 the issues that Doctor Wishner presented, and I'd like
24 to show you, since -- has just been approved and
25 launched, this is a trial which was recently completed

1 in type 2 diabetics, there were 175 patients. You can
2 see at the end of the six-month trial that there was
3 about a 4-1/2 percent weight loss, the red bars
4 indicate the completers, the yellow dashed lines are
5 last observation carried forward analysis. Again,
6 this is substantial weight loss in a diabetic
7 population.

8 If we look at the number of patients who
9 achieved at least five percent of weight loss from
10 initial weight, again, this is a draft, we've just
11 completed this study, about 27 percent in the LOCF
12 analysis versus a third of the patients who completed
13 the study achieved this goal of five percent weight
14 loss.

15 If we look at the mean change in fasting
16 glucose, change from baseline, the reductions are
17 pretty consistent across time. There are about 25
18 milligrams per deciliter throughout the study.

19 The hemoglobin A_{1c}, again, these are the
20 five percent responders, the hemoglobin A_{1c} is about
21 a 1/2 a percent throughout the study, .4 to .5.

22 If we look at some of the other
23 parameters, if we look at lipids, for example, if you
24 look at the fasting triglycerides, it's a little hard
25 to see that one, if we look at fasting triglycerides

1 you can see reductions ranging from -70 to -50
2 compared to placebo, and if we look at the HDL, which
3 is another important parameter to look at, you can see
4 increases compared to placebo at the end of 24 weeks
5 of around five percent difference.

6 And so, what I'd like to say is, I think
7 that when we look at weight loss agents that we really
8 -- that these should be indicated for the treatment of
9 diabetes, and it's not only -- I think part of this is
10 also a political reason, when you look at how weight
11 loss drugs are reimbursed, diabetic patients will not
12 be reimbursed unless weight loss drugs are reimbursed
13 in general. And, I think unless we have indications
14 in diabetes, unless weight loss can be proved for
15 diabetes, that it would be very difficult for this
16 patient group to be treated effectively by what is
17 considered a cornerstone of diabetic therapy.

18 And, in closing, I would just like to take
19 off my diabetic hat a minute and just comment that,
20 when we were looking at trials in Sweden a number of
21 years ago when I was working at Bayer, we tried to
22 find patients with elevated hemoglobin A_{1c} levels to
23 enter in trials, we could not find patients above
24 eight. And so, in different countries, where they
25 have very strong standards of care, you can get good

1 controlled diabetes. Diabetes control in this country
2 is abysmal for type 2 diabetes, and I urge this
3 committee to really try and make an impact on this to
4 make sure we can get drugs out there as quickly as
5 possible to treat this devastating disease.

6 Thank you.

7 CHAIRMAN BONE: Thank you very much.

8 The next speaker, Doctor Cheatham, will be
9 speaking from Novo Nordisk Pharmaceuticals.

10 DOCTOR CHEATHAM: Chairman Bone, Doctor
11 Fleming, Doctor Misbin, distinguished members of the
12 Advisory Committee, I come to you as Medical Director
13 of Novo Nordisk Pharmaceuticals, but also as an
14 academician, as a clinical endocrinologist and
15 diabetologist.

16 I wish to congratulate you on this attempt
17 to move the proverbial bar upward in regard to
18 readdressing the challenge of designing and making
19 available drugs for the effective therapy of diabetes
20 mellitus.

21 For the Agency to take this step in
22 addressing new guidance demonstrates leadership in the
23 development of needed treatments and sensitivity to
24 the recent advances that have been made in
25 understanding the genetics, the biochemistry, the

1 cellular biology, and the pathophysiology of this
2 myriad of metabolic disorders that we call diabetes
3 mellitus.

4 The community of individuals who have
5 diabetes and those of us who are involved in the
6 provision of care, and research for the treatment of
7 this disease, look forward to governmental agencies,
8 such as the FDA, to provide leadership in helping us
9 to continue the support and the design of therapies to
10 promote present knowledge and to apply that present
11 knowledge to ensure that the best treatments are made
12 available.

13 As the draft document that Doctor Misbin
14 brought forward has indicated, tremendous strides have
15 been made in the past ten to 20 years in regard to our
16 knowledge and understanding of diabetes mellitus and
17 its associated complications. The landmark diabetes
18 control and complications trial brought forward and
19 confirmed what Doctor Joslin and others of similar
20 prominence in past years had postulated, and that was
21 that lowering glycemic levels would lead to a marked
22 alleviation, in this case in type 1 diabetes, of the
23 complications of that disorder.

24 Similar studies in Japan and also in
25 Europe are pointing to, perhaps, the same being true

1 in type 2 diabetes, and we have no reason to suspect
2 that that is not the case.

3 Now, the recognition of the role of
4 glycation products, the accumulation of atypical
5 amounts of intermediate carbohydrates in the
6 development of the microvascular complications of
7 diabetes has matured for almost two decades. Valiant
8 efforts have been made to interdict these agents and
9 to provide protection for the end organs that they
10 devastate.

11 New recognition of the almost ubiquitous
12 presence of insulin resistance in essential
13 hypertension, in obesity, and, of course, in type 2
14 diabetes, has given prominence to discovery efforts to
15 counteract this problem.

16 But, just as important as the role of
17 research and discovery in the area of the beta cell
18 defect, without which, despite insulin resistance,
19 type 2 diabetes in its most prevalent form would not
20 exist.

21 Methods of protecting the beta cells from
22 immune attack in type 1 diabetes, and of replacing
23 beta cells are receiving intense support, although the
24 progress is slow.

25 Methods of reproducing the delivery of

1 insulin, via the portal system, with promise of more
2 appropriate physiology of response and improvement of
3 lipid metabolism are making headway. Until that
4 technology is in hand, however, we are finding that
5 insulin analogs assist those who already have
6 maximized all other components of diabetes care in the
7 insulin user, with a possibility of altering the time
8 lag between insulin administration and the onset of
9 effect.

10 New, fast-acting, short-acting oral beta
11 cell stimulators are now coming onto the scene and
12 hold promise of taking advantage of the physiology of
13 the portal route of insulin augmentation, while
14 minimizing endogenous hyperinsulemia and late post-
15 absorptive hypoglycemia, and the company that I
16 represent is very pleased to have been able to work
17 with the FDA and to have presented to this body the
18 first of those agents which soon will be introduced to
19 the public.

20 Despite the overwhelming excitement that
21 took hold of the community of specialists and
22 researchers, as well as those who treat diabetes, the
23 valiant efforts of your sister agency, the Centers for
24 Disease Control and Prevention, the solid information
25 that has come from the DCCT, as promoted by that

1 agency, has not as yet, after half a decade, been
2 taken up by the bulk of physicians who treat this
3 country's patients with diabetes.

4 The failure of translation of science and
5 technology to care delivery as a whole must not only
6 be recognized, but its cause analyzed by this Agency
7 and by others, and methods developed to overcome
8 whatever barriers there are to its implementation.

9 Currently, we have very powerful agents at
10 hand, agents including insulin, which are potent
11 enough to effectively lower glucose levels in
12 virtually every person with diabetes, whether type 1
13 or type 2, the challenge now emerges to fine tune the
14 capabilities of our therapeutic approaches, even as we
15 also continue our efforts into new areas of discovery.

16 While waiting for this intelligence to
17 take root and bring clinical applicability, we must
18 take advantage of the perspective we have gained by
19 having drawn closer to horizons, we now see type 2
20 diabetes clearly as not a defect of either the beta
21 cell alone or of insulin resistance alone, but as a
22 syndrome in which both defects must be recognized, and
23 which to achieve total, but more accurate, control one
24 cannot focus on one aspect without recognizing and
25 alleviating deficiency in the other.

1 And so, Mr. Chairman, the guidance
2 statement uses wisdom in advancing the cause of
3 achieving clinically meaningful reductions in
4 hemoglobin A_{1c}, while minimizing hypoglycemia, the
5 fear of which I would agree, and many others would see
6 as a major impediment to good control of glucose with
7 the powerful agents that we now have.

8 We at Novo Nordisk champion not only the
9 reduction in end organ damage the control of glucose
10 would assist in, but also the development of agents to
11 selectively protect organ pathology.

12 Mr. Chairman, we know that over 12 percent
13 of our health care budget is spent on diabetes and its
14 complications, but beyond that the impairment of joy,
15 livelihood and life itself to the citizens of this
16 nation comes from those complications that make
17 protection imperative and the work of this committee
18 so important.

19 And so, we recognize a three-fold task.
20 In our eyes, the FDA and industry must, number one,
21 assure that proper application of science and
22 technology presently available, as agents are
23 developed some attention must be given to how the
24 drugs will be effectively used and how they will not
25 be misused. Number two, the stimulation of aggressive

1 but ethical pursuit of new technology and applications
2 in diabetes care, with the priority of filling
3 vacancies in therapeutics which science has now
4 identified, is imperative. And, number three, the
5 assurance that the technology has validity and
6 provides efficacy and safety across the heterogenous
7 genetic mix of the U.S. population is extremely
8 important.

9 There is still work to be done in areas
10 that hold back just fast-paced progress. The
11 millstone that has hung around the neck of development
12 within the grouping of oral antidiabetic agents left
13 over from the age of the UGDP study needs to be
14 lifted. New full-scale analysis of what currently
15 market agents and those coming on the scene have to
16 offer need to be looked at.

17 Mr. Chairman, we at Novo Nordisk wish to
18 commit ourselves to the continued effort to improve
19 the well-being of individuals with diabetes in this
20 country and around the world, and proceed with new
21 advances in preventing and treatment diabetes
22 mellitus.

23 Thank you.

24 CHAIRMAN BONE: Thank you very much.

25 The next and final sponsor presentation

1 this morning is from Doctor Rappaport, and I believe
2 that I should note that the order was alphabetical,
3 but we are all hoping that we have saved the best for
4 last as well.

5 Doctor Rappaport represents Smith Kline
6 Beecham.

7 DOCTOR RAPPAPORT: Thank you, Doctor Bone.

8 Members of the Advisory Committee, Doctor
9 Fleming, Doctor Misbin, I really appreciate the
10 opportunity this morning to comment on the draft
11 guidance for the development of drugs for the
12 treatment of diabetes.

13 During the early '80s, I was a medical
14 officer in this division, and worked very closely with
15 Doctor Sobel and Doctor Bildstein. In fact, I
16 inherited Jim Bildstein's office for a short period of
17 time. They taught me the importance of open and
18 honest collaboration between scientists from the
19 division and scientists working for industry sponsors.

20 The draft guidance that we are discussing
21 today is the latest example of the division's effort
22 to forge a partnership with industry, so that we may
23 work together toward a common goal, to make better
24 therapies available to diabetic patients, therapies
25 with the potential to improve the health and well-

1 being of large numbers of patients in the United
2 States and throughout the world.

3 Last year, Doctor Misbin gave us and other
4 industry sponsors an opportunity to comment on the
5 early draft guidance, and we are happy that many of
6 our comments were incorporated in the current draft.

7 Regarding efficacy assessments, we agree
8 that consideration should be given to both mean change
9 relative to placebo and to assessments on the basis of
10 favorable response rates. For example, the proportion
11 of patients who achieve a 30 milligram per deciliter
12 decrease in fasting plasma glucose, or as another
13 example, a one percentage point change in reduction in
14 hemoglobin A_{1c}.

15 Over the past two and a half years, as
16 Doctor Misbin mentioned, antidiabetic drugs from
17 several new classes have been approved, and we must
18 now face the challenge of designing trials that will
19 help us determine which patients are the most likely
20 to benefit from each of these therapies or from
21 combinations of these compounds.

22 The guidance document begins to address
23 these issues, and we certainly look forward to further
24 debate on this topic.

25 The new diagnostic criteria for impaired

1 glucose tolerance and for type 2 diabetes have
2 recently been issued. As mentioned in the guidance
3 document, additional studies will be required to
4 determine the best ways to manage these patients,
5 based on the new criteria.

6 We expect that the division and the
7 committee will continue to engage in constructive
8 dialog with industry, with organizations such as the
9 ADA, and with public health agencies such as the
10 National Institute for Diabetes, Digestive and Kidney
11 Diseases, to develop appropriate clinical trials
12 designed to address these critical questions.

13 We at Smith Kline Beecham applaud the
14 Division's approach to working with industry toward
15 efficient development and approval of valuable new
16 therapies for diabetes, and we look forward to our
17 continuing fruitful collaborations with Doctor Misbin
18 and his colleagues, and to listening to the
19 committee's deliberations today.

20 CHAIRMAN BONE: Thank you very much.

21 This concludes the presentations by the
22 sponsors for the open public hearing. We will return
23 in 20 minutes at 11:15.

24 (Whereupon, at 10:57 a.m., a recess until
25 11:21 a.m.)

1 CHAIRMAN BONE: The remainder of the
2 morning session will be devoted to discussion. We got
3 into discussion a little bit on a number of points
4 after Doctor Misbin's presentation of his views on
5 these topics, but we mainly were trying to get
6 clarification, I think.

7 So, really, now we'd like to go into
8 discussion of issues per se.

9 I think first Doctor Fleming, however,
10 wanted to make some remarks regarding how we might do
11 this as a basis for proceeding.

12 DOCTOR FLEMING: Thank you, Mr. Chairman.

13 Again, I think the discussion has been
14 very helpful, but we've got more work to do. It may
15 be helpful, first of all, to, again, stress that we
16 are in the very early stages of developing this
17 guidance, and so we should not feel that we are on the
18 verge of having to settle any particular issue. In
19 fact, I suspect we are all going to go back and
20 scratch our heads a bit before we go too much further.

21 It would also be important to point out
22 the conventional approach that we now generally take
23 in the development or the evaluation of any therapy at
24 the FDA and, perhaps, to contrast and compare that
25 approach with some of the proposals that have been

1 made in this guidance.

2 Let us certainly affirm that the placebo-
3 controlled trial has been the gold standard for
4 evaluating the efficacy of a drug, and that can
5 certainly go a long way in giving us a sense of the
6 benefit that will be achieved, at least in the
7 intermediate term. There remains the challenge of
8 knowing what the durability is, and we certainly have
9 always asked that question.

10 We have not set down a firm set of
11 descriptions of what or how durability would be
12 defined. Certainly, we would like to have a cohort of
13 patients that were followed for a longer period of
14 time, so that we can see what the degree of durability
15 is, and in some cases if it appeared to be negligible
16 then that would be very pertinent. But, that is not
17 an absolute requirement, and I think the guidance says
18 that it's written, it's not specific on this point,
19 but certainly it is a very important consideration in
20 our evaluation of drug products.

21 The next point is to emphasize that we
22 have never insisted that a new therapy be superior to
23 existing therapies, and I don't think Doctor Misbin
24 was proposing that that be the typical approach that
25 be taken. Certainly, he was talking about comparisons

1 between an active therapy and then the experimental
2 therapy, but from a regulatory standpoint we are,
3 again, relying on the demonstration of effectiveness
4 relative to placebo as the starting point. And, when
5 appropriate, active-controlled trials certainly can
6 be. In other therapeutic areas they are mandatory,
7 for example, the development of an antibiotic for
8 streptococcal pharyngitis clearly requires that there
9 be active treatment, and we insist that there be, in
10 effect, an absolute effectiveness of a streptococcal
11 agent to get that indication, given that there are
12 alternatives. So, in certain exceptions there is sort
13 of a comparison made in the final analysis.

14 But here, we would acknowledge, generally,
15 that this is a multifaceted disease that has a number
16 of different subgroups which are poorly defined and
17 are likely to respond in very different ways with
18 different therapies, but ultimately physicians and
19 their patients should have the ability to choose among
20 these therapies and to have some assurance that they
21 will be using a therapy that is likely to work to some
22 degree, but the proof will ultimately be how that
23 individual patient responds to that treatment.

24 It takes us to the point about the level
25 of clinical significance, another very important point

1 to emphasize. We have had a great deal of difficulty
2 in defining what is and is not clinical significance.
3 The bottom line is, is that certainly you start with
4 statistical significance and you make a judgment as to
5 what that means.

6 We would have a hard time, I believe, in
7 defining what is a minimum level of improvement in
8 glycemic control that we could consider as a one phase
9 or a one-size-fits-all standard. As I mentioned
10 earlier, it's conceivable that we could have a therapy
11 that provides a minimal change, but with, essentially,
12 negligible risk, and that might have ultimately a
13 favorable benefit risk relationship.

14 And, that's, finally, the point I would
15 emphasize, that we evaluate drugs and ultimately make
16 the decisions about approvability on the basis of the
17 benefit to risk relationship, that we do not insist on
18 an absolute level of response, nor on comparing
19 favorably with another treatment, but that we look at
20 what a drug does for a population of patients, and
21 what the overall cost, in terms of safety and other
22 considerations, is.

23 So, those are just a few points that I
24 would make in terms of our standard approach. I think
25 that the guidance, the draft guidance that has been

1 written is largely consistent with that approach, but
2 in some ways may have given the impression that a
3 different set of approaches were being taken. And, it
4 remains for us in the next few hours to sort some of
5 the specific issues out with, perhaps, this
6 clarification added.

7 CHAIRMAN BONE: Thank you very much,
8 Doctor Fleming.

9 Doctor Bildstein, did you have anything to
10 add to that? All right, thank you.

11 All right. Doctor Hirsch?

12 DOCTOR HIRSCH: I'd like to begin my time,
13 but may I first ask a question as a sort of prelude to
14 this, of the remarks we just heard from Doctor
15 Fleming. Would you, under any circumstances, ever
16 sanction or suggest that the treatment of
17 streptococcal pharyngitis, as you mentioned, be
18 studied by the use of an antibiotic versus hot saline
19 gargles or nothing?

20 DOCTOR FLEMING: No, that's quite right,
21 and this really gets back to the principles of drug
22 development that I think Doctor Bone was asking that
23 we flesh out a bit more, about how you would start in
24 the early phases of assuring that you have a
25 reasonable probability of response in the population

1 that is being tested.

2 DOCTOR HIRSCH: Well, I want to take off
3 from that, if I may.

4 CHAIRMAN BONE: Could I ask --

5 DOCTOR HIRSCH: Yes, please.

6 CHAIRMAN BONE: -- just hold that just in
7 abeyance for a few minutes, Doctor Hirsch, because I
8 wanted to depart briefly from the planned outline in
9 a way that I think may help us go forward.

10 I'm going to construe our charge here from
11 this point through the rest of the day as not simply
12 providing some editorial comments or input on just
13 specific points in a draft guidance, but, really,
14 maybe going a little beyond that to looking at what
15 the committee and perspective sponsors would like to
16 have in the draft guidance, incorporating some of
17 these elements that we've seen, but maybe we want to
18 take a little broader view as to what the overall
19 thing might look like, and then fit some of these in,
20 and then maybe add some other questions or areas that
21 we want to talk about.

22 There's a couple of elements about
23 structure that were brought up earlier, and I'm not
24 going to talk about issues, but just more about
25 structure for a moment here, and I think I can clean

1 a lot of this up, if I haven't made a mistake, about
2 some structural aspects of this that might be
3 clarifying and help us get through the rest of the day
4 more efficiently.

5 So, if I could just take a minute or two
6 to do that.

7 It seems to me that there were a number of
8 points in Doctor Misbin's presentation and the
9 questions and the comments concerning that, and also
10 that came out of the sponsors' comments earlier, that
11 might be focused somewhat more if we, in effect,
12 looked at the structure in a more classical way for
13 guidance documents, which would be to look at pre-
14 clinical, phase I pharmacokinetic and pharmacodynamic,
15 phase II and phase III trials, and separated the
16 indications of type 1 and type 2 diabetes recognizing
17 that there would be substantial overlap, but
18 organizing the information in that kind of way.

19 I think that might be responsive to a
20 number of points the committee members raised earlier.
21 Would there be general agreement that that would be a
22 useful way to have the document organized? What we
23 have here is some really comments about phase III
24 trial endpoints for the most part, that were discussed
25 here, and that's certainly an important part of it,

1 but that kind of overall structure I think might be
2 useful, and maybe we don't need to have a lot of
3 discussion since nobody seems to be disagreeing with
4 that.

5 I think one other point that we might want
6 to just touch on briefly before we go into the more
7 specific discussion is, and this does get into the
8 meat a little bit, for purposes of what we've heard
9 earlier today, and for the most part up to now we've
10 looked at the indication -- treatment of diabetes
11 mellitus as largely controlling blood sugar in
12 diabetes mellitus. And, I think we may want to think
13 during the day, as we discuss this, about whether we
14 may want to regard this as a somewhat more complex set
15 of indications and may even distinguish between
16 adjunctive therapies, which have ameliorative effects
17 on co-morbidities, as well as simply directed toward
18 glycemic control, and I think this is where this
19 balancing came in between minimal effect on glycemic
20 control and potentially significant adjunctive effect.

21 So, if we could just bear in mind as we go
22 along that there might be a way of writing indications
23 that would permit a distinction between elements that
24 are -- aspects of treatment of this very complicated
25 problem, and treatment of everything all at once in

1 one trunk.

2 And, with that, Doctor Hirsch, please.

3 DOCTOR HIRSCH: Well, I don't know exactly
4 where my comments fit in that framework, but these are
5 some strongly held views that I'll be very brief and
6 tell you about them.

7 The first thing is, the issue of, you
8 know, -- that in our jobs as physicians,
9 investigators, FDA or whatever you are, is do no harm,
10 and this is not an ethical matter because of the
11 climate of the times, it's a fundamental ethical issue
12 of physicians, and always has been, and, hopefully,
13 will be. So, I cannot see the issue here, in terms of
14 putting people on placebo versus not, because I think
15 the ethical thing is incontrovertible would stop it
16 there.

17 But, fortunately for us, it turns out, I
18 believe, that it isn't only by an ethical
19 consideration, the better studies, it seems to me,
20 would utilize the following paradigm. One would take
21 a group of diabetics and give them ideal treatment,
22 and observe the ideal treatment because there may be
23 some issues there which will help in the next step,
24 which is a randomization into arm A and arm B.

25 And, arm A is ideal treatment, and you can

1 introduce a placebo element in that by different
2 colored capsules or whatever, and arm B is an
3 examination of the proposed new treatment, whether
4 that's monotherapy, polytherapy, whatever. The
5 endpoint doesn't bother me that much, it could be even
6 quality of life or whatever, so long as this is a
7 significant and important endpoint, but always you
8 measure against ideal therapy, and either your new
9 treatment is as good, or better, or worse, and we have
10 to talk about the degree of change of the things, but
11 this is what we are after.

12 Now, finally, one last comment, I think
13 it's extraordinarily important in these arms, in arm
14 B, the new treatment, to examine at the six to 12-
15 month interval, let's say, or whatever we think is a
16 specified interval, of what the time course is, and at
17 that point a decision made as to whether this is or is
18 not a durable therapy on the basis of an algorithm
19 which emerges by observations, let's say, in the first
20 half of the -- the last half of the first year of
21 treatment, as to what the duration should be for this.

22 So, I feel very strongly that what we were
23 told this morning is a very important message, and
24 should color very much what we suggest as guidelines.

25 CHAIRMAN BONE: Thank you.

1 Doctor Hirsch, if I could just ask you to
2 clarify something for me. Would you propose then,
3 let's say we have ideal therapy being whatever it is,
4 that patients would then be randomized to continue
5 ideal therapy or to be treated with this other therapy
6 plus this ideal therapy, would that be an additive or
7 a substitute for the ideal therapy?

8 DOCTOR HIRSCH: I see the first arm as
9 being a continuation of ideal therapy, but, perhaps,
10 with some alterations in terms of the color of the
11 drug or whatever it is to make a placebo effect, and
12 that arm B, whatever is suggested, in other words,
13 that new agent A should be used when you wear purple
14 pants, or when you dance, or whatever it is, anything
15 that anyone wants to do, and then we examine that
16 proposal in the light of the difference in whatever
17 results we wish, whether it's quality of life, or
18 frequency of hypoglycemic episodes or whatever, on
19 that basis.

20 CHAIRMAN BONE: Well then, let me ask you
21 a question, which I'm sure everyone in the audience is
22 thinking, is how would you determine whether the test
23 drug in that situation was beneficial if it were less
24 beneficial than what had been determined for those
25 individuals to be ideal therapy?

1 DOCTOR HIRSCH: Either it works by itself
2 or it's working by virtue of an interaction with the
3 other drugs, and that doesn't bother me that much.

4 CHAIRMAN BONE: Well, I guess what I'm
5 saying is, if you have -- if it's less -- if it's
6 effective therapy, but less effective than idealized
7 therapy for the individual, optimized therapy might be
8 another way of putting that for that individual, how
9 would you know, compared to what, how would you be
10 able to tell that it's doing something if it's only be
11 compared to something which is almost certainly going
12 to be better?

13 DOCTOR HIRSCH: It's got to be equally
14 better, even better or worse, and that's all I want to
15 know. If I want to examine pathogenesis or mode of
16 action, that's another kind of study.

17 CHAIRMAN BONE: So, you are really
18 advocating only approving a drug that was effective,
19 more effective or as effective than best available
20 therapy, and not approving a drug that would be
21 beneficial but not as good as the optimized therapy.

22 DOCTOR HIRSCH: I wouldn't take it and I
23 wouldn't approve it.

24 CHAIRMAN BONE: Okay.

25 Doctor Sherwin?

1 DOCTOR SHERWIN: Just to take off on that,
2 wouldn't it be better than to have three arms, to look
3 at optimal therapy, monotherapy with the ultimate
4 treatment, and the combination of the two, because one
5 therapy may not be as good by itself, but it may
6 amplify the optimal effect of the optimal treatment.
7 And so, wouldn't -- if you take that approach of
8 determining optimal therapy for a patient and then
9 dividing them up into a new therapy versus the
10 optimal, if you have a three-armed approach, and the
11 drug neither amplified optimal therapy, nor was as
12 good as the optimal therapy, then the drug would not
13 have a place.

14 DOCTOR MOLITCH: That's only going to work
15 if there are different mechanisms of action.

16 DOCTOR HIRSCH: That is correct.

17 Well, hold on, if the sponsor proposes
18 that this is adequate monotherapy, that should be
19 tested. If, on the other hand, the sponsor proposes
20 that this is not meant to be for monotherapy, but in
21 combination with another, that should be tested. If
22 the sponsor wishes both to be tested, that ought to be
23 tested.

24 But, what we are asking for is a result
25 and a mathematically definable endpoint under

1 circumstances where ideal therapy is tested.

2 Now, by the way, early in the study, if
3 things turn out to be much less than ideal, then one
4 stops the study, and those criteria should be
5 established as well.

6 DOCTOR SHERWIN: You would want a placebo-
7 controlled trial somewhere along the way earlier on,
8 is that right?

9 DOCTOR HIRSCH: Perhaps, in normal
10 subjects, to look at pharmacodynamics or whatever, but
11 I do not want to ever take a diabetic patient and
12 place them under harm.

13 Now, you may ask me in turn, what
14 constitutes arm? Well, all I know is that every
15 diabetes association in America recommends that
16 diabetics be immediately diagnosed, because of the
17 lurking immense potential for damage without diagnosis
18 and treatment. So, I would be very, very conservative
19 in taking diabetics and saying, please don't exercise,
20 don't change your diet, don't eat differently, don't
21 take drugs, don't do anything, until I can find out
22 what I want to know about you.

23 CHAIRMAN BONE: I think Doctor Fleming had
24 a comment which relates to policy probably.

25 DOCTOR FLEMING: Well, we don't have to

1 make the point again about our difficulty with a
2 comparative approach as you are proposing, I think
3 Doctor Bone pursued that. I guess, of course, at the
4 bottom of this is your concern about the ethics of
5 taking a patient off therapy.

6 I guess, personally, I think we are still,
7 unfortunately, at the stage of clinical equipoise, in
8 terms of type 2 diabetes. Yes, we know that we can
9 reduce microvascular complications probably on the
10 basis of the DCCT, but that's all we can conclude, I
11 think, or all we can infer from the DCCT about
12 treating type 2 diabetics, that you may reduce -- you
13 probably will reduce microvascular complications by
14 affecting better glycemic control.

15 Now, going back to the original UGDP
16 study, as you well know, the sulfonylureas and the
17 biguanides were tarnished by the excess in
18 cardiovascular mortality, so we might be getting some
19 benefit with glycemic control that ultimately, going
20 back to all the other effects that these drugs, both
21 classes of these oral agents, have on other relevant
22 physiologic areas, we may be doing more harm than
23 good.

24 I agree with what you said --

25 DOCTOR HIRSCH: You're only talking about

1 endpoints, but not structure or design.

2 DOCTOR FLEMING: -- well, I'm really
3 speaking to the ethics, and what is ethically
4 permissible, because that's driving our consideration
5 of alternate approaches to the placebo-controlled
6 trial.

7 Now, just to get to my practical approach,
8 I believe that it is not unethical to take patients
9 off for, say, three months, maybe a fairly mild group
10 for as long as six months.

11 DOCTOR HIRSCH: I think it is unethical,
12 but more importantly I think it's not necessary.

13 DOCTOR FLEMING: Well, I'm afraid it is
14 necessary for us to get the kind of information we
15 need, that we do need to conduct placebo-controlled
16 trials, at least for a short period of time --

17 DOCTOR HIRSCH: Why?

18 DOCTOR FLEMING: -- in diabetics.

19 DOCTOR HIRSCH: Why?

20 DOCTOR FLEMING: Because we can't -- we
21 cannot assess the treatment effect. We would be
22 automatically locked into a comparative paradigm,
23 which would mean that we could only approve drugs
24 which were as good as current therapies. The
25 combination approach wouldn't really get us there,

1 where you are testing drugs in the same class.

2 So, that would mean that we would be
3 considerably hampering the development of drugs which
4 ultimately may prove to have great value.

5 I don't think that there is an ethical
6 problem in taking a patient off an oral agent, which
7 may be doing, unfortunately, things that are far worse
8 than the microvascular complications that its
9 improving.

10 DOCTOR MARCUS: May I put this discussion
11 into some perspective, and it may be that --

12 CHAIRMAN BONE: This is Doctor Marcus
13 speaking.

14 DOCTOR MARCUS: -- it may be that -- and
15 you may be right if you accuse me of that, but you may
16 say that I'm only thinking about a very specialized
17 case, but I think that it's not so specialized, or at
18 least a number of people who represent what I'm going
19 to describe is not a very small percentage.

20 As you know, I'm a bone head, I'm not
21 particular a diabetes person, but I do see diabetics
22 in the setting of going every week to the endocrine
23 clinic at the Veterans Affairs Hospital where I hang
24 out, and I would say that we are talking about
25 glycosylated hemoglobins of eight or 8.5, I say, what

1 planet are these people on? Our average glycosylated
2 hemoglobins are like 14 or 15, and we don't do the
3 experiment of taking people off medication to see --
4 as part of a placebo-controlled trial, but the
5 experiment is done for us by the pharmacy not --
6 because the VA only gives them, you know, 30 or 60
7 days worth of medication at one time, and they don't
8 get the refill.

9 But, I'm here to tell you that being off
10 of medication for three months has absolutely no
11 impact whatsoever on glycemic control of these people,
12 their glycosylated hemoglobins are 13 when they have
13 bene taking the medication, and they are 13 three
14 months after they've stopped the medication.

15 That doesn't mean that they are not
16 getting some elements of -- I won't ever say ideal
17 care, but some sort of optimal things, that is, their
18 feet are being examined, and their foot care is being
19 managed, they are getting angiotensin converting
20 enzyme inhibitors because they have microalbuminuria,
21 attempts are being made to control the lipoproteins
22 and their blood pressures and other elements of
23 primary care medicine, you know, they are getting
24 their vaccination for pneumococcus and for influenza
25 and stuff, the only thing that seems not to be treated

1 is specifically their glycemia and, assuredly, their
2 obesity, which is a complex reason why they don't get
3 effective control of that.

4 So, I think that there are, perhaps, in a
5 patient population which is huge like that, there is
6 no problem, I see ethically, with doing -- if somebody
7 has -- some pharmaceutical company has a drug which is
8 going to be effective in that population, I have no
9 problems whatsoever against using it against placebo.

10 So, it's important to categorize the types
11 of patients you are dealing with.

12 I also -- I tend to agree with Doctor
13 Fleming, that if you are really dealing with a
14 population whose glycosylated hemoglobins are, you
15 know, eight or below, that for a three-month period I
16 don't see much problem there, but then in the
17 intermediate zone I agree with Doctor Hirsch exactly.
18 But, I think it all depends on the types of patients
19 you are dealing with, what type of study you are going
20 to incorporate.

21 CHAIRMAN BONE: Doctor Davidson, and then
22 back to Doctor Hirsch.

23 DOCTOR DAVIDSON: Well, the first advice
24 I have for your patients in the VA is to move to
25 another hospital where treatment is better, you know,

1 because in 1998 that is clearly unacceptable.

2 The second thing is that, you know, we are
3 talking about apples, oranges, pears and everything
4 else, and I think that there is trials where placebo
5 control is very important, and there are trials in
6 which, you know, the natural history of type 2
7 diabetes, you know, type 2 diabetes is a long story,
8 you know, and we know that after about five to seven
9 years of type 2 diabetes, you know, if you stop one of
10 the agents that works very well, you know, I think
11 oral agents are good drugs if doctors know how to use
12 them, and if patients take them appropriately.

13 You know, I think the UGDP was a study not
14 designed to look at cardiovascular endpoints, and if
15 you look at the control of those patients, you know,
16 and if you look at the DCCT, even though at the end
17 the cardiovascular events were not statistically
18 significant, if you look at the number of MIs, there
19 were three times more in the conventionally treated
20 group than in the intensive treated group, and the
21 cardiovascular events in general were more.

22 Then, I think oral agents are good drugs
23 if they know how to use them, and if we take diabetes
24 control into consideration, you know, and we
25 extrapolate from there, it's a different story.

1 But, we are talking about different phases
2 of studies. We are talking about phase II, where I
3 think ideally a study should be done with placebo
4 control, and then you go to phase III, depending on
5 where the patient is, I don't see a problem with what
6 Doctor Misbin is suggesting, you know, a study where
7 a patient is partially well controlled, you know, with
8 an A_{1c} in the range of eight to nine, you know, or
9 nine to ten, and instead of taking that patient off
10 from that drug, you know, have an arm where you add
11 either placebo or the active drug.

12 You know, and there are many ways of
13 designing studies, you know, I have no objection to
14 the design study that was given before, patients, you
15 know, with three-armed study, but I think this is not
16 a simple problem, it's a very difficult and complex
17 problem, and there are different stages where we need
18 to do it with patients with type 2 diabetes.

19 CHAIRMAN BONE: Additional -- Doctor
20 Hirsch, I think, wanted to comment.

21 DOCTOR HIRSCH: Doctor, I don't want to
22 respond to each one, because it would be forever, I
23 think that's your role rather than mine, but Doctor
24 Marcus reminds us that there really is no such thing
25 extant as placebo versus drug study, because,

1 inevitably, people will lose weight, change diets, get
2 their toes taken care of, whatever it is, so you will
3 understand that we are making a very arbitrary thing
4 of just in the complexity of a whole system of
5 treatment we really will have drug X, or drug Y, or no
6 drug, in one little element of the overall treatment
7 of the same.

8 But, I would like to hear some
9 conversation on what is the fundamental scientific,
10 absolute necessity of a placebo versus a drug trial in
11 this circumstance, when, in fact, that's not the way
12 are going to be treated in the long run, they are only
13 going to be getting a complex set of things happen to
14 them.

15 CHAIRMAN BONE: Well, maybe I'll just talk
16 a little bit about -- or, Doctor Critchlow, why don't
17 you --

18 DOCTOR CRITCHLOW: Well, it seems to me
19 anyway that it depends on whether the drug is -- there
20 are different considerations if the drug is a new
21 class, with a new mode of operation, I would think the
22 desire for a placebo control would be stronger than,
23 perhaps, in a situation where it's a drug that has
24 the same method of action or the same whatever as
25 things that are currently out there.

1 For things that are currently -- or a drug
2 that is to operate with the same mechanism as
3 something that's existing, I would think that
4 certainly in a shorter phase II trial you might want
5 a placebo, but in a phase III you'd want either the
6 relevant comparator plus, perhaps, an arm of the
7 relevant comparator, plus the active drug, if that's
8 appropriate, but for a drug where there's not much
9 information known, in terms of either action, you
10 would clearly want certainly more placebo trials,
11 either in the -- certainly in a phase II setting, but
12 maybe in a phase III setting, where there is a placebo
13 to begin with and then you would cross over to
14 something, but I think one needs to take into account
15 what the circumstances are for that particular drug
16 that's being tested.

17 CHAIRMAN BONE: Doctor Cara?

18 DOCTOR CARA: I like your comment, and I
19 think Doctor Zawadzki had alluded the fact that maybe
20 we need to separate all the apples and oranges that we
21 are talking about and start defining specific
22 situations or specific diagnostic entities or whatever
23 it is that we need to do to better define the issues
24 at hand, because we are talking about different
25 situations, and I think that you are talking about new

1 classes of drugs versus drugs that work by well-
2 recognized mechanisms, or accepted mechanisms, or
3 whatever you want to call it, is maybe a first step in
4 that direction.

5 CHAIRMAN BONE: In the drug development
6 and evaluation process, I think we have to be mindful
7 that a lot of things have to be accomplished apart
8 from looking at the primary endpoint of the phase III
9 trial. We need to understand the pharmacokinetic and
10 pharmacodynamic behavior of the drug, not only in the
11 type of short-term data that we get in phase I, but in
12 the longer-term exposures where changes in metabolism,
13 for example, or in physiologic compensatory mechanisms
14 may be very important.

15 That sort of analysis can be seriously
16 confounded by co-administration of another active
17 agent. It may not be absolutely impossible to conduct
18 that kind of study, but the fact that there is a
19 constant element of interaction that has to be taken
20 into account would make it extremely difficult. I
21 think certain types of information probably would be
22 very difficult to isolate with an active agent
23 present.

24 One of the most important things to obtain
25 information about is the adverse experiences which are

1 such an important consideration here, especially when
2 we are talking about drugs for adjunctive therapy of
3 type 2 diabetes, where a major point -- one of the
4 major points made earlier today was that comparative
5 safety or innocuousness, if I could put it that way,
6 of an agent would be an important consideration in the
7 evaluation of a modestly or moderately effective
8 agent.

9 And, again, when one looks at the adverse
10 experience profile of a drug like that, it would be
11 very important to have placebo-controlled data and
12 monotherapy data, because if you don't it would be
13 extremely difficult, it seems to me, to determine
14 whether one was seeing a problem attributable to the
15 drug itself, or due to an interaction.

16 And, since we are probably not going to be
17 in a position of having a trial of adequate size and
18 scope, with every conceivable, possible co-
19 administered drug, in adequate numbers to determine
20 whether we'd get the interactions by looking at
21 potential interactions with every kind of drug, or
22 whether we are looking at an activity of the drug
23 itself.

24 I think the efficiency of the clinical
25 development process, let's say at the very least,

1 would depend on having the placebo-controlled
2 information at several crucial points in the
3 development process.

4 Having said that, I think all of us
5 recognize that we would not like to see patients who
6 were on reasonably good control allowed to deteriorate
7 to a substantial extent for a long period of time,
8 simply for the sake of conducting a trial. So, I
9 think there is probably universal agreement that what
10 really we are asking of the sponsors here is not to
11 abandon, perhaps, the placebo-controlled trial, but to
12 be very mindful of this concern about the long-term or
13 intermediate-term safety of patients in these trials,
14 so that a variety of design strategies might be
15 employed, and we've all thought of several examples.

16 Probably the best approach here is to, I
17 would think, enunciate the principle that the safety
18 and well-being of those patients is of paramount
19 importance, and, perhaps, not to have a guidance
20 document that limits the sponsor's options in
21 designing trials, mindful of that safety, to a single
22 choice.

23 Perhaps, we could say that the sponsor
24 would be expected to provide designs where this is
25 looked at in a careful way, and I think IRBs all over

1 would take the same view.

2 Certainly, there would be positive control
3 trials with all the new drugs one could imagine, and
4 it would be combination, or additive therapy is done,
5 because that's, in fact, how most of these drugs are
6 going to be used. But, at a certain stage in
7 development, it's going to be, I think, the price that
8 we would pay in uncertainty of interpretation of
9 information would be great, and the trials could
10 probably be designed so that the exposure of
11 previously well-controlled patients to protracted
12 periods of poor control would be minimized or
13 eliminated, and still get that kind of comparative
14 information.

15 Doctor Molitch, then Doctor Fleming.

16 DOCTOR MOLITCH: I certainly agree that in
17 phase II we certainly need placebo-controlled trials,
18 and one thing that hasn't been brought up is that we
19 are actually not faced with any lack of new patients
20 with type 2 diabetes. There is an epidemic of type 2
21 diabetes of untreated patients out there, that then
22 come to clinical attention.

23 And, I think that we have a large number
24 of patients that could be entered into trials who
25 were previously undiagnosed or untreated, who could

1 then be randomized to very good dietary monitoring and
2 intervention as the placebo arm, and the same type of
3 dietary intervention plus the active drug for the
4 initial phase II type of study.

5 I think for phase III studies, we may have
6 a much more prolonged type of treatment, and I think
7 a year's study with an active comparator is a very
8 reasonable thing. You don't necessarily need the
9 placebo arm for that type of long-term study, but I
10 think in phase II we absolutely need it, and I think
11 that with a good diet, as in the six-month phase II
12 studies, is a very reasonable thing to do.

13 I would not be terribly happy about taking
14 patients who are under good control, taking them off
15 drug, and then entering them into a phase II study for
16 six months.

17 But, we really have no lack of new
18 patients coming in.

19 CHAIRMAN BONE: I think one other issue we
20 may need to be mindful of is the overall policy
21 position of the Agency regarding this question of
22 placebo versus active comparator trials.

23 Doctor Fleming?

24 DOCTOR FLEMING: Yes, I agree with both
25 your comments and Doctor Molitch's.

1 To put it in a different way, I did not
2 want to give the impression that we would not rely on
3 comparative trials. In fact, we have to.

4 I think the repaglinide development is a
5 good example of how this might be done. It takes
6 relatively few patients to show efficacy, and so you
7 can usually do that in phase II, and this goes back to
8 the point that Doctor Davidson is making, it doesn't
9 have to be one or the other, it's both, you need both
10 placebo-controlled trials for a limited period of time
11 to define the treatment effect, but then you need a
12 much larger number of patients to describe the safety
13 profile.

14 Again, the Prandin NDA is a good example.
15 We had the expectation that because of its very
16 rapidly acting and offset of action property that it
17 would have a lower incidence of hypoglycemia. Now,
18 they conducted five large comparative studies with
19 major or with other frequently used oral agents, and
20 they were not able to even show a difference in the
21 incidence of severe hypoglycemia. There was a trend
22 in that direction, but they did not -- it did not
23 reach statistical significance.

24 But, these were very large trials, and it
25 just shows that it becomes difficult, even with that

1 large number of patients, to show relatively small, or
2 to demonstrate differences between treatments when
3 there is a fairly infrequent event like severe
4 hypoglycemia.

5 But, I think that would be the general
6 approach, that you do small placebo-controlled trials
7 in the appropriate populations where it's ethically
8 permissible, these are going to be followed by
9 comparative trials, not to show efficacy, and that was
10 not the point of the Prandin active-controlled
11 studies, but to show or to contribute to the
12 understanding of the drug safety.

13 CHAIRMAN BONE: Doctor Hirsch, anything?

14 DOCTOR HIRSCH: Just a very brief one.
15 Doctor Molitch suggests a very interesting point, and
16 that is that there's a subset of patients in whom
17 ideal therapy may be construed as diet, and if that,
18 in fact, is the case, one can study as one arm of this
19 thing with placebo, and the other arm can be diet with
20 the drug, so that would fulfill your requirements for
21 placebo versus no drug, but some therapy is
22 entertained.

23 In fact, if you don't do that you are
24 fooling yourself, because the moment you see a patient
25 you've instituted a kind of treatment, so simply that

1 itself is an important interaction. So, I think we
2 are sort of -- in answer to your last thing, it's too
3 bad about the Prandin then, but that's the life
4 situation, big groups of patients taking all sorts of
5 things, doing things, and we want to know is the
6 institution of this new treatment beneficial vis-à-vis
7 hypoglycemic episodes or not. The answer was no, it
8 wasn't statistically significant. Stop.

9 CHAIRMAN BONE: One other technical
10 problem, the people who are responsible for
11 calculating sample sizes will be mindful of this, the
12 grave difficulties in deciding what constitutes
13 equivalence in positive-controlled trials. That's a
14 challenging and unsolved problem, which I don't think
15 the committee is going to be able to solve today, but
16 it's one we must be mindful of, and I think that's
17 another consideration in the mind of the Agency when
18 they, as a matter of policy, did not restrict
19 themselves to positive-controlled trials for this sort
20 of evaluation.

21 I think we have dealt with some of these
22 issues that came up in the morning's presentation to
23 a certain extent here. What I'd like to suggest that
24 we do is go into the section that we originally had
25 planned for 10:45. I think some of these will be

1 topics that we may not have to spend a great deal of
2 time on, but I'd like to make sure that we've covered
3 these. There were several issues that Doctor Misbin
4 indicated he particularly would like input from. The
5 committee may very well have the idea that there might
6 be some additional points on which we'd like to have
7 input, and we will, I'm afraid, have to presuppose
8 that everyone has reviewed the original draft.

9 Doctor Marcus?

10 DOCTOR MARCUS: Yes. I'm happy to kick
11 the ball off here, and just to tell you that I'm a
12 little uncomfortable with the apparent relegation to
13 secondary status of measurements of blood glucose,
14 solely in favor of glycosylated hemoglobin. The
15 reason for that, actually, when it came to light, I
16 was reading on the airplane last night, rather than
17 sleeping, the Diabetes Care issue, February, 1998, and
18 I just happened to notice a paper here, "Correlations
19 of Glycosylated Hemoglobin with Average Blood
20 Glucose," and there's a table here showing, this was
21 all in type 1 diabetics, but if one monitored over
22 time the correlation between changes in average blood
23 glucose, and changes in glycosylated hemoglobin, we're
24 talking about correlation coefficients ranging from .4
25 to .6, in other words, that the glycosylated

1 hemoglobin could account for somewhere up to maybe 36
2 percent or so of the variance in changes of average
3 blood glucoses.

4 Now, I don't know, a person who is an
5 advocate for glycosylated hemoglobin may say, that
6 just shows you how bad blood glucose measurement is,
7 on the other hand, you could say the same thing in
8 reverse. Therefore, I think it would probably be
9 intelligent to have both blood glucoses and
10 glycosylated hemoglobins appear as primary endpoints
11 in this study, and I don't know that this experience
12 in type 1 diabetes would necessarily transfer to type
13 2 diabetes, but I'd wager that it would. And so, in
14 the absence of that information I think we shouldn't
15 just focus exclusively on hemoglobin A_{1c}.

16 CHAIRMAN BONE: Doctor Sherwin.

17 DOCTOR SHERWIN: I haven't seen that
18 study, so how often was the glucose measured, and how
19 -- is this home monitoring measurements, or is this
20 laboratory measurements in the hospital, because I
21 think that if they are home glucose measurements you
22 are really getting selected numbers, and, really, I
23 think the type 1 patients, the problem has been,
24 actually, I think, that in people -- the best data is
25 from the DCCT, because it was done in type 1 it's much

1 easier to assess control in type 1, I think, with
2 Glycohemoglobin, so I would argue the opposite way,
3 that in type 1s it's going to be very hard to use
4 glucose levels because they are so variable, whereas,
5 in type 2 diabetes, actually, fasting glucose is not
6 a bad index of control because it tends to be
7 constant.

8 The problem with it is it doesn't take
9 into account postprandial hypoglycemia, and in the
10 early stages of diabetes that's a dominant feature.
11 So, I don't know, I mean, the poorly controlled type
12 2s is probably a pretty good measure of control, and
13 type 1s I'd be very skeptical.

14 CHAIRMAN BONE: Doctor Cara?

15 DOCTOR CARA: I agree with the issue of
16 blood glucose determinations, and maybe, you know, I'm
17 shaded by the fact, or I'm influenced by the fact that
18 we see a lot of adolescents who often times are not
19 entirely, should we say, truthful in their blood sugar
20 measurements.

21 But, I think that the -- it is, in fact,
22 a problem in terms of the validity of the measurement,
23 and I think the ability to do Glycohemoglobin
24 determinations has been a tremendous advantage to us,
25 because we can finally objectivize, if you will,

1 control.

2 DOCTOR MARCUS: I have no doubt about
3 that, I mean, I certainly know enough about it to know
4 that glycosylated hemoglobin has been a bone, and it
5 certainly is for me, my only question was whether we
6 wanted to throw out or relegate completely to a back
7 water blood glucose, which the guidance document seems
8 to have done. I was just trying to make a case that
9 it would be good to have glucose measurements as well.

10 CHAIRMAN BONE: And, maybe what we need to
11 do is to define in which sort of situations of blood
12 glucose determinations might be appropriate, or in
13 which situations they may not. Again, you know,
14 differentiating between, perhaps, type 1 and type 2.

15 DOCTOR MARCUS: Well, absolutely, and I
16 have to say that the way I view this is almost
17 exclusively from the type 2 perspective.

18 CHAIRMAN BONE: Doctor Molitch?

19 DOCTOR MOLITCH: I think the only way that
20 blood glucose can be used as a measure, and the reason
21 why it had good correlation in DCCT was that there
22 were seven point correlations done where blood sugars
23 were measured pre and postprandially in a capillary
24 tube that was sent to a central laboratory for
25 measurement of the glucose.

1 And, I think under those objective
2 conditions it has pretty good correlation. I think we
3 know that home glucose monitoring has lots and lots of
4 problems, and I would be very hesitant to use that as
5 a major outcome. It could certainly be a secondary
6 outcome.

7 I think a primary outcome could be this
8 more objective measurement of the glucose with a seven
9 point testing every month or whatever was decided, it
10 could be a code system, primary outcome.

11 DOCTOR MARCUS: Presumably, in a phase III
12 clinical trial they would do more than just home
13 glucose monitoring.

14 CHAIRMAN BONE: Remember that when we are
15 talking about the primary efficacy variable here, we
16 can only be talking about one for a trial in most
17 cases, because a sponsor has to pick an efficacy
18 variable with which they are going to live or die, and
19 if they have two, when they have an either/or, they
20 are going to have to pay a big penalty on their
21 multiple analyses.

22 So, in general, the trial design is going
23 to pick a single measurement that will be the
24 determinant of whether the drug has been effective or
25 not, in general. So, I think it's a question of

1 hierarchy here.

2 DOCTOR MARCUS: The -- trial was powered
3 for primary variables.

4 CHAIRMAN BONE: Well, that may well be,
5 but that wasn't the usual kind of drug testing trial
6 that we are talking about here, and I think that,
7 Doctor Marcus, would you object to ranking
8 glycosylated hemoglobin higher than blood glucose
9 measurements if somebody has to just pick one?

10 DOCTOR MARCUS: I have no objection to any
11 of this. I just want the question to be considered
12 thoughtfully and not to have arbitrarily glucose
13 thrown out.

14 CHAIRMAN BONE: Okay.

15 I think glycosylated hemoglobin has to be
16 number one, because that's the only one that's
17 actually been tied to development of long-term
18 complications. So, I think that has to be the primary
19 outcome variable.

20 DOCTOR MARCUS: I have no problem, that
21 certainly is true.

22 CHAIRMAN BONE: Yes, okay.

23 The section we're discussing here are the
24 criteria and the clinical significance. We had had
25 some discussion earlier, trying to have some

1 clarification about what was meant by that reference
2 to historical information about the sort of change in
3 glycosylated hemoglobin that had been approved. I
4 think if I understood Doctor Fleming's remarks well,
5 that did not mean that that's a threshold which has
6 been adopted by the Agency.

7 I think one of the themes that was
8 recurrent in this morning's earlier discussion was the
9 idea of taking into account, not only the change in
10 glycosylated hemoglobin, but also other beneficial or
11 harmful effects, and I think it's very challenging to
12 try to write a guidance document which would in some
13 way relate all those potential variables, but I think
14 it would be useful, both to the sponsors and the
15 Agency, to have discussion from the members of the
16 committee about how they would play off changes in
17 glycosylated hemoglobin against changes in frequency
18 of hypoglycemia in type 1 diabetics, presumably, and
19 changes in glycosylated hemoglobin and potential other
20 adjunctive beneficial effects that we might see with
21 co-morbid conditions.

22 Doctor Molitch.

23 DOCTOR MOLITCH: I'm not sure we are there
24 yet, are we done with glycosylated hemoglobin to begin
25 with?

1 CHAIRMAN BONE: Well, I'm sort of
2 continuing with glycosylated hemoglobin, but go ahead,
3 please.

4 DOCTOR MOLITCH: Well, I mean, I think
5 there are two other issues just dealing with
6 glycosylated hemoglobin.

7 CHAIRMAN BONE: Please.

8 DOCTOR MOLITCH: One is, do we look at an
9 absolute percentage change, or do we in some way have
10 to take into consideration the baseline glycosylated
11 hemoglobin and think about a percentage change from
12 baseline. That's one issue. And then, the second
13 issue is the actual assay that's used, and I think
14 that many in the audience realize that every
15 glycosylated hemoglobin assay is not necessarily the
16 same, and that, certainly, if we are going to be
17 recommending this as our primary outcome that it
18 should be a well-validated assay that can be in some
19 way tied to the DCCT assay, and that that kind of
20 validation would be necessary in part of any study
21 that's being designed.

22 CHAIRMAN BONE: I think we would all agree
23 with the latter point. What about the first point,
24 that the -- the question of whether a specific amount
25 of reduction in glycosylated hemoglobin versus a

1 relative reduction in taking into account the
2 baseline, how do the members of the committee feel
3 about that?

4 Doctor Cara, it looks like he wants to say
5 something. No?

6 DOCTOR CARA: No, I think it's a good
7 question, because, obviously, the significance of the
8 Glycohemoglobin drop depends to a large extent on what
9 the baseline is, and I'm torn on the one hand between
10 the demonstration from the DCCT that any drop in
11 Glycohemoglobin carries with it a significant impact
12 on complications, whether it be, you know, half a
13 percentage, one percentage, two percentage points or
14 whatever.

15 For that reason, I would be more inclined
16 to use an absolute value, because of the fact that, as
17 I said, I think any drop in Glycohemoglobin carries
18 with it a long-term consequence.

19 I would propose that a level of, you know,
20 greater than half a point is probably significant.

21 CHAIRMAN BONE: Well now, would that be
22 greater than half a point in starting at 15?

23 DOCTOR CARA: At any point.

24 CHAIRMAN BONE: At any point.

25 DOCTOR CARA: At any point.

1 CHAIRMAN BONE: And, would it be -- what
2 would you feel about a smaller drop in patients who
3 started off under relatively good control?

4 DOCTOR DAVIDSON: Can I ask for a
5 clarification --

6 CHAIRMAN BONE: Yes.

7 DOCTOR DAVIDSON: -- you know, for your
8 question?

9 You know, the first thing is that from
10 placebo or from baseline, you know, first question,
11 and second is, you know, when we talk about studies we
12 talk about the average drug from -- you know, from the
13 group, and not for individuals.

14 DOCTOR CARA: Let me answer that question
15 that you just asked in, perhaps, a different point of
16 view. I would be more impressed with a patient that
17 dropped, you know, two percentage points and goes from
18 14 to 12 than a patient that goes from eight to 7.5,
19 because I think theoretically the larger drop in the
20 higher Glycohemoglobin range is going to be more
21 significant.

22 CHAIRMAN BONE: I'm sorry --

23 DOCTOR CARA: So, the question of --

24 CHAIRMAN BONE: -- I guess the question I
25 had was, if they had to --

1 DOCTOR CARA: -- a smaller drop --

2 CHAIRMAN BONE: -- if they had the same
3 percentage drop.

4 DOCTOR CARA: Clinically, it doesn't
5 really carry that much of an impact.

6 CHAIRMAN BONE: So, you are saying, any
7 drop at all is good.

8 DOCTOR CARA: Any drop at all is good.

9 CHAIRMAN BONE: Okay.

10 Doctor Davidson?

11 DOCTOR DAVIDSON: You know, you didn't
12 answer my question, you know, my clarification. Is
13 that from baseline, is that from placebo, and, you
14 know, is this the average drop in the trial? What's
15 -- you know, you need to identify the test parameters.

16 DOCTOR CARA: I don't think we've gotten
17 there yet.

18 CHAIRMAN BONE: I think I'm asking you to
19 give --

20 DOCTOR DAVIDSON: Well, I think that, you
21 know, number one, if you look at every trial, the
22 higher the A_{1c} the larger the drug, you know, and,
23 therefore, I think we need to take the median from the
24 trial in the A_{1c} drug, and I would like to see the
25 drug not from placebo, but from baseline personally.

1 CHAIRMAN BONE: From personal baseline,
2 that goes back to this issue of what kind of control
3 we have. Obviously, people will find this difficult
4 if there did turn out to be in the study, after the
5 fact, when the data was analyzed, a slight rise in the
6 placebo group that they might find a larger drop, a
7 difference between the treatment in placebo group than
8 they did between the treatment and baseline.

9 Of course, that's why they have placebo
10 groups, I guess.

11 Doctor Hirsch.

12 DOCTOR HIRSCH: Just a brief comment. It
13 would seem as though you can only answer what you are
14 getting at if you knew the exact mathematical
15 relationship between incidence of complications versus
16 A_{1c} hemoglobin.

17 Now, if you don't know that you can't
18 answer your question. If you do know that, if it's a
19 straight line it's absolute drop that counts, if it's
20 a curvilinear relationship then you've got to do
21 something else.

22 So, I mean, I think an algorithm for the
23 solution of this problem should be an and --

24 DOCTOR CARA: It's a semi-straight line.

25 CHAIRMAN BONE: It's been called to my

1 attention that Doctor Lachin, is it?

2 DOCTOR MOLITCH: Lachin.

3 CHAIRMAN BONE: Lachin, is here, who was
4 the DCCT statistician, and he may be able to actually
5 answer that question. So, we'll depart slightly from
6 our usual procedure and ask him to briefly do so.

7 DOCTOR LACHIN: Can I show a couple of
8 slides?

9 CHAIRMAN BONE: Very concisely, please.

10 DOCTOR SHERWIN: You mean we are going to
11 have data?

12 DOCTOR LACHIN: Okay.

13 I'm John Lachin -- well here, I have a
14 slide that shows you this, I'm the Director of the
15 Biostatistics Center and Professor of Statistics here
16 at George Washington University, and I was the
17 Director of the DCCT and the EDICT Coordinating
18 Centers, and if anybody wants to reach me that's my E-
19 mail address.

20 I'd like to briefly point out that the
21 DCCT has had a series of publications relating to the
22 relationship of glycemc exposure and the risk of
23 complications. The major paper appeared in Diabetes
24 in 1995, and for those of you who are interested, all
25 of the details, statistical analyses, and the actual

1 raw data files are available from the National
2 Technical Information Service. If you write to the
3 NTIS in Springfield, Virginia, and you ask for these
4 documents, you can purchase them for a nominal fee.

5 We also conducted analyses relating
6 hypoglycemia, both in a separate paper related to
7 hypoglycemia, and also in a paper relating adverse
8 events in the DCCT, and also all of that data is
9 available from the National Technical Information
10 Service.

11 Now, the question is, what is the
12 relationship between glycemia and complications, and
13 first of all people have asked, how did we come up
14 with the curve that we presented in our regional
15 paper. The first thing we did was to look to see what
16 was the nature of the relationship between the risk of
17 complications and the level of A_{1c} , and what we
18 determined is that when you looked at the log rate,
19 and this is an instantaneous risk, versus the log of
20 the mean A_{1c} , the relationship was nearly linear.

21 And, this just shows the deciles of risk,
22 but, in fact, we had six monthly evaluations of
23 retinopathy in the DCCT, and we had, therefore,
24 thousands of observations, and when you fit a straight
25 line to those thousands of observations this is what

1 you obtain, a linear relationship between the log of
2 risk versus the log of the mean A_{1c} .

3 So, what this demonstrates is that a
4 proportionate reduction in risk is associated with a
5 proportionate reduction in A_{1c} . And, if you take this
6 relationship and now plot it by exponentiating both
7 the log of the weight and the log of the A_{1c} you then
8 get a simple exponential curve, and that simple
9 exponential curve demonstrates that there is a 43
10 percent risk reduction associated with a ten percent
11 lower value of HBA_{1c} , so we do reduce the A_{1c} from ten
12 to nine, or from nine to 8.1, or from eight to 7.2,
13 you are associated or you are encountering a 43
14 percent reduction in the risk of retinopathy
15 progression.

16 We saw the same thing for other
17 complications, whether it was a three-step progression
18 in retinopathy or the appearance of SNPDR, significant
19 non-proliferative diabetic retinopathy, or
20 microalbuminuria or albuminuria.

21 And, based on that what we then have is
22 the fact that a fixed -- now I'm looking for the one
23 critical slide that I hoped to show today, just a
24 second here, here it is -- we talked about a .7
25 reduction in A_{1c} as demonstrated by acarbose, the

1 question to me is, well, a .7 percent reduction from
2 what?

3 If it's a .7 percent reduction from an A_{1C}
4 of 12, then that's a 5.8 percent reduction in the A_{1C} ,
5 which would be associated with a 27 percent reduction
6 in the risk of retinopathy.

7 On the other hand, if we are talking about
8 a seven percent reduction from an A_{1C} of eight, then
9 that's an 8.75 percent reduction in the A_{1C} , which is
10 associated with a 38 percent reduction in the risk of
11 retinopathy.

12 So, whether or not a given reduction is
13 meaningful, in terms of a reduction in risk, needs to
14 be presented in terms of a relative reduction in A_{1C} ,
15 not a fixed reduction in A_{1C} .

16 CHAIRMAN BONE: Take the log of it or
17 what?

18 DOCTOR LACHIN: I'm sorry?

19 CHAIRMAN BONE: Do you take the log of it?

20 DOCTOR LACHIN: Well, there's an equation
21 that you can use to compute this. I mean, this is all
22 based on that simple exponential curve that I just
23 showed you.

24 CHAIRMAN BONE: But, if I understand you
25 correctly, what you are saying is that a certain

1 percentage reduction, for instance, a seven percent
2 reduction from whatever baseline we have in the
3 glycosylated hemoglobin would be associated with the
4 same reduction in risk as a seven percent reduction
5 from some other starting point.

6 DOCTOR LACHIN: Right.

7 CHAIRMAN BONE: So, the percent reduction
8 from baseline is a very useful figure.

9 DOCTOR LACHIN: Yes, right, right.

10 DOCTOR MARCUS: But, the absolute risk is
11 certainly higher for the person who starts out at 12,
12 that's true, if you do it the way the, what do they
13 call it, evidence-based guys calculate number of
14 patients needed to treat to save one event, clearly,
15 do you have any estimate of --

16 DOCTOR LACHIN: Well, the number needed to
17 treat is based on the relative risk, not on the
18 absolute risk difference. To compute a number needed
19 to treat, you take the relative risk of the
20 effectiveness for that treatment, and then you can
21 translate that into a number needed to treat.

22 So, a relative risk of two is going to
23 give you the same relative number of needed to treat,
24 regardless of what those absolute risks are.

25 CHAIRMAN BONE: But, you are telling us

1 that if -- to the extent that we can generalize from
2 the DCCT to the other sorts of trials that we're
3 looking at, which are with different agents and in
4 type 2 diabetes in many cases, that we could -- if we
5 had two treatments which produced similar proportional
6 reductions in the starting hemoglobin A_{1c}, they should
7 have equivalent risk reductions for morbid events.

8 DOCTOR LACHIN: Proportionate risk
9 reduction.

10 CHAIRMAN BONE: Proportion, percentage --

11 DOCTOR LACHIN: The absolute risk
12 reductions, of course, are going to depend on what the
13 level of A_{1c} is that they started with.

14 But, usually in evaluating treatments, we
15 are looking to assess them in terms of their relative
16 risks, as opposed to their absolute risks, and if
17 that's the framework within which you are trying to
18 address the problem, then you need to be thinking
19 about a relative reduction in A_{1c} rather than a fixed
20 reduction.

21 CHAIRMAN BONE: Thank you.

22 Doctor Davidson?

23 DOCTOR DAVIDSON: It is quite interesting
24 because if you read the slide, you know, the percent
25 reduction, if you reduce the A_{1c} 5.8 percent, and you

1 reduce it ten percent and you look at the decreased
2 reduction in retinopathy it's almost identical in the
3 percentages. Then, you know, I agree, any reduction
4 is beneficial, but better the reduction in percentage
5 the better off the patient in the future.

6 CHAIRMAN BONE: Doctor Hirsch.

7 DOCTOR HIRSCH: I was confused. I want a
8 solution to the following equation, which is what they
9 are looking for, delta risk equals K times a function
10 of something that has to do with A_{1c} hemoglobin, now
11 what is that, is that logarithm, is it percent or
12 what? You want delta absolute risk equals K times F
13 of X.

14 CHAIRMAN BONE: Delta absolute risk or
15 relative risk?

16 DOCTOR HIRSCH: Well, this is trying to
17 find that out, delta risk, an absolute delta risk, the
18 number of, you know, whatever you establish, ten fewer
19 cases of coronary occlusion, whatever.

20 DOCTOR LACHIN: Well, this is the same
21 thing, or the same relationship, but when looked at in
22 terms of the log of risk versus the log of A_{1c} .

23 DOCTOR HIRSCH: So, what should they
24 measure?

25 DOCTOR LACHIN: I'm sorry?

1 DOCTOR HIRSCH: What should someone
2 measure if he's interested in delta risk in absolute
3 terms?

4 DOCTOR LACHIN: The delta risk -- well,
5 you can compute it whether you look at a delta risk
6 here and then convert it to absolute values, or from
7 the other curve, and you can always -- if you tell me
8 that the A_{1c} was ten, or it was reduced to eight, I
9 can tell you what the delta risk will be.

10 DOCTOR HIRSCH: Well, they want to know
11 how you do that. They have to know how you do that so
12 they can tell industrial people, or sponsors, or
13 whatever, just what to look for.

14 DOCTOR LACHIN: The way you would do it,
15 based on the data you've generated from the DCCT is to
16 use the relationships that we've observed and to
17 estimate what the risk was at baseline and then what
18 the risk would be at follow-up, based on what the
19 change in the A_{1c} was.

20 DOCTOR HIRSCH: So, you are saying you
21 can't do that by percent or by absolute, is that
22 right?

23 CHAIRMAN BONE: No, I think what he said
24 was, you get a 43 percent reduction in risk for each
25 ten percent --

1 DOCTOR LACHIN: Ten percent reduction --

2 CHAIRMAN BONE: -- in the --

3 DOCTOR LACHIN: -- in the A_{1c}.

4 CHAIRMAN BONE: -- A_{1c} based on the
5 starting point. In other words, if you go from ten to
6 nine, you get the same proportionate reduction in risk
7 as you do from going from nine to 8.1, or from 8.1 to
8 7.4.

9 DOCTOR HIRSCH: That's true up and down
10 the line.

11 DOCTOR LACHIN: Up and down the line.

12 DOCTOR HIRSCH: Okay.

13 CHAIRMAN BONE: Okay.

14 Doctor Molitch.

15 DOCTOR MOLITCH: John, can we ask you a
16 bottom-line question? If you were designing a study
17 as a statistician of two different treatments, say,
18 for example, intensive therapy versus conventional
19 therapy, in treating patients with diabetes, and you
20 needed to pick one primary endpoint, would you look at
21 a comparison of the percent reduction in hemoglobin
22 A_{1c} or an absolute reduction in A_{1c} as your comparison?

23 DOCTOR LACHIN: Well, in terms of
24 statistical efficiency, whether or not you look at one
25 versus the other will depend on the underlying

1 distributions. So, I'm not so concerned about whether
2 or not you are able to demonstrate statistical
3 significance using an absolute reduction versus a
4 relative risk reduction. I think a relative risk
5 reduction is more meaningful, because then we can
6 interpret that in terms of the risk reduction for
7 complications.

8 To do that for an absolute risk reduction
9 is a little more complicated, but it can also be done.
10 I mean, what you are looking for is a meaningful
11 reduction in the A_{1c} . I think the sponsor should be
12 required to show that there's been a statistically
13 significant change in the A_{1c} and then the question is
14 to whether or not it's meaningful that you can use
15 these types of data to do these types of calculations.
16 What would be the expected benefit in terms of the
17 risks of complications, and we can do that, and then
18 you decide whether or not this is a statistically
19 significant and clinically meaningful effect on blood
20 glucose control.

21 CHAIRMAN BONE: Do you think that one
22 could construct a hypothetical but reasonable sort of
23 matrix where you would compare the decreased risk of
24 morbid events with what the offsetting rate of morbid
25 events occurring on treatment might be?

1 DOCTOR LACHIN: Such as?

2 CHAIRMAN BONE: Well, say, all morbid
3 events, if you group all morbid events with some kind
4 of weighting, this is getting very complicated, but I
5 think it gets to the kind of thing that people will
6 almost need in order to start designing studies, if
7 this is the way we do it, is Doctor Lachin is giving
8 us a way of saying, well, for a certain percentage
9 reduction in glycosylated hemoglobin we could expect
10 to reduce all these risks by a certain other percent.
11 So, if it's seven percent reduction in glycosylated
12 hemoglobin it's about a 20 some percent reduction in
13 risk, and that's consistent across a number of
14 different risks.

15 DOCTOR LACHIN: Right. Well, there are
16 different gradients for different complications.

17 CHAIRMAN BONE: Yes, okay.

18 DOCTOR LACHIN: But --

19 CHAIRMAN BONE: But, there's some kind of
20 way you could compile this --

21 DOCTOR LACHIN: Sure.

22 CHAIRMAN BONE: -- and then say, okay,
23 this would then allow you to estimate how much risk
24 you've -- how much harm you've prevented, or will
25 prevent in the future by this same reduction, and

1 actually then compare that with morbidity observed
2 attributable to therapy during a trial. Is that
3 plausible?

4 DOCTOR LACHIN: Yes.

5 DOCTOR SHERWIN: The data, John, I just
6 want to be sure, is that -- what you show is
7 retinopathy alone or the --

8 DOCTOR LACHIN: That was a three-step
9 sustained change in retinopathy.

10 DOCTOR SHERWIN: Retinopathy.

11 DOCTOR LACHIN: Which is the primary
12 outcome for the DCCT.

13 DOCTOR SHERWIN: Right, so it doesn't
14 necessarily apply statistically to a lumped
15 complication.

16 DOCTOR LACHIN: No, I mean there is a
17 different slope to that log/log relationship for other
18 complications.

19 DOCTOR SHERWIN: That's what I'm getting
20 at.

21 DOCTOR LACHIN: They all show the very
22 strongly linear relationship between the log of risk
23 and the log of the A_{1c} , but the slopes were different,
24 but all of those published in the papers that I cited
25 in the three diabetes papers.

1 DOCTOR MARCUS: May I just ask a
2 statistical clarification? If I were to come to you
3 and say I wanted to design a trial, and I didn't know
4 whether to look -- whether my primary endpoint should
5 be to compare what happens at the end of it in the
6 active group relative to the placebo group, or whether
7 there was an effect on some absolute value relative to
8 baseline, would you tell me that there is any
9 fundamental statistical -- in terms of statistical
10 theory, that either one of those models is more or
11 less strong than the other?

12 DOCTOR LACHIN: Well, as I said, one of
13 the considerations here, in terms of comparing two
14 groups with respect to measures of glucose control, or
15 with respect to lipids, or whatever else you might
16 want to look at, is the efficiency of the test. The
17 efficiency of the test is going to depend on what the
18 underlying distributions are.

19 If the data is more normally distributed
20 looking at it as a change from baseline, then you'll
21 have a more efficient, a more powerful test than if
22 you looked at it using a percent reduction, which may
23 not be normally distributed.

24 Frankly, I have not done an analysis of
25 the changes in the A_{1c} in the DCCT to be able to

1 answer that question, was the change more normally
2 distributed or was the percent reduction more normally
3 distributed? I don't know.

4 But, you know, if you are using a
5 parametric test, then whichever one approaches a
6 normal distribution will be more efficient, will give
7 you more power.

8 That's the reason why I don't think it's
9 important to say that the analysis has to be pinned to
10 one versus the other, because I think it's important
11 as a description.

12 DOCTOR MARCUS: You answered a different
13 question, though. Let me just rephrase the specific
14 question I was asking.

15 DOCTOR LACHIN: Go ahead.

16 DOCTOR MARCUS: We've heard two different
17 models here today. One is, well, the change from
18 baseline was not significant, but the placebos went up
19 and so the difference between placebo and the active
20 group were significantly different. And, I'm asking
21 you to compare that model to say, no, we want to know
22 what happened to the people in the active group, did
23 they have a down slope that was significant.

24 DOCTOR LACHIN: Well, the first slide that
25 Doctor Misbin presented this morning is problematic.

1 I can certainly appreciate the difficulties that he
2 and the members of the committee face in interpreting
3 that data.

4 Frankly, I prefer a design where you try
5 and implement a new treatment in the trial, but where
6 it would be implemented in practice, and I don't think
7 it's realistic to say that you would take patients off
8 of their drugs for, you know, two months before you
9 randomize them or before you assign a therapy in
10 practice.

11 And, if that's the way you would --
12 because you wouldn't treat patients that way in a
13 practice, then it's very difficult to interpret the
14 results of a trial that deviate from that.

15 So, I mean, that whole -- that whole trial
16 clearly holds a lot of problems in terms of its
17 interpretation.

18 Now, what should be the most appropriate
19 analysis? I think the real question is, if you have
20 a patient today whose A_{1c} is ten, and you make a
21 decision to treat them, what is their A_{1c} going to be
22 six months or 12 months from now, to me that's the
23 question.

24 DOCTOR MARCUS: Thank you, that's exactly
25 what I wanted to hear your opinion on.

1 DOCTOR LACHIN: Okay.

2 I want to say one other thing, in terms of
3 the question about blood glucoses, we did all of these
4 analyses it's clear the A_{1c} reflects the level of
5 control, but we don't know what it is about control
6 that influences complications.

7 And, for mechanistic purposes alone, it
8 would be very important, I feel, to get blood glucose
9 data preferably under the best controlled conditions
10 possibly, so we can see whether or not a given agent
11 is associated with just flat reductions in blood
12 glucose or reductions in the postprandial levels,
13 because it may prove that, you know, ten years from
14 now by doing these types of investigations we'll have
15 a much better sense as to what it is about blood
16 glucose control that affects the A_{1c} associated with
17 different agents, and that could then be very
18 important in deciding which agents are most effective
19 for which types of patients.

20 DOCTOR MARCUS: Let the record show that
21 I did not pay him to come out in support of blood
22 glucose control.

23 CHAIRMAN BONE: That's your uncorroborated
24 statement, Doctor Marcus. There is no actual data to
25 that effect.

1 Thank you very much, Doctor Lachin.

2 I think Doctor Molitch had a question or
3 comment.

4 DOCTOR MOLITCH: I just wanted to be sure
5 that I had an answer to the question that I posed to
6 you, John, which was the percent reduction versus the
7 absolute reduction if you had to pick one measure for
8 a study, and it sounds like it depends upon the
9 distribution and which fits the data better.

10 DOCTOR LACHIN: I think in terms -- no, in
11 terms of describing the results, I think the percent
12 reduction is more important.

13 The data should be robust to the way you
14 do the analysis, whether you do the statistical test
15 using a difference or a percent reduction, I don't
16 think that's critical, but I think it's important to
17 present the results in terms of a percent reduction,
18 so you can then, you know, relate that to a percent
19 reduction in risk.

20 CHAIRMAN BONE: Thank you very much.

21 I think we've had a very interesting
22 discussion on some of the aspects of using
23 glycosylated hemoglobin as an endpoint in these
24 trials, and some of the complexities.

25 I think this may be kind of a good

1 stopping point, and it's actually just about when we
2 had scheduled lunch, so somehow this coincidence of
3 information seems very powerful to me.

4 However, I'd like to resume at 1:15, 1:30,
5 I'm being shouted down. We are going to start talking
6 at 1:30, okay, so everybody should be here by 1:25.

7 (Whereupon, the meeting was recessed at
8 12:42 p.m., to reconvene at 1:30 p.m., this same day.)

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

2 1:32 p.m.

3 CHAIRMAN BONE: We are resuming the 69th
4 meeting of the Endocrinologic and Metabolic Drugs
5 Advisory Committee discussing the topic of a draft
6 guidance document for the development of drugs for the
7 treatment of diabetes mellitus.

8 Earlier today, we have had an exposition
9 of certain points in this guidance document and their
10 rationale by Doctor Misbin, and we have had some
11 discussion in the last part of the morning on the
12 important endpoint of glycosylated hemoglobin
13 measurements.

14 I think based on the priority which was
15 assigned to the concern about hypoglycemia by Doctor
16 Misbin and the importance of the occurrence of
17 hypoglycemia as a consideration of -- as an adverse
18 effect in the treatment of Type I diabetes
19 particularly, that it would be timely to have some
20 discussion on that topic. And if I understand
21 correctly, Doctor Kohler from FDA is going to make a
22 short presentation and then the committee will discuss
23 this topic.

24 If I understand correctly, two major
25 issues here are how to actually identify episodes of

1 -- what constitutes a hypoglycemic episode for
2 clinical trial purposes, and then how should this be
3 regarded or weighed. For the record, this is Doctor
4 Elizabeth Kohler.

5 DOCTOR KOHLER: Can everyone hear me?

6 CHAIRMAN BONE: No.

7 DOCTOR KOHLER: Okay, can everyone hear me
8 now?

9 CHAIRMAN BONE: Where is the microphone?
10 Move it up.

11 DOCTOR KOHLER: Is that better?

12 CHAIRMAN BONE: Right.

13 DOCTOR KOHLER: Okay. My name is Beth
14 Kohler, and I am one of the endocrinologists in the
15 Endocrine Division at the FDA. And I am going to talk
16 a little bit about hypoglycemia.

17 Hypoglycemia is clearly an important
18 consideration -- an important endpoint in the clinical
19 trials for diabetes. Defining hypoglycemia for the
20 purpose of clinical trials, however, is somewhat
21 problematic. And to clarify the dilemma that we face
22 in the Agency, I am going to take you through a
23 specific case scenario.

24 For one of the pivotal trials that a
25 sponsor presented, and this trial was done on IDDM

1 patients, they defined hypoglycemia as any time a
2 patient experienced a symptom that he or she
3 associated with hypoglycemia regardless of blood
4 glucose measurement, or a blood glucose measurement of
5 less than 63 mg/dl on routine monitoring not
6 associated with symptoms.

7 As you can see here, the experimental drug
8 group had a hypoglycemic rate for 30 days of 6.44
9 events, whereas the standard drug group had a
10 hypoglycemic rate of 7.1 events per 30 days. The
11 hemoglobin A_{1c} values tended to be somewhat higher in
12 the experimental drug group, 8.24 percent versus 8.17
13 percent with a P value of .09. This value was
14 actually statistically significant when confidence
15 intervals, which is the correct way to assess it, were
16 used. By this definition of hypoglycemia then, we can
17 observe a statistically, although not necessarily
18 clinically significant difference in P values.

19 In addition to being concerned about the
20 adjustments needed for the differences in glycemc
21 control in the two treatment groups and the different
22 definitions of hypoglycemia that were utilized by the
23 sponsor in a variety of their trials, we realized that
24 we needed to consider the other problems that were
25 associated with this somewhat subjective definition of

1 hypoglycemia.

2 The first of these is that glucose meters
3 are notoriously inaccurate and imprecise. And I think
4 people need to recognize that their approval as
5 medical devices does not require testing with patients
6 in routine clinical situations. That is not the way
7 the device law is written. They are just not -- a
8 fairly wide error rate is allowed for approval.
9 Secondly, this trial, like many other trials in
10 diabetes, either by intent or just the way it ends up
11 turning out, it was not blinded. And third, with high
12 blood glucose limits for hypoglycemia, it really was
13 not possible to discern the patients who were unaware
14 of their hypoglycemia because they had actual
15 unawareness or because they were actually not
16 hypoglycemic. And when you have a sponsor trying to
17 claim that patients don't have hypoglycemia or that
18 there is less hypoglycemic unawareness, you really
19 need to know if patients, in fact, were hypoglycemic.
20 You need to have an appropriate threshold.

21 So for this reason, we thought that a more
22 rigorous definition of hypoglycemia was warranted.
23 And we wanted greater objectivity and more specificity
24 for the clinically significant events. For that
25 reason, we defined hypoglycemia as any time a patient

1 had a blood glucose level less than or equal to 35
2 mg/dl or if that person required assistance from
3 another individual. This definition is more similar
4 to that employed during the DCCT and it also tries to
5 account for the differences between serum and blood
6 glucose readings.

7 Now when we recalculated the hypoglycemia
8 rate, this is what we found. The Y axis here
9 represents the number of hypoglycemic events per 30
10 days. The X axis shows the treatment groups by the
11 various definitions of hypoglycemia. This portion of
12 the figure shows the hypoglycemia rate for the
13 experimental drug group. This is done under the old
14 definition. This portion of the cartoon shows the
15 rate for standard therapy under the old definition.
16 Now these two parts of the figure show the
17 experimental and standard therapies respectively under
18 the new definition. And as you can see, there is
19 really a decrease of about 20-fold.

20 Now the hypoglycemia rate for the
21 experimental group was 0.37, and the hypoglycemia rate
22 for the standard therapy group was slightly less at
23 0.34 events per 30 days. And this is under the new
24 definition. Here are the rates under the old
25 definition. These values are more similar to those

1 that were found during the DCCT trial, which defined
2 severe hypoglycemia as that which required
3 intervention from another individual. The differences
4 between these two groups was not significant when
5 hypoglycemia was defined in this way.

6 I think that we can appreciate that a
7 physician would be willing -- I would be willing in my
8 clinic to diagnose and perhaps treat hypoglycemia in
9 a clinical setting with less definitive proof of frank
10 hypoglycemia. However, when you are doing a clinical
11 trial, when you want to make commercial claims that go
12 on a label, I believe that you need to be more
13 rigorous in your definition. This does not mean that
14 during the clinical trial patients cannot be managed
15 for suspected hypoglycemia. But when it comes to
16 actually counting the numbers, I do believe that you
17 need to have some rigor -- some high level of
18 specificity if you are going to make claims. And it
19 would also be ideal if there could be some uniformity
20 as to what we would actually accept. It was quite
21 difficult in this particular NDA when there were at
22 least three different definitions of what hypoglycemia
23 was in the pivotal trials.

24 So I hope that this small example points
25 out to you the dilemma that we face. Some of the

1 things that we might choose to do as clinicians are
2 not the same as we would choose to do when we are
3 evaluating a clinical trial. I hope this will
4 stimulate discussion.

5 CHAIRMAN BONE: Well, I think Doctor
6 Kohler has sort of posed a concern and position but
7 without saying that those specific -- you might want
8 to stay just a minute. She mentioned the 36 mg/dl or
9 requiring assistance criteria. Do you have a view as
10 to whether that particular set of criteria should be
11 employed in a guidance document or are you just
12 setting the stage with that for discussion?

13 DOCTOR KOHLER: Well, I actually -- I feel
14 that it is a reasonable standard. I feel that it is
15 a reasonable standard to be used. As you can see from
16 the data, when we looked at the number of hypoglycemic
17 events, it is a value that is essentially intermediate
18 to that which was found -- the criteria were
19 intermediate to that which were found in the DCCT and
20 the values were that way. Your meters are simply not
21 very good when they get down into the low range, but
22 you have an idea of, well, this is something not too
23 good. But they are notoriously unreliable, and I feel
24 very uncomfortable accepting a value of 50 on a meter
25 because that is really not -- because it is not really

1 reproducible in a clinical setting. It has to do with
2 the way meters -- devices are approved. And you can
3 even have a 20 percent error rate between devices, and
4 it can still obtain approval. And that is under the
5 best situations. The situations for approval are
6 basically the patient will come in and you will draw
7 blood. You will have a tube that goes to the lab and
8 you will have a sample that goes onto the meter. It
9 doesn't necessarily have to be that the patient is
10 putting it on the meter. It doesn't have to be that
11 the patient can read or operate the meter. And these
12 are all things that as clinicians we know impair a
13 patient's ability to provide good glucose values.
14 Some of the newer meters try to eliminate values if
15 you haven't obtained the sample correctly, but it is
16 not fallible. And that is where I really have
17 problems using meters that have just a specific value
18 like 50. I tried to go for something I really thought
19 would give me a high level of specificity, where I
20 could have confidence and I knew that these kind of
21 values made a difference clinically.

22 CHAIRMAN BONE: Thank you. I think Doctor
23 Kohler then has really pointed out two problems. One
24 is the problem of how to define a hypoglycemic episode
25 if we knew what the blood sugar was, and the other is

1 to point out a problem in the way clinical trials are
2 conducted having to do with the accuracy of the
3 measurement. Earlier, Doctor Molitch made a strong
4 point with which there was general agreement that the
5 method of measurement of glycosylated hemoglobin was
6 an important issue in the planning of clinical trials.
7 And even if we don't regard the blood sugar
8 measurements as primary, we certainly regard them as
9 an important secondary measurement, and it sounds to
10 me like we have a much bigger problem than we should
11 in obtaining reliable data with the home monitoring.
12 I would wonder if the diabetologists would comment on
13 whether it is feasible to improve on that by
14 calibrating instruments and instructing patients. Can
15 we do better in a clinical trial setting? Doctor
16 Molitch, do you want to start?

17 DOCTOR MOLITCH: No, I don't think so. I
18 think we struggled with this issue in the DCCT for
19 years and years and essentially abandoned the home
20 glucose measurements or the mild hypoglycemias as a
21 clearly reproducible entity that could be counted and
22 really stuck with the definition of severe
23 hypoglycemia, which was an event that resulted in
24 seizure or coma or that needed assistance by another
25 person to correct the situation and left it at that.

1 CHAIRMAN BONE: I see. Other comments
2 concerning ability to improve on these measurements?
3 No? All right, thank you. What about comments from
4 the committee about the recommendations that Doctor
5 Kohler used for an example that she had used in other
6 trials for a definition. Doctor Davidson?

7 DOCTOR DAVIDSON: I just wonder why you
8 chose 63 instead of 60 or 55.

9 CHAIRMAN BONE: I think she said 36.

10 DOCTOR DAVIDSON: No, for one. And 36 for
11 the other because that is DCCT with symptoms? No?

12 DOCTOR KOHLER: The sponsor is the one who
13 chose 63.

14 CHAIRMAN BONE: Oh.

15 DOCTOR KOHLER: And another time, they
16 chose 50.

17 DOCTOR DAVIDSON: I think it would be nice
18 if this committee can make a recommendation.

19 CHAIRMAN BONE: I think Doctor Kohler's
20 recommendation for what she used was 36 for the
21 glucose.

22 DOCTOR KOHLER: Right. The definition
23 that was placed up there was 63. That came from the
24 sponsor. But they had also conducted other trials
25 using other threshold values such as 50 or 55, and

1 they had a myriad of trials. So in part because we
2 wanted to be able to compare data across trials and we
3 wanted really a value that we thought was meaningful,
4 that is why we chose essentially what was the lowest
5 value on meters, which was 36, so we really knew we
6 were down at the end of the meter. We tried to be
7 somewhat more generous actually than the DCCT because
8 of the number of events. But we wanted to make sure
9 that we really had something that was clinically
10 significant, albeit we understand as clinicians that
11 if I had someone constantly coming in with 45 on their
12 meter, I would be nervous. But on the other hand,
13 that is clinical practice, and I think we need to make
14 the distinction from what is -- the rigor that we need
15 for a clinical trial.

16 DOCTOR DAVIDSON: So what you are telling
17 me is that there is going to be only one definition
18 for hypoglycemia? Is that your recommendation?

19 DOCTOR KOHLER: Well, this was just the
20 definition that several of us chose to evaluate it.
21 We thought it was the more reasonable one. But
22 clearly we are open to input. But we just thought
23 this was really the least ambiguous and I think there
24 are a lot of sponsors here who recognize that we did
25 use this to evaluate data in one trial and they would

1 like to have some idea of whether I made a correct
2 decision or not.

3 CHAIRMAN BONE: What do you think, Jaime?

4 DOCTOR DAVIDSON: Well, you know, I think
5 the first thing is we need to have consistency from
6 trial to trial on the definition of hypoglycemia. And
7 if we are going to choose a number based on a meter,
8 it is a tough one because we know that at that level
9 it is unrealistic to get a decent measurement. I can
10 live with that if we can have in addition to that the
11 other definition, which is the DCCT definition --
12 which is assistance, coma, and so on.

13 CHAIRMAN BONE: All right. Doctor
14 Zawadzki?

15 DOCTOR ZAWADZKI: I have a couple concerns
16 about just using a definition of extreme hypoglycemia
17 in terms of possible applications to clinical practice
18 subsequently. In terms of looking at the effects of
19 hypoglycemia on patients' behavior and patients'
20 ability to function during that time and subsequently,
21 I think hypoglycemia much less severe than what you
22 are describing is an important event. And to exclude
23 that I don't think is appropriate.

24 CHAIRMAN BONE: Well then how would you
25 count it? How would you reliably -- for purposes of

1 the study only -- for purposes of the study, how would
2 you identify a mild or moderately severe hypoglycemic
3 event?

4 DOCTOR ZAWADZKI: I would envision a
5 gradient of hypoglycemia. Just like hyperglycemia is
6 just not one number, hypoglycemia is not just one
7 number. I will give you one example. I was taking
8 care of a patient with gestational diabetes who was
9 ketotic just four days ago, and we just started her on
10 insulin. On the second day, she had a measured blood
11 glucose that was 79 on the meter in the hospital. The
12 nurse called me and said the number is just fine, but
13 the patient is shaking and is sweaty. In that
14 circumstance, is she having hypoglycemia or not? And
15 I think you have to have --

16 DOCTOR MOLITCH: How do you count it?

17 DOCTOR ZAWADZKI: I am sorry?

18 DOCTOR MOLITCH: So how did you count it?
19 As hypoglycemia or not?

20 DOCTOR ZAWADZKI: I definitely counted it
21 as hypoglycemia because I knew the type of meter she
22 was using and I knew what the range of readings on
23 that meter were and the description of symptoms was
24 classic. And I think you have to be able to include
25 that kind of a description as some element of

1 hypoglycemia.

2 DOCTOR MOLITCH: But I think that exactly
3 illustrates the point that it is difficult to know how
4 to count these events like that. Do you count the
5 meter reading? Do you count the symptoms? Or if you
6 have a meter reading that is 35 without any symptoms,
7 do you count that?

8 DOCTOR ZAWADZKI: Well, can you develop a
9 scoring?

10 DOCTOR MOLITCH: No, I think it is very
11 difficult to do so. The 95 percent confidence band
12 around the correlation coefficient expands
13 dramatically as you get down there, so they become
14 more and more inaccurate for the reading. And you
15 also have patients to whom you say, well, did you have
16 any hypoglycemic episodes last week when you count
17 them in a trial and they say, no, I didn't have any
18 hypoglycemia. Then you say, did you ever feel low
19 before a meal? And they say, oh yes, a couple times
20 last week. So do you count that as hypoglycemia or
21 not? It is very difficult to ascertain.

22 CHAIRMAN BONE: Doctor Sherwin?

23 DOCTOR SHERWIN: Well, that case is
24 illustrative because patients that are chronically
25 hyperglycemic when brought into a normal range develop

1 symptoms, which then the patients adapt to over time
2 and then we consider that normal glycemia. For that
3 patient initially, it was relative hypoglycemia. And
4 that illustrates the problem of trying to relate
5 symptoms to clinically significant adverse effects.
6 This is an extremely difficult problem. I know that
7 all of the people that have been involved with insulin
8 trials have struggled over the problem of trying to
9 define mild to moderate hypoglycemia. And when it is
10 all said and done, one has soft data rather than hard
11 data. That is the problem. I think that mild
12 hypoglycemia or a moderate degree of hypoglycemia
13 might be considered a secondary endpoint but not a
14 primary. Now the one problem is that there is this
15 phenomenon of hypoglycemia unawareness. So patients
16 can have a blood sugar of 35 and 40 and look fine and
17 talk to you and not have any appreciable evidence to
18 the outside world of hypoglycemia. And yet, if that
19 person's glucose drops another few points, they will
20 be in coma. And so -- and I have seen patients where
21 we have done clinical studies where we have maintained
22 them at around 30 and then they go to 29 and they go
23 from being lucid to suddenly tipping over and going
24 into a severe cerebral dysfunction. So I think that
25 having a low level of glucose probably is not an

1 unreasonable thing to include. Now whether it is 36
2 or 40 or something like that. Even though the meters
3 are inaccurate, it is probably not a bad idea.
4 Because I think in some patients who are on insulin
5 regimens, it is not unreasonable to be concerned about
6 levels that are unequivocally low. But I think that
7 the DCCT definition is still probably in most cases
8 the hardest endpoint. I would argue in favor of that
9 being the kind of changes that produce cognitive
10 dysfunction and relieving symptoms through help rather
11 than the person relieving their own symptoms.

12 CHAIRMAN BONE: All right. Doctor Cara
13 had a comment or question?

14 DOCTOR CARA: Yes. It seems that the gist
15 of the problem is in developing -- at least as I
16 understand it, and please correct me if I am wrong --
17 it is really to develop an objective definition of
18 hypoglycemia, yet at the same time capture the
19 clinically significant low blood sugars that may not
20 fit that objective definition. Because they are, in
21 fact, important.

22 One thing that may help is if we can get
23 any information from the DCCT. I don't know if Doctor
24 Lachin might have this information, but whether there
25 is any correlation between the incidence of severe

1 hypoglycemia and the incidence of milder hypoglycemia.
2 In other words, if we know that patients that have
3 severe hypoglycemia as defined by the DCCT also tend
4 to have a higher incidence of mild hypoglycemia and
5 there is in fact a correlation, then that might solve
6 the problem.

7 CHAIRMAN BONE: Because you would be able
8 to use the severe episodes as an indicator of the
9 overall problem.

10 DOCTOR CARA: Right.

11 CHAIRMAN BONE: Whereas, if they weren't
12 related, then you would almost be talking about two
13 different problems.

14 DOCTOR CARA: Right. So do we know that?

15 CHAIRMAN BONE: I don't know. Doctor
16 Lachin is approaching the microphone and he will be
17 able to tell us yes or no -- does he know the answer
18 to that question?

19 DOCTOR LACHIN: No, I don't know the
20 answer to that question.

21 CHAIRMAN BONE: Okay.

22 DOCTOR LACHIN: I will say this.
23 Hypoglycemia tended to beget more hypoglycemia in the
24 DCCT. Patients in both treatment groups, once they
25 experienced episodes of hypoglycemia, they were at

1 markedly increased risk of additional episodes.
2 Almost 30 percent of the patients in both treatment
3 groups experienced a second episode of severe
4 hypoglycemia within a year of their first episode.
5 Now this also is remarkably related to attempts to
6 intensify treatment as opposed to the insulin level --
7 I am sorry, the blood glucose or the A_{1c} levels
8 themselves.

9 So in terms of looking at this data,
10 ascertainment is one of the major problems that we
11 found. We selected this definition of severe
12 hypoglycemia because we felt we could reliably detect
13 a difference between treatments with this definition,
14 and anything short of that is just too much noise.
15 You can't detect what is signal from noise here. And
16 in trying to detect a difference between treatments on
17 hypoglycemia, you need to have something that is very
18 specific.

19 CHAIRMAN BONE: Thank you. I think Doctor
20 Davidson and then Doctor Kohler.

21 DOCTOR DAVIDSON: Well, actually Bill
22 Sherwin made most of the comments I wanted to make.
23 Just to be certain, during gestation the glucose
24 levels are actually lower than in regular. Then, for
25 sure, I would not consider that level of glucose as a

1 true hypoglycemic event. And we need to differentiate
2 between a sudden drop to a normal level blood sugar,
3 symptoms of hypoglycemia, and true hypoglycemia. And
4 I think that what this committee -- the question is
5 what is true hypoglycemia.

6 CHAIRMAN BONE: Well, I think even a
7 sharper way of putting that question is the way that
8 Doctor Kohler put. Not what is a hypoglycemic episode
9 for purposes of managing a patient in your clinic, but
10 what is a hypoglycemic episode for purposes of
11 counting it as an event in a clinical trial where we
12 are going to generalize from the information to
13 potentially thousands or millions of other people.
14 Doctor Kohler, you had an additional comment?

15 DOCTOR KOHLER: Yes. It would seem by
16 logic that if you had lots of mild hypoglycemia that
17 you would be more prone to having severe episodes.
18 And since we don't really have data from the DCCT, I
19 do think that we do need to sort of point out an
20 anomaly that we found in this particular study. There
21 were many patients that it didn't matter which of the
22 drug treatments they were on what kind of hypoglycemia
23 they had. But there were clearly certain patients who
24 had many more episodes on one treatment than they did
25 on the other. So I am not really sure how well we can

1 use -- exactly what the relationship is between mild
2 hypoglycemia and severe hypoglycemia. Logic would
3 dictate one thing, but Doctor Misbin and I are not
4 sure how to account for the data that we saw in the
5 trials.

6 CHAIRMAN BONE: All right. Well, Doctor
7 Zawadzki?

8 DOCTOR ZAWADZKI: It really sounds like
9 these episodes of severe hypoglycemia that are being
10 described are episodes that we tend to observe more in
11 patients with Type I diabetes. And we really rarely
12 see such severe episodes in patients with Type II
13 diabetes. However, we often see milder episodes in
14 patients with Type II diabetes that are an
15 encroachment on their daily life. And I think those
16 are important episodes. So maybe the definition would
17 need to be adjusted depending on what population is
18 being studied as well.

19 CHAIRMAN BONE: Well, you still have the
20 verification issue, don't you?

21 DOCTOR ZAWADZKI: In terms of -- you mean
22 in terms of documenting a number to go with the
23 symptoms?

24 CHAIRMAN BONE: Yes. Doctor Sherwin?

25 DOCTOR SHERWIN: Yes. I think your point

1 is well taken because I was sort of writing notes to
2 myself and all this data is accumulated in patients
3 with Type I, where the frequency of severe
4 hypoglycemia is substantive and sufficient enough to
5 detect from a statistical standpoint differences in
6 treatment. It is much harder, though much less
7 common, to see severe hypoglycemia producing
8 unconsciousness, for example, in patients with Type
9 II. And, in fact, because they still make some
10 glucagon during hypoglycemia, they very rarely get
11 that low, I think. So the problem then becomes having
12 accurate measurements in a setting where milder
13 hypoglycemia is a significant potential problem.
14 Perhaps we need to collect samples like they did in
15 the DCCT in patients. There are methods of collecting
16 at-home glucose measurements, and perhaps that could
17 be worked into a trial to get standardized glucose
18 measurements at times when the risk is greatest in
19 that population, at certain times of the day, and
20 perhaps use that. Because it is going to be very hard
21 to get a 60-year-old person to get accurate
22 measurements in the low range during a hypoglycemia
23 event. I mean, it is going to be very hard to be
24 convinced from patients' home blood glucose monitoring
25 that we really have hypoglycemia. I think there will

1 be enough noise in the system that we won't really get
2 the answer. But perhaps an objective measurement to
3 detect mild hypoglycemia in that group might be in
4 order.

5 CHAIRMAN BONE: All right. Well, let me
6 see if I can summarize a little bit and then specify
7 a couple of questions I would like different responses
8 on if possible from the committee. Firstly, everybody
9 agrees that the type of severe episode using the DCCT
10 definition constitutes a significant event and ought
11 to be counted. It seems to me that the next question
12 is what about the patient who doesn't have such severe
13 symptoms and doesn't require assistance or have a
14 seizure, but nevertheless has a very low blood sugar
15 measured on their monitor and maybe just feels bad.
16 Should those be counted at a blood sugar of 36 or 40
17 -- those were the two numbers that were mentioned --
18 should those be counted as events or not?

19 DOCTOR DAVIDSON: If they had a seizure,
20 they require assistance.

21 CHAIRMAN BONE: No, no, no. I said
22 setting aside the people who have seizures, pass-out,
23 require assistance -- in other words, the DCCT
24 symptomatic episode. Do we want to -- ought we
25 capture blood glucose data to identify relatively

1 severe hypoglycemia without neurologic impairment? I
2 guess that would be one way of calling that. Doctor
3 Molitch has said that efforts in the DCCT to even do
4 this were not very rewarding.

5 DOCTOR MOLITCH: Just inaccurate.

6 CHAIRMAN BONE: Because of problems with
7 inaccuracy. Are those problems ones that would be
8 fatal to a clinical trial or just create a lot of
9 noise?

10 DOCTOR MOLITCH: I think it creates -- I
11 think nobody is denying the importance of the
12 hypoglycemia. It is just the ability to ascertain
13 this accurately that is really the critical issue.
14 And I think Doctor Sherwin's comment is correct. You
15 get somebody whose blood sugar may really be 45 and is
16 60 years old and they are not doing all that well and
17 they don't get a full drop of blood on the meter and
18 they get a lower meter reading of 20. That is not
19 accurate. And it is just very difficult to really get
20 appropriate information.

21 CHAIRMAN BONE: Okay. Does anyone think
22 we can use that information? Doctor Davidson?

23 DOCTOR DAVIDSON: I think the meters that
24 we had during the DCCT were not as good as the ones we
25 have today. And I think that with some of the meters

1 we have today, I think that my position would be I
2 would like to keep the 36 as part of the hypoglycemia.

3 CHAIRMAN BONE: Well, Doctor Kohler has
4 given us an interesting insight into the regulatory
5 process by which these meters are marketed. Doctor
6 Kohler, would it be your view that if a trial wished
7 to capture this data that for purposes of the trial,
8 meters should be used which have had -- let's say have
9 been qualified in some way beyond what is required for
10 marketing?

11 DOCTOR KOHLER: Well, I think that would
12 probably be idea, but I am not sure that any of them
13 could even pass that way. It really stems -- the
14 meters get marketed on -- you can say that we think
15 that the newer meters are better. But to apply to
16 have a meter to be made, you just make a 510K. And if
17 it is already -- if something like it has already been
18 approved and your thing is pretty similar to it, it is
19 going to be approved. So there is really no proof
20 that the newer meters are better than the older
21 meters. It would be nice if we had clinical trial
22 data like that, but I don't believe that that exists,
23 and I think it would be expensive for a company to
24 pursue that.

25 CHAIRMAN BONE: Yes. Doctor Critchlow?

1 DOCTOR CRITCHLOW: You said there was a 20
2 percent or so variability between the same brand. But
3 if a trial provided a meter of a particular type to
4 all the study participants, would that be any better
5 or does it matter?

6 DOCTOR KOHLER: Well, you see the 20
7 percent variability is just when it has been given
8 essentially optimal testing. When I described that
9 they took the tube of blood. Those are the kind of
10 tests that they need to perform. So they don't need
11 to have really any clinical data in order to get the
12 meter approved. So your 20 percent gets wider and
13 wider and wider. And it probably also -- they had
14 discussions like this with meters like fructosamine.
15 The problem is that your ability to operate the meter
16 is partly dependent on education --

17 CHAIRMAN BONE: And your blood sugar.

18 DOCTOR KOHLER: Yes, and your blood sugar.
19 So it becomes very difficult. I don't, myself, have
20 too much problem accepting an extremely low value, but
21 that is why we picked 36 because we knew it was pretty
22 bad.

23 CHAIRMAN BONE: Because it was so low.
24 Doctor Zawadzki and then Doctor Molitch, and we will
25 try to wrap this up.

1 DOCTOR ZAWADZKI: Well, some of the
2 comments I was going to make have just been eluded to.
3 But when a patient is hypoglycemic, first of all, none
4 of the meters are that accurate in the range below 80.
5 I mean, that variability is much greater and they
6 often overread those values. Second of all, if a
7 person indeed has hypoglycemia, they may not be able
8 to obtain a sample as well. They may have peripheral
9 vasoconstriction and they may not have the usual
10 skills they have when their blood sugar is 150 and
11 they are measuring it. So I think there are a lot of
12 factors that are not just the meter. It is the
13 meter/person interface that cannot be controlled in
14 those circumstances.

15 CHAIRMAN BONE: Right. Thank you. Doctor
16 Molitch?

17 DOCTOR MOLITCH: I think given all of the
18 inaccuracies, it has to be clearly a very distant
19 secondary type of adverse outcome. But I would have
20 to say that the same noise levels of the measurements
21 apply equally across two different treatment groups,
22 I would think. So, therefore, that would account for
23 some of this stuff, like we have talked about
24 yesterday. So, therefore, it could be used, although
25 my guess is that it would be difficult to really get

1 good statistical significance.

2 CHAIRMAN BONE: A final comment from
3 Doctor Kohler, and then I will try to summarize.

4 DOCTOR KOHLER: I guess that one of the
5 problems that we had though is that many patients will
6 enter a clinical trial, particularly if they are told
7 that the agent is likely to lead to less hypoglycemia.
8 And many of these trials are not blinded. So then you
9 end up going, well, did the patient report? Did they
10 report accurately? Did they tend to deny because they
11 believed they were getting benefit from the drug?
12 There again that is why I feel that we need to use
13 fairly solid criteria. It is not the same as I would
14 do in clinical practice. It is different for
15 pharmaceutical trial.

16 DOCTOR SHERWIN: Well maybe -- I just
17 wonder whether we could have the companies provide
18 patients with these little tubes that allow you to
19 accurately measure glucose and tell the patients if
20 they have symptoms to collect blood and treat
21 themselves. And that way, you could get objective
22 information and not rely on meters at all. And use
23 that as the study criteria for defining hypoglycemia.

24 CHAIRMAN BONE: Let me try something on
25 and see if --

1 DOCTOR SHERWIN: Because they are very
2 good. I can tell you. We used to collect blood all
3 the time on patients and the glucose holds up fine in
4 these little tubes because there are preservatives in
5 them to prevent glucose degradation. It is easy to
6 collect. You get it from a drop of blood. It is a
7 very simple task. As part of a clinical trial, that
8 way you could probably define the information you want
9 and get an objective number and not rely on the
10 patient or the meter or anything else. Why not have
11 that information?

12 CHAIRMAN BONE: Well, let's try this on if
13 I may. Would the committee sort of agree for the
14 purposes of this relatively informal discussion in the
15 early stage of developing this part of the guidance
16 that we would all agree that the type of severe
17 symptomatic episode that we have described ought to be
18 counted. But that if a sponsor wished to provide data
19 on hypoglycemia that these technical problems would
20 have to be addressed in the planning of the trial, for
21 instance by the type of solution that Doctor Sherwin
22 has recommended or in some other way. So that we
23 would begin the trial with reasonable confidence in
24 the verifiability of the glucose measurements. Is
25 that a fair summarization of the view?

1 DOCTOR MOLITCH: As long as you took away
2 the word reasonable before confidence.

3 CHAIRMAN BONE: Okay. Point taken. All
4 right. Thank you very much, Doctor Kohler. We
5 appreciate your help with that. We are talking about
6 definitions, and we wanted to kind of make sure as we
7 went through that we were all talking about the same
8 thing.

9 I would like to take just a couple of
10 minutes here. I don't think this is a major issue, so
11 we don't want to spend excessive time on it. But we
12 had this issue now of modifications of the diagnosis
13 of diabetes and impaired glucose tolerance. That has
14 some implications for selection of subjects for trials
15 and what actually we mean by the indication diabetes.
16 And maybe one way we could deal with this concisely
17 would be to get a comment or two from each of the --
18 particularly the diabetologists in the committee and
19 see if those are useful. Doctor Misbin's paper
20 discussed this in somewhat more detail than in his
21 talk, but there is a little bit of an issue here.
22 Maybe Doctor Misbin would be good enough to just
23 summarize in one or two sentences the point here, and
24 then we will go around the table and ask for comments.

25 DOCTOR MISBIN: Well, as you say, I think

1 these are not the major issues. But I think there are
2 two and they are somewhat unrelated. The first, of
3 course, reflects the modification of the diagnosis of
4 diabetes which was adopted by the ADA and the World
5 Health Organization. So there are a lot more patients
6 now, as has been said before, who have Type II
7 diabetes than by this new definition. Now the ADA did
8 not change the recommendations for treatment. So
9 actually there should not be any more treated patients
10 than there were before. But I think we have some
11 concern that if you ask what is the evidence of safety
12 and efficacy in these new patients, it doesn't exist.
13 Because these are now a new type of diabetes or new
14 patients and new criteria. Efficacy, I think we can
15 take for granted. But I think safety is really the
16 concern. So really the question posed is should FDA
17 take some action in this area. And I don't know
18 exactly what action would be appropriate. But I think
19 the question I would just pose to the group is is this
20 change something that we should worry about? And if
21 not, then we can move on. Or if it is, what should
22 our reaction be to it?

23 CHAIRMAN BONE: Well, we can take that
24 topic first and then deal with impaired glucose
25 tolerance, I guess. Doctor Marcus, did you want to

1 comment on this question?

2 DOCTOR MARCUS: Well, I personally think
3 that as long as it is defined in the setting of the
4 trial that this is going to be a trial with people who
5 have diabetes within the range of fasting glucoses
6 from X to Y. I am a little nervous when I think about
7 agencies setting diagnostic criteria only because of
8 my own experience, and yours too I dare say, in the
9 osteoporosis field. Where what was sort of a
10 consensus regulatory body definition that was reached,
11 World Health Organization criteria specifically, for
12 the point of having all trials conform to some
13 reasonably close approximation of each other, that
14 what happened is that the insurance industry took
15 those definitions and used them as gold standards as
16 a way to avoid reimbursing for the cost of the drugs.
17 So I think it would be very treacherous for us to set
18 some criterion for diabetes which would then have as
19 a distant outfall that the insurance industry was able
20 to say, well, your patient didn't qualify for diabetes
21 because of not meeting the FDA criteria, and therefore
22 we are not going to pay for that medication.

23 DOCTOR MISBIN: I am not sure I made it
24 clear. The criteria have already been established
25 independently. I have nothing to do with FDA. The

1 question is should we adapt some changes in the
2 current labels. That, I think, is really the
3 question. Currently drugs are labeled and
4 theoretically they could be used to treat any diabetic
5 patients, but in fact they have not been studied in
6 those patients, and that is actually a very large
7 number.

8 CHAIRMAN BONE: The second thing is would
9 trials include patients now recognized as diabetic but
10 not recognized as meeting criteria for intervention --
11 for treatment. I guess that is probably a very
12 important point going forward. Would you expect that
13 all the patients enrolled in clinical trials meet the
14 recommended criteria for treatment or not just the
15 diagnostic criteria for diabetes?

16 DOCTOR MISBIN: Well, this issue has come
17 up. We have had protocol subsequently. And the new
18 definition that sponsors have used is the current
19 definition of diabetes, meaning you can be a -- you
20 can enter the trial of Type II diabetes provided that
21 your fasting glucose is 126 or greater according to
22 the current recommendations. I, myself -- and I would
23 like to hear everyone's view -- I, myself, don't see
24 any real objection to that because we are doing a
25 study. We are not committing them to life-long

1 treatment. And I think whether or not -- even though
2 the ADA doesn't say these patients should be treated,
3 it certainly doesn't say they should not be treated.
4 That, I think, is a question up to individual
5 clinicians as to whether or not to use the drugs in
6 those patients or not.

7 CHAIRMAN BONE: Well, we will just --
8 Doctor Fleming, and then we will just go around the
9 table and finish up on this topic.

10 DOCTOR FLEMING: Well, to some extent on
11 a practical level it is addressed by the simple fact
12 that the ultimate label that goes with the indication
13 states that the drug is indicated for a patient in
14 whom diet, et cetera, are not adequate to achieve
15 control. So probably the trials should be designed to
16 screen out patients who have gone through a period of
17 diet and other measures and randomize only patients
18 who really fall into what would be treated in the
19 community.

20 CHAIRMAN BONE: Thank you. Doctor
21 Sherwin?

22 DOCTOR SHERWIN: I sort of agree with
23 Doctor Misbin on this one. My view is these people
24 have diabetes. I wouldn't get too exorcised about it.
25 I agree with Doctor Fleming that obviously with a

1 patient with mild diabetes, you would recommend diet
2 and exercise. But if that didn't bring the patient
3 into the normal range within the context of the study,
4 I would see no reason not to include these patients in
5 a clinical trial.

6 CHAIRMAN BONE: All right. Thank you.
7 Doctor Molitch?

8 DOCTOR MOLITCH: I agree with Doctor
9 Sherwin.

10 CHAIRMAN BONE: Doctor Davidson?

11 DOCTOR DAVIDSON: I agree too. You know,
12 very few people will be enlisted with a blood sugar of
13 126 twice, and that is only 14 mg less than the
14 previous criteria. I think that we should continue
15 and use the new criteria.

16 CHAIRMAN BONE: Doctor Critchlow?

17 DOCTOR CRITCHLOW: I agree as well.

18 CHAIRMAN BONE: Doctor Cara?

19 DOCTOR CARA: I agree. I have some
20 difficulty and maybe we can discuss this at some
21 length too. But I have some difficulty in
22 differentiating at times what constitutes Type I
23 versus Type II, but I agree with the basic definition.

24 CHAIRMAN BONE: And for Doctor Hirsch?

25 DOCTOR HIRSCH: Oh, I agree with that as

1 far as I know. Is there any merit, I would ask anyone
2 who knows about this, to also measure insulins in
3 these people? Is that going to be a -- that is just
4 another whole ballpark, I understand.

5 DOCTOR SHERWIN: That is a whole -- yes,
6 we don't know. There was a consensus conference on
7 this and there is no consensus right now. So I would
8 say that probably we could not utilize that as a
9 criteria, even though it might be of value.

10 CHAIRMAN BONE: And the other definitional
11 issue that was raised was this one of impaired glucose
12 tolerance and it was in the context of whether
13 individuals identified as having impaired glucose
14 tolerance were then suitable candidates for prevention
15 studies, if I understood the point correctly. Doctor
16 Misbin, is that a fair summary?

17 DOCTOR MISBIN: Well, I think just to put
18 it in context, there have been a number of sponsors
19 who have come and made this kind of request. They
20 have said the DPP is being done. Let's assume that
21 the DPP is positive and triglidazone and/or metformin
22 are shown to decrease the development of diabetes in
23 the patients with impaired glucose tolerance. What
24 trials do we have to do in order to get that kind of
25 labeling? that is basically the request that was

1 made. Implicit in that request is that the labeling
2 would, in fact, reflect that change. And the reason
3 that this is in the document is that it is not clear
4 to me that in fact the labeling would necessarily
5 reflect that change. I think that there is a question
6 in my mind as to whether or not, even if one assumes
7 -- and of course we don't know the data yet -- but
8 even if one assumes that the 50 percent of patients
9 with impaired glucose tolerance that might otherwise
10 develop diabetes now will not develop diabetes, so it
11 is a very positive result, it doesn't necessarily
12 follow that that means that all patients should be
13 treated indefinitely to prevent the development of
14 Type II diabetes in just 50 percent. And I, therefore
15 then, kind of responded this way to that question.
16 And I think there was a lot of surprise from sponsors
17 who kind of assuming -- that assuming the NIH study
18 was positive that automatically that would basically
19 change the use of these drugs. And I would just like
20 the input from this group as to how to respond to that
21 kind of question.

22 CHAIRMAN BONE: All right. So in this
23 case, we are not talking about the definition?

24 DOCTOR MISBIN: No. The definition of
25 impaired glucose tolerance hasn't changed. It is a

1 question --

2 CHAIRMAN BONE: No. We are talking here
3 about definition of a group. We are really trying to
4 talk about definition of an indication in a way.

5 DOCTOR MISBIN: Yes.

6 CHAIRMAN BONE: All right. And your
7 question is would we regard impaired glucose tolerance
8 as an indication for treatment presupposing the sort
9 of result that you just described?

10 DOCTOR MISBIN: Another question might be
11 should we address this in the guidance altogether.
12 Because in fact given the kind of comments I have
13 gotten about this, I actually regret having included
14 it. Because it really has created a lot of confusion
15 and we have been accused of not wanting to prevent
16 diabetes and all kinds of crazy things. So I think
17 maybe that would be the first issue. Should a
18 document at this stage -- you know, three years or
19 more before we get the result or five years before we
20 get the result -- should we address that at all? Or
21 perhaps we should just take it out entirely.

22 CHAIRMAN BONE: Well, that would be
23 another way of saying it is not an indication at the
24 moment, at least.

25 DOCTOR MISBIN: Yes.

1 CHAIRMAN BONE: Comments as we go around?
2 I will start with Doctor Molitch and then go around
3 this way.

4 DOCTOR MOLITCH: As a current participant
5 in the DPP, I think your response to these companies
6 coming to you is don't count your chickens before they
7 are hatched. We don't have results of this study. We
8 are not going to have them for a good four or five
9 years, and even then there may be lots of questions of
10 interpretation. So I think this is way too premature
11 and just shouldn't be addressed at this point.

12 CHAIRMAN BONE: Doctor Davidson?

13 DOCTOR DAVIDSON: Well, I have the
14 opposite view. You know, diabetes is a progressive
15 disease. That is one of the stages of diabetes. I
16 know we don't have all the answers. But if they have
17 a program that looks viable and that can answer some
18 of the questions that we have, I will not see a reason
19 why not have some guidelines for impaired glucose
20 tolerance.

21 CHAIRMAN BONE: Doctor Critchlow?

22 DOCTOR CRITCHLOW: That is something that
23 doesn't meet the current definition for diabetes,
24 correct? Then I would say not put it in these
25 guidelines anyway.

1 CHAIRMAN BONE: Doctor Cara?

2 DOCTOR CARA: I agree with Doctor
3 Molitch's comments.

4 CHAIRMAN BONE: All right. Doctor Hirsch?

5 DOCTOR HIRSCH: I agree also. Is there
6 even the remote possibility that a drug could be
7 developed which is specifically effective in this
8 condition and is not meant for diabetes? In that
9 unlikely case, which I can't imagine, I would be for
10 testing this sort of thing. If not, it seems to me a
11 better arena for testing these drugs is in the
12 definite frank diabetes situation. So that is one
13 exception.

14 CHAIRMAN BONE: I should think that that
15 would then be regarded as a distinct and separate
16 indication altogether.

17 DOCTOR HIRSCH: Right.

18 CHAIRMAN BONE: Probably an immunological
19 drug or something. Okay.

20 DOCTOR DAVIDSON: And we are talking about
21 Type II diabetes?

22 CHAIRMAN BONE: Yes, I am sorry. Excuse
23 me. Disregard my last remark. I was distracted by my
24 beeper going off here for a second. Doctor Zawadzki?

25 DOCTOR ZAWADZKI: I would agree with the

1 more conservative approach at this point in terms of
2 not dealing with impaired glucose tolerance in this
3 document.

4 CHAIRMAN BONE: Okay. Doctor Marcus?

5 DOCTOR MARCUS: Absolutely. I agree
6 entirely.

7 CHAIRMAN BONE: Doctor Marcus agreed.
8 Doctor Sherwin?

9 DOCTOR SHERWIN: I agree.

10 CHAIRMAN BONE: Okay. Well, good. I
11 think we have -- I am sorry? Okay. The other topic
12 here I would kind of like to review -- we have talked
13 about some of the primary efficacy measures and we
14 have eluded to some secondary efficacy measures. And
15 I think one of the things that we didn't really cover
16 would probably be regarded for the most part as
17 secondary efficacy measures, but might be looked at
18 differently in a different context. Doctor Kolterman
19 alluded to this in his remarks. And that is the
20 effect on end-organ or co-morbid effects of diabetes;
21 let's say the effect on end-organ consequences of
22 diabetes in the setting of a drug with relatively
23 modest effect, perhaps, on glycemia itself. And it
24 seems to me like this would be -- it would be very
25 interesting to have the committee's comments on how

1 those might be weighed in two situations. One would
2 be a drug which was seen to act mainly through its
3 effect on glycemia and thereby mitigating end-organ
4 effects, and another would be drugs which might be
5 acting to mitigate end-organ effects by some other
6 mechanism or mechanisms. Any comments or thoughts
7 about this? How would we weigh the contribution of
8 evidence of end-organ protection in a drug that had a
9 minimal hypoglycemic effect? Doctor Zawadzki, do you
10 have a comment?

11 DOCTOR ZAWADZKI: I'm sure I don't have a
12 definitive comment, but I have some thoughts about it.
13 I think it is -- particularly in Type II diabetes and
14 also I think in Type I diabetes to a large extent, the
15 end-organ effects are very important ones. And has
16 been eluded to in this discussion, we do have
17 therapies that affect the end-organ complications that
18 may affect glycemia very minimally. There is definite
19 value for those. I think, as was also pointed out in
20 some of the comments by the members of the
21 pharmaceutical industry, there are many composite
22 parts to the treatment of people with diabetes that
23 are equally important and perhaps we don't even have
24 an understanding of what is really most important yet.
25 And so I don't think glycemia is the first and only

1 approach that we should take.

2 CHAIRMAN BONE: Doctor Fleming, did you
3 have a comment on that point?

4 DOCTOR FLEMING: Well, I was just wanting
5 clarification of your question in that I don't think
6 anybody would deny that a sponsor should not be able
7 to get an indication for having shown a particular
8 end-organ damage benefit. Are you asking if there are
9 surrogates which we could accept in lieu of having
10 shown the hard long-term outcome data?

11 CHAIRMAN BONE: Well, I guess I am trying
12 to get -- that is correlated. That is a related
13 question, I guess. I guess I wanted to get into a
14 little bit of an open-ended discussion here about how
15 people responded to the several comments to the effect
16 that we might regard a drug as approvable if it had --
17 even with a very modest effect on glycemia if using
18 whatever criteria we agreed on it was shown to have a
19 mitigating effect on end-organs. For instance,
20 prevention of retinopathy or prevention of
21 proteinuria, for instance.

22 DOCTOR FLEMING: But if you've got that,
23 then that trumps the glyceemic effect.

24 CHAIRMAN BONE: Well, there was some
25 question about that based on what we read.

1 DOCTOR FLEMING: Well, obviously if you
2 had a mild glycemc effect or improved glycemia with
3 the drug, you might be able to say something about
4 that as well. But it seems to me that the thing that
5 would really carry the drug is the end-organ damage
6 that it is preventing.

7 DOCTOR HIRSCH: I think a more interesting
8 way to look at this would be to take the data that
9 were presented this morning on sibutramine. Let's say
10 we didn't have sibutramine approved for obesity, but
11 that was coming to you as a fresh drug for treatment
12 of Type II diabetes in obese patients. Would you
13 consider that adequate to have a diabetes indication?
14 The glucoses went down and presumably with it so did
15 hemoglobin A_{1c} and thereby all the end-organ
16 consequences. That is an interesting cross-over.

17 CHAIRMAN BONE: And was actually the next
18 topic I wanted to introduce. It was the question of
19 just that. Maybe we could just come back to that for
20 a minute. So Doctor Fleming is telling us that if we
21 had a drug which mitigated end-organ effects with
22 minimal hypoglycemic effects, we would accept that as
23 an approvable drug with probably some very careful
24 wording of its indication for the treatment of
25 diabetes, but with probably some clarification within

1 that that it wasn't much of a hypoglycemic agent. Is
2 that what you are saying?

3 DOCTOR FLEMING: Well, sure. And, of
4 course, there are a number of drugs that are under
5 development for various complications of diabetes that
6 have no effect on glyceemic control.

7 CHAIRMAN BONE: So everybody is
8 recognized, Doctor Hirsch and then Doctor Molitch.

9 DOCTOR HIRSCH: I think this is very
10 important, but I think it is extremely arbitrary into
11 what bin this is put. In other words, there are
12 fibrotic acid derivatives and statins which are very
13 important for the lipids in diabetes -- ACE
14 inhibitors, maybe anti-androgenesis factors like
15 thalidomide for the retinopathy, whatever. So I think
16 these are terribly -- I don't see it fitting in here
17 except as an additional statement that there are all
18 kinds of drugs that can attack pieces of this picture,
19 but within the rubric we are working, it is through
20 the pathogenetic steps of glycemia, et cetera, it
21 seems to me. Or make a bigger additional document in
22 which you take each of these up. But you have to do
23 it sort of systematically because there will be
24 different guidelines for each one of these
25 interventions.

1 CHAIRMAN BONE: So you would describe the
2 indication really in a different way then?

3 DOCTOR HIRSCH: That is correct.

4 CHAIRMAN BONE: Yes. Doctor Molitch?

5 DOCTOR MOLITCH: My guess is that as we
6 see new drugs being developed specifically for
7 diabetes, it is unlikely that any of the trials that
8 will be ongoing will be long enough to really look at
9 endpoints as you are describing them with any
10 significance. What may be much more likely, however,
11 is to see other metabolic parameters that might change
12 at the same time. So that you may see a drug with
13 modest changes in glucose levels, but substantial
14 elevations of HDL or decreases in LDL levels or
15 perhaps a decrease in systemic blood pressure,
16 diastolic or systolic blood pressure, by 5 mm or
17 weight loss or something like this that in their
18 aggregate -- that those things that we know are other
19 contributory risk factors for macrovascular disease
20 may in their toto be enough to sway us in addition to
21 a very modest glyceemic effect.

22 CHAIRMAN BONE: And then you would regard
23 that as the indication as diabetes there?

24 DOCTOR MOLITCH: Yes. Diabetes -- but it
25 is a whole picture of helping a variety of risk

1 factors.

2 CHAIRMAN BONE: All right. Who else --
3 somebody else? No? Oh, Doctor Misbin?

4 DOCTOR MISBIN: I just wanted to make a
5 point of clarification just to explain why this is in
6 the guidance altogether. It was actually to cover the
7 opposite situation. I think everybody knows that IGF₁
8 was being evaluated as a possible treatment for
9 diabetes, and there was a lot of concern that IGF₁
10 might independently increase the risk of retinopathy.
11 And the question was if it were shown that IG₁
12 improved hemoglobin A_{1c}, would that then be a
13 approvable as a surrogate endpoint. And it was -- my
14 position was that that would not be enough. That you
15 would actually have to -- given our doubt, one would
16 actually have to show that it did not -- at least that
17 it did not make retinopathy worse. Perhaps not that
18 it made it better, but at least that it didn't make it
19 worse. And that was really the reason why this was
20 addressed in the guidance altogether.

21 CHAIRMAN BONE: Thank you. I think having
22 covered that element of the topic, I would like to
23 return to Doctor Marcus's point, which is also one
24 that Doctor Misbin raised originally. And that would
25 be sort of which is the chicken and which is the egg

1 here. If we had an agent that appeared to be
2 effective in reducing body fat and also improved
3 glycemic control but was approved for neither
4 indication, how would we view that if it were
5 submitted for registration for the indication of
6 diabetes primarily rather than obesity.

7 DOCTOR MARCUS: Well, you would have to --
8 you couldn't just do it globally for diabetes because
9 not all Type II diabetics are obese. One would not
10 presume that drug would have any utility outside of
11 the weight loss that it would induce. So a thin Type
12 II diabetic would presumably get no benefit. That is
13 why I would say that that would not -- unless you were
14 careful to include in your indication obese diabetics,
15 then it wouldn't fly with me.

16 CHAIRMAN BONE: I see. All right. So you
17 would say that would be -- but the indication you
18 would be considering then would be diabetes in obese
19 patients as opposed to obesity in diabetic patients?

20 DOCTOR MARCUS: Or as opposed to obesity
21 in general regardless of whether they are diabetic or
22 not.

23 CHAIRMAN BONE: Okay. All right. And
24 what do you think about that?

25 DOCTOR MARCUS: Well, I could see some

1 sense in that. I could see sense in extending the
2 indication specifically to include management of
3 diabetes in obese patients.

4 CHAIRMAN BONE: But you would draw that
5 indication a little bit more narrowly to at least that
6 particular group.

7 DOCTOR MARCUS: Yes. Right. Yes.

8 CHAIRMAN BONE: Other comments? Doctor
9 Critchlow and then Doctor Davidson.

10 DOCTOR CRITCHLOW: I just wanted to ask if
11 in that case, given the durability or lack thereof for
12 obesity once people started gaining weight, do the
13 A_{1c}'s go up?

14 DOCTOR MARCUS: Well, that is a very
15 interesting question. I am not here to --

16 DOCTOR CRITCHLOW: No, I know. It just
17 entered my mind.

18 DOCTOR MARCUS: But if you look at the
19 weight loss studies and glucose control, the amount of
20 weight that has to be lost is very small to see
21 substantial changes in glucose regulation.

22 DOCTOR CRITCHLOW: But when you regain 75
23 percent of your weight loss, would you still see --

24 DOCTOR MARCUS: You still see a pretty
25 durable effect on glucose for a while -- I mean, at

1 least longer than you see the durable effect on
2 weight. Eventually, I think it all comes back.

3 DOCTOR CRITCHLOW: The question I would
4 have is is that still enough to warrant an indication
5 for diabetes.

6 DOCTOR MARCUS: Yes, I don't know. It
7 depends on the durability.

8 CHAIRMAN BONE: Doctor Davidson?

9 DOCTOR DAVIDSON: Well, I think if the
10 clinical trial is designed to address the issues of
11 A_{1c}, glycemia, hypertension, and everything that is
12 related to diabetes in that definition and the study
13 shows to be a positive study, I will approve the drug.

14 CHAIRMAN BONE: Other comments?

15 DOCTOR FLEMING: Well, this is a really
16 important subject. And the question is how would we
17 label the drug in that case when there is a variety of
18 mild but desirable effects. We generally like to
19 identify a single outcome that would lead the
20 indication. And certainly we can make our overall
21 risk/benefit assessment on the basis of all the
22 benefits that have been shown, but we would have a
23 hard time saying this is indicated for the improvement
24 of risk factors related to diabetes, or example.

25 CHAIRMAN BONE: I think what was being

1 proposed was that Doctor Marcus was going to enter
2 patients who were obese and diabetic in the trial and
3 if -- but Doctor Davidson was going to conduct a trial
4 according to the diabetes rules rather than the
5 obesity rules.

6 DOCTOR FLEMING: Yes. No, I thought we
7 had taken care of that issue. I was coming back to
8 the one that I thought Doctor Davidson was raising
9 about having shown a variety of benefits in a study
10 and feeling favorably disposed towards the drug.

11 CHAIRMAN BONE: I think his last comments
12 were directly to the obese diabetic issue.

13 DOCTOR FLEMING: I apologize. But I do
14 think the other issue is important and to make the
15 point that it is hard for us to deal with a large
16 number of outcomes and to compress them into a single
17 indication.

18 DOCTOR SHERWIN: Why wouldn't you use the
19 same criteria as you would for any diabetes drug? I
20 mean, if you corrected obesity, we wouldn't have Type
21 II diabetes, and it would be far more effective than
22 any medication we have. So the question is if you
23 enter into a trial where the endpoints are identical,
24 the same as a glyburide trial, and you have the same
25 outcomes --

1 DOCTOR FLEMING: No, I have no problem at
2 all with the idea of a drug working by reducing
3 weight. That is straightforward. That is no problem.

4 CHAIRMAN BONE: I think Doctor Fleming was
5 returning to the issue of the drug with a minimal
6 hypoglycemic effect but multi-organ system benefits.

7 DOCTOR FLEMING: Or other biochemical
8 benefits -- lipids, blood pressure, whatever.

9 CHAIRMAN BONE: That is a thorny issue,
10 but I think the sense of the committee was that they
11 would be interested in something along those lines
12 having a benefit in diabetes, but obviously there is
13 some difficulties in precisely defining that. Yes,
14 Doctor Hirsch?

15 DOCTOR HIRSCH: But each would need a
16 different set of guidelines from what we are talking
17 about here. So in terms of a document, you might want
18 to state these and indicate that. I mean, in the
19 extreme case for example -- someone has a skin
20 manifestation. They have necrobiosis lipoidica
21 diabetorum and a fellow comes along with a good
22 salve, well you don't want us to review that for you
23 or these guidelines to go into the complexity of that
24 issue. So in each instance, I think -- for example,
25 the obesity drug, the durability becomes the

1 monumentally important side of this. Because these
2 drugs tend not to work for a long time, whereas that
3 may not be so for ACE inhibitor with nephropathy or
4 whatever.

5 CHAIRMAN BONE: Would the members of the
6 committee be inclined to want to see relatively long
7 trials in the obesity type situation -- in the obese
8 diabetic situation? Would we be thinking about
9 perhaps two-year after treatment studies? Well,
10 everybody is sort of nodding, but we all have to get
11 on the record here. This is Doctor Cara.

12 DOCTOR CARA: I don't know why couldn't
13 use the obesity guidelines or the guidance for
14 obesity. I mean, it is pretty well documented there
15 that -- I mean, efficacy guidelines are fairly well
16 documented and they include co-morbidities associated
17 with these things.

18 CHAIRMAN BONE: It is a question really of
19 which is the primary indication and which is the
20 secondary.

21 DOCTOR CARA: Well, but isn't that up to
22 the sponsor to determine?

23 CHAIRMAN BONE: Well, that is the point.
24 Suppose the sponsor wishes to have their drug reviewed
25 as an anti-diabetic agent even though its major

1 mechanism of action is reduction of body fat?

2 DOCTOR HIRSCH: What I am saying is in the
3 review of that, we have to state in this document that
4 we have dealt mostly with hypoglycemia, et cetera. So
5 we have additional paragraphs saying in these other
6 instances, there will have to be a dual guideline
7 approach to this thing because of the specific issues
8 brought up. Instead of going into -- otherwise, we
9 have a monumentally large document to handle always.

10 CHAIRMAN BONE: Yes. I think what is
11 being contemplated here though is if someone has a
12 drug with that mechanism of action who just applies
13 for registration as a hypoglycemic agent and it
14 worked. And I think several members of the committee
15 indicated that they would be favorably disposed toward
16 reviewing that as an anti-diabetic agent. But I guess
17 I was asking the question, would we expect -- because
18 of the major issue that was being raised was this one
19 of durability of effect, would we expect longer term
20 trials in that situation than we might for the typical
21 hypoglycemic agent?

22 DOCTOR HIRSCH: Absolutely. Yes, very
23 much so in the case of obesity particularly where
24 durability becomes a major issue.

25 CHAIRMAN BONE: And that was the point

1 raised by Doctor Critchlow originally, I think, and I
2 see Doctor Davidson and Doctor Cara nodding. Doctor
3 Molitch -- on the right-hand side of the table, we see
4 nods all around. Everybody in the committee seems to
5 agree that longer term trials would probably be
6 required in that situation. I see nodding as we go
7 down the table into the FDA section as well.

8 That brings up a point that I was
9 wondering about earlier. And that is one of the
10 concerns the Agency always has is to have the longest
11 possible experience with a drug, but this is always
12 limited in a placebo-controlled trial by how long we
13 are willing to let the placebo-controlled patients,
14 who presumably are not benefitted to the same extent,
15 go without treatment. Since there was a lot of
16 emphasis on positive control trials in the morning
17 discussion, would members of the committee -- how
18 would they feel about the duration of positive control
19 trials of the usual kind for the diabetes indication?
20 Was a year still sufficient in that situation?

21 DOCTOR MARCUS: I think the reason you
22 would prolong treatment is to --

23 CHAIRMAN BONE: This is Doctor Marcus.

24 DOCTOR MARCUS: Mostly for safety and also
25 to test one aspect of efficacy and that is the

1 durability. So I would think that one could, after
2 some defined period adequate enough to do whatever
3 placebo comparisons you are interested in doing, could
4 then switch to open label and just maintain everybody
5 for a longer period of time to address just those two
6 issues.

7 CHAIRMAN BONE: I had a different
8 question. I am not talking about in a placebo-
9 controlled trial in the first place. I am talking
10 about in the comparator positive-control trial where
11 all the patients in the study were on active
12 treatment. I don't disagree with what you just said
13 for a placebo trial.

14 DOCTOR MARCUS: There is still benefit for
15 durability and also for toxicity for long-term.

16 CHAIRMAN BONE: So you would be willing to
17 have a longer term randomized blinded trial against a
18 positive control for that kind of information?

19 DOCTOR MARCUS: Against a positive
20 control, sure.

21 CHAIRMAN BONE: Others?

22 DOCTOR CARA: So what you are saying is
23 that we are modifying --

24 CHAIRMAN BONE: I am just asking.

25 DOCTOR CARA: Or what you are proposing is

1 that you are modifying the one-year?

2 CHAIRMAN BONE: No, I am just asking. The
3 question came up. Somebody mentioned it and I am just
4 asking. For example, would you have a blinded
5 extension, for example, where the same randomization
6 was maintained after one year for additional
7 comparative safety and efficacy?

8 DOCTOR CARA: What is the point? Why?

9 DOCTOR SHERWIN: Yes, I am confused also.

10 CHAIRMAN BONE: Well, because if you want
11 to adequately assess adverse events and so forth, you
12 have to have a blinded trial for that.

13 DOCTOR DAVIDSON: I think what Doctor
14 Marcus said is after one year it is an open label. You
15 finish the study and you continue the patients but not
16 blinded anymore, just to assess long-term safety. And
17 I think that is acceptable.

18 CHAIRMAN BONE: I am not talking about a
19 placebo-controlled trial here. I am talking about a
20 trial where all patients were assigned to a treatment.

21 DOCTOR CARA: If you are thinking about
22 extending a study, it really needs to be done in a
23 blinded manner.

24 CHAIRMAN BONE: Yes.

25 DOCTOR CARA: Because otherwise, it

1 doesn't really hold up.

2 CHAIRMAN BONE: Do you think that that
3 would be --

4 DOCTOR CARA: And -- I mean, I think you
5 are raising a good point, especially if we consider
6 drugs that are geared towards issues like weight loss
7 in terms of diabetes control and the whole issue of
8 durability. I mean, I wouldn't be adverse to
9 considering a two-year study.

10 CHAIRMAN BONE: Well, or a blinded
11 extension. That would be another way of having your
12 one-year endpoint.

13 DOCTOR DAVIDSON: For clarification?

14 CHAIRMAN BONE: Yes.

15 DOCTOR DAVIDSON: I think we all agree
16 that in the obesity drugs, it is two years blinded.
17 I think the question now is --

18 DOCTOR CARA: I am talking about other
19 therapies.

20 CHAIRMAN BONE: This is another anti-
21 diabetic drug.

22 DOCTOR CARA: Right. I mean, we know that
23 with obesity, there is a tendency for regain of
24 weight. We don't know with other therapies that are
25 potentially out there, maybe not even invented yet,

1 whether there is that same sort of phenomenon. I
2 think the issue of durability is a very important
3 issue.

4 CHAIRMAN BONE: It is a problem in a
5 placebo-controlled trial. But if we did have as part
6 of a development program a positive comparison, it
7 just seems like a away of addressing that. And that
8 extension phases can be going on while the review is
9 being conducted and so on and so forth. It doesn't
10 have a big impact on the development time.

11 DOCTOR CARA: As long as the extension
12 phase is blinded is what you are saying?

13 DOCTOR HIRSCH: It depends totally on the
14 endpoints selected and the organ that is diseased. I
15 mean, suppose someone said I have a drug which affects
16 longevity in diabetes, but it doesn't change blood
17 sugar. You would have a hell of a problem on your
18 hands.

19 CHAIRMAN BONE: You have one too? I am
20 talking about a classical hypoglycemic agent.
21 Something very straightforward. Doctor Molitch?

22 DOCTOR MOLITCH: I haven't seen evidence
23 based on any studies that have been done previously to
24 suggest that we need to go out past one year except
25 for potentially the weight-loss group that we have

1 just talked about. So I don't see a need to go past
2 one year for the active comparator.

3 CHAIRMAN BONE: Okay. I agree.

4 DOCTOR MOLITCH: Unless there is something
5 new and different that made it compelling to do so.

6 CHAIRMAN BONE: All right. I am just
7 raising the question. I am not advocating. I am just
8 asking the question.

9 DOCTOR MARCUS: But I think, though, that
10 just like some of our organizations in the
11 osteoporosis field, if I may dwell on that for a
12 moment, have agreed to go on with unblinded
13 continuation of observations of patients on treatment
14 another five years. That is terrific information that
15 you get. But if you insisted on them maintaining the
16 blind and continuing it as a major clinical trial, I
17 think the resources and the time involved, they would
18 just say no, we are not going to do it.

19 CHAIRMAN BONE: All right. Well, it is
20 something -- I just wanted to mention it and it is
21 something to think about. I am not trying to press
22 the point to closure at all or even taken a position
23 on it, but it had come up and I thought it was worth
24 having a little discussion about it.

25 I think the other topic about which Doctor

1 Misbin expressed concern, but without getting into it
2 very much in his presentation this morning, was this
3 subject of pregnancy and gestational diabetes. And
4 perhaps he would be good enough to sort of say exactly
5 what it is that is worrying him about pregnancy and
6 gestational diabetes.

7 DOCTOR MISBIN: I was hoping this wouldn't
8 come up actually. Even though it is --

9 CHAIRMAN BONE: Well, you actually said
10 you wanted help with this, so you are getting it.

11 DOCTOR MISBIN: I know. We do want help,
12 but I don't look forward to explaining this. I think
13 we generally recognize that drugs are used in --

14 CHAIRMAN BONE: Stay closer to the
15 microphone.

16 DOCTOR MISBIN: I think antidiabetic drugs
17 are used in pregnant women or patients who become
18 pregnant while using the drug, but I think the data
19 base here is not very great, particularly with respect
20 to oral hypoglycemic agents. I think there is -- that
21 is not considered to be a treatment for diabetes in
22 pregnancy, even though I don't think there is any good
23 data really to tell us one thing or the other.

24 Now really this -- I will just put the
25 setting. This came up really in a question of a drug

1 used which might be able to prevent the development of
2 diabetes in patients who had previous gestational
3 diabetes. And the study design that was being
4 proposed was to take these patients, now post-partum,
5 and to treat them with the drug in a randomized way to
6 see if it prevented future diabetes. But that if the
7 patient became pregnant, which of course is quite
8 likely since that is how they entered the trial, that
9 the drug would be stopped. And this generated some
10 discussion.

11 It seemed really that the question was
12 this. The patient may be taking the drug and realize
13 that they are pregnant and this may take several
14 months. And the major teratogenic effect or presumed
15 teratogenic effect of the drug will have already have
16 taken place in that patient. On the other hand, the
17 potential benefit of this drug would really be related
18 to the macrosomia, which is later in the pregnancy.
19 And if you then stop the drug when you then make a
20 diagnosis of pregnancy, it appears, at least to me,
21 that you may be exposing the patient to the risk of
22 the teratogenicity and then denying them the potential
23 benefit of improving the diabetes later in the
24 pregnancy. And so the proposition was that in fact
25 the drug would be continued during the pregnancy,

1 assuming that it did not have -- that in our animal
2 studies -- and this is just underlined -- in the
3 animal studies that there was no evidence for any
4 teratogenicity.

5 The principle investigator actually was
6 very much in favor of this, but the sponsor really
7 wouldn't hear of it. And wouldn't hear of it, it
8 seemed to me, not based on discussion of the facts of
9 the issue, but just that they didn't want -- they just
10 would not consider the possibility of not stopping the
11 drug in a patient who became pregnant. And that is
12 really what I would like input from the committee on.

13 CHAIRMAN BONE: Doctor Sherwin is anxious
14 to address this.

15 DOCTOR SHERWIN: Oh, right. If I was in
16 charge of that study, I wouldn't have gone ahead
17 either. Because I think that there are a lot of legal
18 issues revolving around an untested drug and one would
19 -- it is going to be very hard, I think, for the
20 Agency to legislate this on sponsors to make them do
21 studies if they don't want to because of their concern
22 about the legal issues. So I think that we do have
23 medications that work during pregnancy to treat
24 hyperglycemia. I don't think if I was running a
25 company that I would want to take that liability in my

1 hands either. So my view would be that insulin is an
2 acceptable treatment during pregnancy and I would not
3 force sponsors to utilize drugs that may even in the
4 most remote case produce a problem.

5 DOCTOR MISBIN: Would you go so far as to
6 not to force them, but would you even do any trial
7 with an oral agent in patients who are pregnant?

8 DOCTOR SHERWIN: Well, I am not an expert
9 in this area. I wouldn't want to comment. I think it
10 would really depend upon how strong the preclinical
11 data was. I don't think I am qualified to answer that
12 in terms of -- I wouldn't want to.

13 CHAIRMAN BONE: Doctor Molitch, would you?

14 DOCTOR MOLITCH: I think there might be
15 some very interesting drugs to use during pregnancy,
16 but I think in the medical/legal climate that occurs
17 these days, it is not going to happen. I think this is
18 a non-issue. It is just not going to happen period.

19 CHAIRMAN BONE: Doctor Davidson?

20 DOCTOR DAVIDSON: I don't know if any IRB
21 will approve such a protocol.

22 CHAIRMAN BONE: Any different views
23 amongst the committee? No. Okay.

24 DOCTOR SHERWIN: It is an area you don't
25 want to touch. But the pregnancy -- I mean, not the

1 pregnancy side but the pediatric side --

2 CHAIRMAN BONE: We are going to get to
3 that in a minute.

4 DOCTOR SHERWIN: Are we going to get to
5 that?

6 CHAIRMAN BONE: So the next thing, which
7 is also -- I mean, if there is anything that is as
8 remotely as touchy as doing testing of experimental
9 drugs in pregnant women, it would be testing
10 experimental drugs in children. So just to get to the
11 next hot potato here, the subject was raised of use of
12 oral hypoglycemic agents in children. And I don't
13 know if this was intended to be referred to as
14 adjunctive therapy in Type I or in children with Type
15 II diabetes.

16 DOCTOR MISBIN: This was children with
17 Type II, but I think Doctor Davidson knows something.

18 DOCTOR DAVIDSON: Well, the biggest
19 difficulty we are facing is we have a small new
20 epidemic of Type II diabetes in children and
21 adolescents. And I think that we are seeing only the
22 tip of the iceberg. In Texas, we have more than 500
23 children clearly obese with all the symptoms and all
24 the characteristics of Type II diabetes with
25 acanthosis, massive obesity, hyper-insulinemia, and we

1 don't have an approved therapy for these children
2 other than insulin. I am not saying insulin is not a
3 good drug. Insulin is the gold standard. But if we
4 can make the hyperinsulinemia, the weight down, and all
5 the other parameters with an appropriate clinical
6 trial, I think that we have a lot to benefit these
7 children. And right now, there is no indication for
8 any of the oral agents. I am not saying every oral
9 agent should be indicated for the treatment of Type II
10 diabetes in children, but clearly some clinical trials
11 should be done in these children and adolescents.

12 CHAIRMAN BONE: I would be very interested
13 in comments from the other committee members about how
14 this might be approached. Perhaps Doctor Cara would
15 be willing to start the discussion about how would we
16 test oral hypoglycemic agents in children and
17 adolescents.

18 DOCTOR CARA: I think -- I mean I think
19 you have hit on a very important topic. On the one
20 hand, I think that it is very important to be
21 cautious, especially with children. On the other,
22 what we don't realize is that we oftentimes rob
23 children of potential therapies that could really make
24 a significant impact on their disease and disease
25 process. So that said, I think that there is

1 definitely a place for at least some oral hypoglycemic
2 therapy in children. Unfortunately, part of the
3 difficulty that we have is in establishing a diagnosis
4 of Type I versus Type II. In the typical situation,
5 such as the patient described by Doctor Davidson, it
6 is not all that hard. But it oftentimes is difficult
7 because even patients with what later proves to be
8 Type II or maybe what we want to call Type I and a
9 half, they may present, in fact, with mild ketosis at
10 initiation of treatment, and at that time it is
11 oftentimes difficult to decide which way that is going
12 to turn out. We have actually gone ahead and started
13 using oral hypoglycemic agents in some of our
14 patients, recognizing that some of the newer oral
15 hypoglycemic agents designed primarily to increase
16 insulin sensitivity have the most benefit. The
17 problem in most of the patients that we see is a
18 combination of insulin resistance and mild
19 insulinopenia, but primarily insulin resistance. A
20 lot of our patients have responded to that type of
21 treatment.

22 Unfortunately, this is the type of thing,
23 this somewhat individualistic approach if you will, is
24 going on at other centers. And as a result, we don't
25 have good guidelines. We end up with small groups of

1 patients that we can't generalize upon. So I think
2 developing some sort of guidelines that will help us
3 to at least get more information on optimal therapy is
4 important.

5 I would not have a problem in starting
6 oral hypoglycemic agents in the older adolescent, say
7 beyond 13 to 14 years of age. I think the issues get
8 a little bit more difficult when you start talking
9 about younger and younger children.

10 CHAIRMAN BONE: At what stage in the
11 compounds development process would you be willing to
12 start trials in children?

13 DOCTOR CARA: I think as part of any Phase
14 III study, at least an older adolescent component
15 needs to be considered.

16 CHAIRMAN BONE: So you would definitely
17 start adolescent trials prior to completion of the
18 adult trials, but what about trials in children?

19 DOCTOR CARA: I think that is a stickier
20 issue. What I would suggest is that trials in
21 children be initiated once we have information on what
22 happens to the adolescents.

23 CHAIRMAN BONE: So you would take this as
24 a step-wise kind of thing?

25 DOCTOR CARA: Right. I would definitely

1 take a step-wise approach. I would be a little antsy
2 about starting younger children on therapies that have
3 not proven their safety or their efficacy at least in
4 the older adolescents.

5 CHAIRMAN BONE: Now would you expect to
6 see separate pharmacokinetic and pharmacodynamic
7 studies and a Phase II type approach for the
8 adolescents and for the children?

9 DOCTOR CARA: Yes. In general, children
10 tend to be faster metabolizers, so that
11 pharmacokinetics are oftentimes different. I think it
12 is important when considering therapy in adolescents
13 that they not be considered small adults and that data
14 really be obtained for them in terms of
15 pharmacokinetics and time course studies and so on and
16 so forth. I think that is the responsibility that
17 really falls on the sponsor and really needs to be
18 undertaken. But I think -- the point that I want to
19 underscore again is the issue that they really should
20 not be considered small adults.

21 CHAIRMAN BONE: Thank you.

22 DOCTOR MARCUS: How can you do PK studies,
23 and presumably that would have to be done in normal
24 children -- PK or pharmacokinetic studies?

25 DOCTOR CARA: I would have difficulty with

1 that.

2 DOCTOR MARCUS: Yes. That is --

3 DOCTOR CARA: I think what I would offer
4 as perhaps a compromise is to do PK studies as part of
5 the Phase II.

6 DOCTOR MARCUS: Part of the treatment,
7 yes.

8 CHAIRMAN BONE: Surely not part of Phase
9 III.

10 DOCTOR CARA: No, no, no, but a late Phase
11 II trial.

12 DOCTOR MARCUS: A study of physiology in
13 the children that Doctor Davidson talked about.

14 DOCTOR CARA: In the targeted population
15 rather than the "normal" child.

16 CHAIRMAN BONE: I think -- yes, that is
17 the point.

18 DOCTOR SHERWIN: In the diabetic
19 population?

20 DOCTOR CARA: I am sorry?

21 DOCTOR SHERWIN: In the diabetic
22 population.

23 DOCTOR CARA: In the diabetic population,
24 right.

25 CHAIRMAN BONE: But surely you would have

1 to do those studies before you could properly design
2 longer term trials.

3 DOCTOR CARA: Exactly. Right.

4 CHAIRMAN BONE: So what you are really
5 saying is not that you would do it as -- you would do
6 it in parallel with the adult Phase II, but you would
7 do it in diabetic children?

8 DOCTOR CARA: Yes.

9 CHAIRMAN BONE: Is that clear?

10 DOCTOR MARCUS: The point I was making is
11 that it is traditional to do your Phase I studies in
12 a population of healthy adults -- you know, single
13 dose or dose escalation studies. And that I think you
14 would have to modify that part. I would not be
15 comfortable doing those kinds of studies in healthy
16 children.

17 DOCTOR SHERWIN: Wouldn't you need to
18 finish Phase II before doing pharmacokinetic studies
19 in people?

20 DOCTOR CARA: You mean Phase II in adults?

21 DOCTOR SHERWIN: Yes.

22 DOCTOR CARA: Oh, yes.

23 DOCTOR SHERWIN: You would want to be sure
24 that there is efficacy before embarking and exposing
25 children to drugs.

1 DOCTOR CARA: I mean, a whole side-line
2 issue that really bears on this, and I don't know what
3 the FDA's position is, is the issue of how to attain
4 assent in children.

5 DOCTOR SHERWIN: But I think that is
6 doable within the guidelines of IRB's.

7 DOCTOR CARA: I think it is doable too.

8 CHAIRMAN BONE: Let's see, we had several
9 questions. I think, Doctor Davidson, did you have a
10 question? And then Doctor Hirsch and then Doctor
11 Molitch.

12 DOCTOR DAVIDSON: You know, it is actually
13 a comment. I feel that this population is going to
14 continue to increase and that we need to make an
15 attempt of doing clinical studies in these
16 populations. I agree that we cannot do the PK's in
17 healthy children. I think we need to do it at the end
18 of Phase II in children with diabetes, and we should
19 do it after we finish the safety data on adults.

20 CHAIRMAN BONE: Right.

21 DOCTOR CARA: And again, I think that part
22 of the difficulty that we are faced with in terms of
23 treating children is that we oftentimes don't have
24 data regarding efficacy or safety in children, or for
25 that matter, PK studies or the sort. So we have to

1 guess a lot of times when we utilize therapies that
2 have been approved in adults and teenagers. So having
3 that information would really be very helpful.

4 CHAIRMAN BONE: Absolutely. Doctor
5 Hirsch?

6 DOCTOR HIRSCH: I just wanted to note for
7 the record, and I am sure you probably all know this,
8 that in the Federal Register are exact guidelines for
9 treatments of this sort or studies of this sort in
10 children, and this is managed by the OPR of the NIH.
11 As I recall, principle number one is that for studies,
12 you may not do anything that is more hazardous than
13 the hazards of every day life unless you specifically
14 have an ill child and what you are planning to do
15 would have advantage to this particular child or set
16 of children. So that it is much more rigid than with
17 the adults. It would be absolutely impossible to do
18 PK studies according to those guidelines. So that
19 whatever is done in our report, I think we should make
20 reference to that and that this be done in
21 collaboration with the IRB and consultation with OPR.

22 CHAIRMAN BONE: Thank you. Doctor
23 Molitch?

24 DOCTOR MOLITCH: I think some of the major
25 concerns we all have are risks to the children that

1 might not be present in adults. And one of the two
2 major classes of risk to children that we are always
3 concerned either during adolescence or pre-adolescence
4 is alterations in growth and development and
5 alterations in pubertal development. We know that
6 obese children in general tend to have earlier
7 development. They tend to have earlier height
8 development and tend to progress more rapidly through
9 the stages. It is possible -- I don't know what the
10 natural history of these children now with Type II
11 diabetes -- whether their abnormal glucose tolerance
12 counteracts that effect of obesity, whatever that
13 effect of obesity is. So I don't know what the
14 natural history data are, if there are such, to
15 compare them to non-diabetic obese children. So that
16 is one set of data set that is needed to see whether
17 that has changed. Because there is certainly a
18 possibility that if you used an oral agent that might
19 help to prevent weight gain and that would improve
20 glucose tolerance, you may see a whole confounding set
21 of changes so that you may actually slow growth and
22 development back to normal, whereas that that may then
23 appear to be a detrimental effect. So this has to be
24 done very, very carefully with the proper controls.
25 And clearly insulin is the accepted standard of

1 treatment for a diabetic child, which of course may
2 make the obesity worse and may hasten this growth, and
3 a better treatment may actually be something that
4 reduces insulin resistance, which may have the
5 opposite effects. So I think that these kinds of
6 studies have to be carried out very, very carefully
7 with very careful controls of obese non-diabetic
8 children as well.

9 DOCTOR CARA: As a comment, most of the
10 patients that we have seen with this Type I and a half
11 or Type II diabetes tend to typically be post-
12 pubertal.

13 DOCTOR SHERWIN: They are almost always.
14 And that is why the issue of prepubertal is really not
15 a major one. Because virtually 95 percent are
16 adolescents already. And also, they are approaching
17 completing their growth phase. But I would like to
18 echo and just to make the point that this is a major
19 problem that is developing, particularly as the
20 minority populations are increasing within our general
21 population. It is really becoming much more evident
22 clinically than it ever was before, the appearance of
23 Type II diabetes in that population. And I really
24 believe very strongly that we have to do proper
25 studies. Because the problem is that the studies that

1 have been done have been piecemeal. And really
2 defining what would be the most appropriate treatment
3 in this group I think is very important as we get into
4 the next century, where we are going to have a
5 significant problem with adolescent Type II diabetes.

6 DOCTOR MARCUS: Are we talking about a
7 fundamental problem of obesity, which then allows the
8 Type II diathesis to emerge? Or are you seeing this
9 even in --

10 DOCTOR SHERWIN: No, these are obese
11 children.

12 DOCTOR MARCUS: Obese children. So that
13 is the --

14 DOCTOR SHERWIN: And the problem of
15 childhood obesity --

16 DOCTOR MARCUS: The kernel of the issue is
17 childhood obesity.

18 DOCTOR SHERWIN: Well, it is surely a
19 major factor. Obviously, they inherit certain genes
20 that may affect their beta cell function as well. But
21 the obesity is bringing out the majority of the cases
22 -- the vast majority.

23 CHAIRMAN BONE: All right. We have
24 actually covered -- I am sorry, Doctor Zawadzki.
25 Excuse me.

1 DOCTOR ZAWADZKI: I just have a question
2 regarding clarification here. I understand that some
3 of the individual physicians on the panel are seeing
4 many of these children. Does this represent a large
5 number in the whole population? Are we seeing
6 isolated numbers at certain clinical settings? What
7 are the -- what is the actual denominator? And is it
8 worthwhile to consider studies given the denominator?

9 DOCTOR DAVIDSON: Well, I did not attend
10 the second -- there have been two annual meetings on
11 Type II diabetes in children and adolescents, and I am
12 pretty sure somebody from the Agency was there, or I
13 believe they were. In the first one, there were many
14 people from CDC and NIH. Like in Texas, I can tell
15 you that we have identified at least over 500 children
16 with diabetes. I went to Tucson, Arizona, and in only
17 one of the tribes of Pimas that were below the age of
18 18, about 45 children diagnosed with Type II diabetes.
19 There are many children diagnosed in southern
20 California and other areas of Oklahoma, Texas,
21 Arizona, and Colorado. I think it is more a problem
22 than it appears. I think we are seeing the tip of the
23 iceberg.

24 DOCTOR CARA: I would echo those comments
25 and say that to a large extent, it is not a trivial

1 problem. The difference is the ethnic differences
2 between the typical Type I patient and the Type I and
3 a half and Type II patient. But we are seeing a
4 tremendous number right now, to the point where we
5 almost have a one for one ratio.

6 DOCTOR ZAWADZKI: I am sorry, one for one
7 ratio? What do you mean?

8 DOCTOR CARA: For every child that we
9 diagnosis as having insulin-dependent diabetes, we
10 diagnose one as having non-insulin dependent.

11 DOCTOR ZAWADZKI: But those are very small
12 numbers still. I mean, if we are looking across the
13 whole population, Type I diabetes has a prevalence
14 of --

15 DOCTOR CARA: It is not trivial.

16 DOCTOR ZAWADZKI: It is not trivial, but
17 it is not a prevalence as high as we see in Type II
18 diabetes in adults.

19 DOCTOR CARA: But remember, this is what
20 we are actually diagnosing. I agree with Doctor
21 Davidson's comments in the sense that it is the tip of
22 the iceberg. I mean, I can almost guarantee you that
23 for every patient that we see in the clinic and we
24 diagnose, there are probably 10 out there that are
25 still walking around undiagnosed.

1 CHAIRMAN BONE: All right. Doctor Misbin
2 had a --

3 DOCTOR MISBIN: I would like just to ask
4 what action would the committee recommend that we take
5 with respect to already marketed drugs. We are being
6 asked really to consider what to do about that, and
7 there is a whole spectrum of action that --

8 DOCTOR CARA: Do you mean in children?

9 DOCTOR MISBIN: Yes, yes, in children.
10 There is a whole spectrum of action that could be
11 taken going from doing nothing and just allowing
12 people to use it based on the current labeling or
13 adding that indication based on anecdotes or requiring
14 short-term clinical trials or requiring large clinical
15 trials. What action -- the whole spectrum is
16 possible. What would be recommended?

17 DOCTOR DAVIDSON: I believe we need to
18 have clinical trials. We really don't know exactly
19 how the drugs behave in children based on different
20 circumstances. And I don't really know if all the
21 drugs out there are safe. If you look at the
22 mechanism of action, are they safe drugs to use in
23 this population. I think that we need to have
24 clinical trials short term and some observational
25 trials of longer term to see the safety of these drugs

1 in this particular population. And I think the
2 existing drugs should be considered for clinical
3 trials.

4 DOCTOR MARCUS: I certainly agree with
5 that. My colleagues at Stanford in pediatrics tell me
6 that nationwide about 75 or 80 percent of
7 prescriptions in pediatric use are off-label.

8 DOCTOR CARA: That is exactly right.

9 DOCTOR MARCUS: This is certainly a bad
10 situation. I am sure that the Agency doesn't like --
11 wouldn't be happy if that is accurate. And I think
12 here is a chance to get them on label and particularly
13 for toxicity follow-up. I have a little bit of
14 knowledge about a class of anti-convulsant medication
15 which in adults seemed to be fine, but then it turned
16 out in children had some extraordinarily unacceptable
17 prevalence of Stevens-Johnson syndrome. I think you
18 have to learn those things, and there is only way you
19 are going to learn them and that is by doing the
20 trials.

21 CHAIRMAN BONE: Well, let me ask the
22 committee a question then. It seems to me that from
23 the -- if I can interpret Doctor Misbin's question a
24 little bit, there are a couple of different levels of
25 information that might justify different kinds of

1 labeling. One would be clinical trials demonstrating
2 safety and efficacy in the usual way, which presumably
3 would, without any real question, justify labeling for
4 the indication of Type II diabetes mellitus in
5 children. And the other would be shorter-term studies
6 which would have the kind of pharmacokinetic and
7 pharmacodynamic information that is not available, but
8 wouldn't be of sufficient duration and wouldn't
9 provide sufficient information, perhaps, to reach the
10 level of certainty that would get a full indication,
11 but it would at least be allowed to be in the
12 pharmacology section of the package insert. And I
13 guess I am interested in both what the Agency and the
14 committee members would feel about those two
15 approaches. I guess there is no question about the
16 first. If you have the trials, you would award the
17 indication. But the second, would you be interested
18 in having an intermediate level of information while
19 those trials were being conducted and to have that
20 information available?

21 DOCTOR MISBIN: I would like to ask Doctor
22 Billston, actually, would it be possible to have
23 trials on children in the pharmacology section but not
24 actually have that as an indication? Is that even
25 regulatory feasible? It is.

1 DOCTOR BILLSTON: Well, there is a special
2 pediatric criterion or regulation -- a special
3 pediatric exception that deals with those types of
4 things.

5 DOCTOR MISBIN: But not to have an actual
6 indication. In other words, just give something in the
7 pharmacology, but then in the indication section, not
8 discuss pediatric use and presumably then sponsors
9 would not be able to advertise that if it isn't an
10 indication.

11 DOCTOR CARA: How would the Agency enforce
12 this testing? I mean, let me give you a scenario.
13 You are talking about drugs that are routinely being
14 used off label by a variety of different patients and
15 physicians. Why should the drug company -- or what
16 can you do to get the drug company really to do some
17 further testing?

18 DOCTOR SOBEL: You are touching on a very
19 current subject at the Agency. We are trying to give
20 some advantage for a company to do this in the form of
21 exclusivity. If a company comes in asking for a
22 pediatric indication and we agree that this is a
23 situation where clinical studies would be valuable,
24 then there is a means of giving a carrot, so to speak,
25 to do this study in the form of exclusivity. In other

1 words, that company would have exclusive rights for
2 that indication in advertisement. So there are --
3 this has been something we have wrestled with for a
4 long time, but now there is a great deal of
5 Congressional interest in getting more specific
6 information for the pediatric AIDS group, and an
7 initiative which we are currently involved in is
8 identifying drugs that would qualify for an
9 exclusivity status if a clinical study is done.

10 CHAIRMAN BONE: Would these be drugs which
11 might be off patent?

12 DOCTOR SOBEL: Well, that is a good
13 question. If a drug is off patent, essentially what
14 you are granting is the right for advertisement in an
15 exclusivity situation.

16 CHAIRMAN BONE: But you couldn't prevent
17 substitution.

18 DOCTOR SOBEL: Pardon?

19 CHAIRMAN BONE: But you couldn't prevent
20 substitution.

21 DOCTOR SOBEL: No. You know, in every
22 situation a use patent is not that valuable if
23 clinicians recognize that it is the same thing. But
24 there is an advantage in general advertisement for a
25 company that has exclusivity.

1 CHAIRMAN BONE: And presumably in that
2 situation then only a company with that exclusivity
3 would be allowed to manufacture the pediatric
4 formulation or dosage form and trade dress and so
5 forth that would be --

6 DOCTOR SOBEL: Yes, if that would be
7 necessary for easier administration, that would be
8 part of it.

9 CHAIRMAN BONE: Let's see, everybody has
10 gone once. Doctor Hirsch, Doctor Critchlow, and
11 Doctor Misbin.

12 DOCTOR HIRSCH: I would just like to speak
13 in favor such studies, because I think some very
14 valuable information could be garnered. We have
15 already spoken, if properly designed -- we have
16 already spoken about the acceleration or deceleration
17 of growth, which would be a very important thing to
18 know. And one thing I would like to point out is that
19 there is a lot of mythology surrounding the
20 relationship of insulin administration to obesity as
21 though insulin from a needle is that different from
22 insulin from a beta cell. This might help put that
23 thing to bed also. I would very much doubt that
24 insulin administration in these children would make
25 them in any degree fatter. If that were an arm of the

1 study, that would be very valuable.

2 CHAIRMAN BONE: Thank you. Doctor
3 Critchlow and Doctor Misbin.

4 DOCTOR CRITCHLOW: I was just going to ask
5 if in a particular trial, would you have an insulin --
6 I mean, you would want an insulin control rather than
7 a placebo. You probably couldn't do a placebo
8 control.

9 DOCTOR HIRSCH: I would have to think more
10 about that. That would be very valuable at least in
11 terms of our knowledge. I would like to think about
12 that more in terms of the propriety of doing this in
13 the setting of such a study. I would hope that it
14 might be done.

15 CHAIRMAN BONE: Doctor Misbin, you had a
16 further --

17 DOCTOR MISBIN: Just one other point.
18 Recognizing that it is generally obesity which
19 precipitates the diabetes in these patients, is there
20 any concern that by treating patients or young
21 children with pharmacological agents this young in
22 life that you might in fact not be doing them good and
23 perhaps that is an easy way out and maybe it would be
24 better to really continue to stress dietary
25 management. It just seems to me that to take a child

1 of 12 and start them on an agent, I am not certain
2 that that is the right thing to do.

3 DOCTOR HIRSCH: Well, since dietary
4 management doesn't work in these mammoth cases of
5 obesity, which is what you are seeing, or are very
6 unlikely, there is a symmetrical situation that the
7 drug is as likely to do good in the long run as do
8 bad, and this is exactly the purpose of the study.
9 But there is no a priori reason why better control of
10 carbohydrate metabolism is going to be an adverse
11 event to them.

12 CHAIRMAN BONE: Doctor Davidson and then
13 Doctor Cara.

14 DOCTOR DAVIDSON: Plus, the biggest
15 problem is physicians are using these drugs and they
16 don't know how to use them and the proper way to use
17 them. I think it is essential for these studies to be
18 done to prove the efficacy of these drugs, the
19 reliability of these drugs, and the effect of these
20 drugs in children. There is no question in my mind
21 that these studies need to be done.

22 CHAIRMAN BONE: A final comment on this by
23 Doctor Cara.

24 DOCTOR CARA: I forgot what I was going to
25 say.

1 CHAIRMAN BONE: All right. Doctor Misbin
2 will speak and then perhaps --

3 DOCTOR MISBIN: I just wanted to ask about
4 the --

5 DOCTOR CARA: You were talking about the
6 obesity issue and I totally lost track. I apologize.
7 But part of the problem is that the prognosis of
8 obesity in teenagers is just as poor as it is later in
9 life. As a matter of fact, there is good data to show
10 that beyond the age of 12, you have pretty much lost
11 it in terms of weight loss. So unfortunately, we
12 don't have any data regarding the long-term course of
13 this diabetes in teenagers. I would assume that it is
14 probably very similar to what happens with Type II in
15 adults. The compounded problem is that if you start
16 as early as in your late teenage years, does that mean
17 that you are going to have significant microvascular
18 and macrovascular complications when you are in your
19 30's? I would almost say that it is probably more
20 critical to treat these adolescents than it is even to
21 treat the older people with Type II diabetes, simply
22 because they start so young.

23 CHAIRMAN BONE: Right.

24 DOCTOR MISBIN: Just a final question.
25 Since this is really a practical problem we are facing

1 on Monday morning, would people make distinctions
2 among the drugs that are presently available,
3 specifically triglidazone, for instance, we know
4 causes dipycyte hyperplasia in animals. The
5 sulfonylureas, of course, and triglidazone also are
6 both associated with weight gain in the circumstances
7 where they are effective, whereas metformin is not.
8 Should all these agents basically be studied if those
9 studies are presented to us, or would we be wiser to
10 choose one versus the other or how would you all react
11 to that.

12 DOCTOR DAVIDSON: I think you need to
13 choose based on safety profiles and effects of the
14 drugs on previous studies. But I think you need to be
15 very careful how you choose your drugs.

16 CHAIRMAN BONE: Well, based on what you
17 know at the moment, Doctor Davidson, could you pick
18 drugs?

19 DOCTOR DAVIDSON: You want me to commit,
20 huh? Well, I think that based on the picture of these
21 children and knowing the drugs that have been used, at
22 least in California, Arizona, and Texas, I will tell
23 you that the two most common drugs used are metformin
24 and acarbose.

25 CHAIRMAN BONE: I see. Doctor Cara?

1 DOCTOR HIRSCH: I think it makes it all
2 the more important to do insulin studies as part of
3 this because that becomes a way of analyzing really
4 the drug effect. I would say that you would not want
5 to use the drug that was most recently put into the
6 adult public, like triglidazone, until there is more
7 evidence of the long-term efficacy and issues with
8 that, number one. Number two, it would seem to me
9 that metformin and that group would be perhaps the
10 wiser choice rather than pure beta cell stimulants.

11 CHAIRMAN BONE: Doctor Cara?

12 DOCTOR CARA: I agree with the final
13 comment. But in terms of metformin versus
14 triglidazone, I think both should really be looked at.
15 I understand the issues regarding cell hyperplasia in
16 animals, but it is a potent drug that has significant,
17 at least theoretical, potential and really needs to be
18 evaluated.

19 CHAIRMAN BONE: All right. Thank you. I
20 think this has been a very interesting discussion.
21 There are a few topics that we haven't covered yet,
22 but I think we will take our 3:30 break at 3:26, and
23 we will start again at 3:40.

24 (Whereupon, at 3:28 p.m. off the record
25 until 3:43 p.m.)

1 CHAIRMAN BONE: This is the continuation
2 of the 69th meeting of the Endocrinologic and
3 Metabolic Drugs Advisory Committee. The topics which
4 were not already discussed can be, I would say,
5 loosely grouped together, and these have to do with
6 combination therapies and then formulation and
7 delivery issues such as various insulin mixtures,
8 insulin analogues and their mixtures, and delivery
9 systems. These are all topics which are discussed in
10 the draft but were not really presented this morning.

11 I think the most useful way for us to
12 proceed now would be to ask Doctor Misbin to identify
13 from those topics of combination therapy, insulin
14 mixtures, analogues, and delivery systems, the topics
15 he thinks he would most like to have the committee's
16 input in over the next short while. And then we would
17 discuss those and then try to summarize the day's
18 work.

19 DOCTOR MISBIN: Insulin delivery systems
20 I don't think need to be discussed.

21 CHAIRMAN BONE: Okay. That was mainly
22 referring to oral, I think, in the document.

23 DOCTOR MISBIN: Yes. I guess --

24 DOCTOR CARA: I am sorry, what do you mean
25 when you say insulin delivery systems?

1 DOCTOR MISBIN: This is really just a
2 paragraph that deals with studies of non-parenteral
3 insulin. And I don't really think it is necessary to
4 go into this. I will if you want to, but I really
5 think it is not necessary.

6 DOCTOR CARA: What about insulin delivery
7 systems that are meant to inject insulin
8 subcutaneously?

9 DOCTOR MISBIN: Right. That is not what
10 was intended in that paragraph.

11 DOCTOR CARA: But I think that is a very
12 important issue. I mean, there are a lot of them out
13 there and none of them have any regulatory control or
14 for that matter --

15 DOCTOR MISBIN: Are you talking about the
16 pumps?

17 DOCTOR CARA: No, I am talking about the
18 jets -- the injected jets and freedom jets and those
19 sorts of things.

20 DOCTOR MISBIN: I can't --

21 CHAIRMAN BONE: Perhaps that will be a
22 topic for -- obviously, we are going to go through
23 several more iterations here and further discussions.
24 So maybe that particular issue is a less burning one
25 and may also be actually more under the regulatory

1 authority of the devices people. Although as much as
2 we would like to comment on that in a joint meeting
3 with them sometimes perhaps. But perhaps -- what
4 other topics, Doctor Misbin?

5 DOCTOR MISBIN: Well, I think the topic
6 that really needs to be discussed is the insulin
7 mixtures. Here there is a position taken in the
8 guidance which I think should be discussed. Maybe
9 Doctor Fleming would like to state this position
10 because it was established long before I was in the
11 Agency.

12 DOCTOR FLEMING: The issue relates to the
13 pre-mixing of insulin drug products so that as you
14 know we now have on the market about four different
15 insulin mixtures. We have had a concern about the
16 proliferation of additional mixtures -- ratios of
17 fast-acting and long-acting insulins -- such that we
18 have attempted to suggest or we have suggested that
19 there should be some difference in how these products
20 perform before there is an additional insulin mixture
21 added. In other words, if a company has a 70/30
22 product and they want to add a 75/25 product, we would
23 like to see a difference in performance, either
24 pharmacokinetic or pharmacodynamic performance, to
25 avoid putting a product on the shelf that would not be

1 significantly different from one that is already there
2 and would not really, therefore, have much benefit and
3 perhaps cause some confusion. Now we probably don't
4 have the legal basis to prohibit these additional
5 mixtures to be put on the market, but we have made the
6 recommendation to sponsors that they simply
7 demonstrate a difference in performance of all of
8 their insulin mixtures prior to putting them on the
9 market.

10 DOCTOR SHERWIN: Why do you feel that way?
11 In other words, is it really so harmful one way or
12 another? I just wonder is it such a big deal?

13 DOCTOR FLEMING: Well, it is really not a
14 big deal. I don't think it would do a lot of harm to
15 have a 75/25 on the market.

16 DOCTOR SHERWIN: I mean, I doubt that a
17 company would make such a subtle difference. I mean,
18 most of the time it would be a larger difference than
19 that.

20 DOCTOR FLEMING: You would think so.
21 There have been at least efforts towards fairly small
22 changes in proportions of the two insulins, and I
23 think that if we had, for example, maybe 20 different
24 mixtures on the market --

25 DOCTOR SHERWIN: Oh, that would be a

1 problem.

2 DOCTOR FLEMING: That would be to the
3 extreme, and I don't think a company would do that.
4 If you are talking about adding one or two other
5 mixtures, that is probably not going to be of any
6 importance either way, either as a public health issue
7 or a particular benefit to patients. But we are -- as
8 it is clear in the document or in the draft guidance
9 -- proposing that at least a sponsor consider whether
10 there is any point in putting out a product without
11 data that show there is a difference in performance.
12 You are absolutely right that there wouldn't be much
13 harm done if they did have two products that were
14 close enough or very close in performance. But it
15 becomes perhaps a theoretical concern that it could go
16 too far.

17 CHAIRMAN BONE: Any comments to this point
18 from the committee? Doctor Davidson?

19 DOCTOR DAVIDSON: You know, most of the
20 time I am opposed to mixtures because they are no
21 patients alike. There are no patients like 70/30 or
22 75/25. But just for clarification, if a new mixture
23 comes, what is required for that mixture to be
24 approved? What are the endpoints that the Agency is
25 asking the companies or the sponsors to have in order

1 to approve a new mixture?

2 DOCTOR MISBIN: Well, the way it is stated
3 at the moment or what we have been telling sponsors,
4 and we would want input about this, is that they would
5 have to do standard PK studies and demonstrate -- in
6 patients generally or not necessarily -- but anyway,
7 to demonstrate that the new product was different from
8 the existing products on either side of it. So, for
9 instance, if we had regular as well as 70/30 and
10 someone wanted to market 85/15, they would have to
11 show that the 85/15 gave a different blood level
12 pattern than either the 70/30 or the -- actually NPH
13 would be on the other side. So in other words, that
14 those three would be able to be distinguished by PK
15 studies.

16 DOCTOR DAVIDSON: And that is the only
17 endpoints that you require?

18 DOCTOR MISBIN: That would be the only
19 endpoints, yes, sir.

20 DOCTOR MARCUS: Do you require that the
21 equivalent of giving say 80/15 would be identical to
22 that if you were to blend certain -- the appropriate
23 amount of NPH and regular separately in that
24 proportion? Is there a requirement that the pre-mixed
25 product be the same as if you were to mix it?

1 DOCTOR MISBIN: No. That is not a --

2 DOCTOR MARCUS: That is not. That is
3 interesting.

4 DOCTOR SHERWIN: What mixtures -- you said
5 there were four different mixtures that are available?

6 DOCTOR MISBIN: We have 70/30 and 50/50.

7 DOCTOR DAVIDSON: And what are the new
8 ones -- the new mixtures that are in the horizon?

9 DOCTOR MISBIN: I don't know if we can
10 discuss this.

11 DOCTOR DAVIDSON: Oh, I am sorry.

12 CHAIRMAN BONE: All right. Well, that is
13 one of the topics. Did you want some further
14 discussion on analogues at this point?

15 DOCTOR MISBIN: Well, the only -- just to
16 make mention of it for a brief discussion if necessary
17 that we do have a precedent with respect to lysepro.
18 This was the first altered insulin that was approved.
19 And we have said, and it is in the draft of the
20 guidance and I have told other sponsors, that if they
21 wish to have other similar types of analogues approved
22 that they would have to do one-year safety studies as
23 was required with lysepro, but that otherwise there
24 would not be the requirement for any kind of
25 superiority. They would have to show that the results

1 with the analogue were roughly equivalent to what is
2 available -- basically following the same principles
3 that were used in the approval of lysepro.

4 CHAIRMAN BONE: I remember that rather
5 vividly, and I recall being quite disappointed in the
6 amount of pharmacokinetic and pharmacodynamic data
7 that was made available, not only in the adults, but
8 in the special cases of pregnant and pediatric
9 patients.

10 DOCTOR MISBIN: You know, I neglected to
11 say that the primary basis for making that claim about
12 a new analogue would be the PK studies. So if one
13 wants to market a long-acting insulin, it would
14 actually have to be shown that it really was a long-
15 acting insulin. But then beyond that, we would not
16 actually require clinical studies demonstrating
17 efficacy, but would require one-year studies to
18 demonstrate safety.

19 CHAIRMAN BONE: Well, to pursue my point,
20 and it was one which I recall being fairly emphatic
21 about at the time, would you not -- are you not at the
22 moment requiring anything except the PK studies in
23 sort of garden variety adults, or are you requiring PK
24 studies in the major populations who might be treated,
25 including particularly pregnancy and perhaps pediatric

1 or adolescent patients?

2 DOCTOR MISBIN: Well, that is not part
3 now. We could certainly do that. I think the same
4 issue as pregnancy and pediatrics, we have already
5 discussed. I mean there is still then the issue of
6 should we require a non-naturally occurring substance
7 to be used in pregnant patients? I mean, these are
8 questions which are open for discussion. But I think
9 the -- in drafting the guidance, I felt that it was
10 fair to say what was required in lysepro that gave
11 approval of lysepro would be kind of a floor that
12 other sponsors could use as a guidance. But
13 additional requirements are certainly possible if the
14 committee thinks they are necessary.

15 CHAIRMAN BONE: Well, I think the
16 committee all shared my disappointment at how low the
17 threshold was with regard to the pharmacokinetic
18 issues at the time, and I am not sure the committee is
19 enthusiastic about maintaining that relatively low
20 floor for the future. I would be interested in the
21 comments of the other members.

22 DOCTOR MARCUS: Well, we certainly were
23 all upset that there was no way to determine whether
24 the PK characteristics of lysepro insulin remained the
25 same if it were mixed with an intermediate-acting

1 insulin. In fact, we were rather shocked that that
2 apparently had not been studied. And I would
3 certainly hope that if a claim was going to be made to
4 get registration of a new kind of insulin based on its
5 PK characteristics, that one would study it under
6 conditions in which it is given, that is, frequently
7 in combination with others.

8 CHAIRMAN BONE: Not only fresh mixture but
9 say over various time periods. Because it is quite
10 common for patients to mix their insulin ahead and
11 then make the injection sometime later, as much as
12 several hours. So I think that was a particularly
13 important issue for the committee. Doctor Sherwin?

14 DOCTOR SHERWIN: That was a concern at the
15 time surely. The data that was presented wasn't
16 convincing in terms of NPH and lysepro at the time,
17 and it was disturbing. But I think in terms of
18 analogues, I think that it would be particularly
19 important in children to assess pharmacokinetics. I
20 don't know as much how I feel about pregnancy and
21 analogues. Because even though theoretically it
22 shouldn't -- I assume the analogues would not cross
23 the placenta, I think there would have to be clear
24 evidence that you really have an advantage in using
25 that drug during pregnancy I think to warrant really

1 trials and studies in pregnancy with analogues. That
2 would be my --

3 CHAIRMAN BONE: Even a PK study?

4 DOCTOR SHERWIN: Well, my concern is that
5 unless there is a real theoretical advantage in
6 pregnancy for an analogue, I would -- we have a
7 naturally occurring substance and I would not test it
8 in pregnant women at all.

9 CHAIRMAN BONE: Well would you then have
10 a disclaimer to that effect?

11 DOCTOR SHERWIN: Yes.

12 CHAIRMAN BONE: Okay. Other members?
13 Doctor Cara?

14 DOCTOR CARA: Yes, I disagree with that.
15 I think there are potential benefits of analogue
16 therapy.

17 DOCTOR SHERWIN: Oh, I didn't say there
18 weren't. I said if you could not come up with a
19 rationale for an analogue. If there was a rationale,
20 yes. Then okay. I was trying to say -- but in many
21 analogues, you have a new long-acting or a new short-
22 acting, and there would have to be a clear benefit.
23 That is all I am saying.

24 DOCTOR CARA: Sure. I guess my point is
25 though that you may not know that there is a benefit

1 until you actually do the study. But as long as there
2 is a rationale for why you would do the study, that
3 would make sense. I think in terms of the PK
4 comments, I would agree. I think unfortunately there
5 is very little information that we know about insulin,
6 even though we all use it, and getting more
7 information would be helpful.

8 CHAIRMAN BONE: Others? Doctor Davidson?

9 DOCTOR DAVIDSON: You know, I want to go
10 back to any mixture. If we are going to approve
11 mixtures -- physicians that use mixtures are many
12 times people that may use a combination of oral
13 agents. We have many drugs in the market. For family
14 physicians that need to see 30 patients in the morning
15 and 30 patients in the afternoon, I think you need to
16 be clear what the advantages will be, for example, of
17 75/25 over 70/30 or 60/40 or 50/50. I think only the
18 PK studies, to me, are not sufficient. I think we
19 need to prove that over a period of time there was an
20 improvement in glucose control with new mixtures,
21 whatever the mixtures are.

22 DOCTOR MISBIN: By that criteria, lysepro
23 would not have been approved.

24 DOCTOR DAVIDSON: Or have some advantages.
25 I was not here for lysepro. I am just telling you, if

1 we are going to have a 75/25 mixture that is
2 clinically irrelevant from 70/30, the only thing we
3 are going to do is confuse the family physicians for
4 another mixture that is almost identical.

5 DOCTOR SHERWIN: The one thing about
6 pharmacokinetic studies is that -- the one thing we
7 haven't mentioned is that when you inject insulin,
8 there is a lot of variation just from that procedure
9 alone. And so the noise is tremendous.

10 DOCTOR MISBIN: That actually works
11 against it. It makes it more difficult to show that
12 it is different.

13 DOCTOR SHERWIN: That is what I am saying.
14 That is the problem. In other words, it is not a
15 simple task to show a difference between 15/85 versus
16 85 and 70/30, even though it would be logical that it
17 would be so because of the variability in the depth of
18 injection, the temperature, the site of injection, et
19 cetera, is so enormous that the small differences in
20 mixture make it almost impossible to show a
21 difference. So you could argue to never do any of
22 these things.

23 CHAIRMAN BONE: Doctor Hirsch and then
24 Doctor --

25 DOCTOR HIRSCH: Assumedly the sponsor is

1 going to make some claim as to what the efficacy of
2 this is as compared with other insulins or for whom it
3 is best. They are not going to take out an
4 advertisement that says, guess what, we have got a new
5 thing and we don't really know if it is any better,
6 why don't you try it. They are going to make a
7 specific claim. And in that case, I think what we
8 should ask for is appropriate PK to document that
9 claim.

10 DOCTOR MISBIN: No. That would be the
11 claim. The claim for the new mixture would just be a
12 different time course. We would not allow a claim of
13 increased or better control or less hypoglycemia or
14 anything else unless there was data to show it.

15 DOCTOR HIRSCH: Then we ought to see that
16 PK is done to document at least that time course or
17 whatever the claim is.

18 DOCTOR SHERWIN: Sure.

19 DOCTOR HIRSCH: I would doubt that they
20 would make just a claim saying, guess what, we have
21 insulin that is another time course. They will show
22 someone who is better in some way or whatever it is.
23 There will be an additional claim, I would imagine.

24 DOCTOR SHERWIN: I guess I was trying to
25 make the point -- it was convoluted -- is that

1 companies are not going to do 5 percent differences.
2 they are not going to go to 75/25. They are going to
3 only go to extremes because they will never show a
4 subtle difference.

5 CHAIRMAN BONE: All right. Doctor
6 Molitch?

7 DOCTOR MOLITCH: I think that the PK is
8 certainly sufficient, although probably as you say,
9 Bob, it doesn't make any difference because the
10 physicians who tend to use these mixtures really don't
11 do an initial titration of NPH and regular to the
12 patient and figure out exactly what the does is and
13 then switch the patient to 70/30. They just give the
14 70/30 and they will just give the 80/20 or 60/40 or
15 whatever it is without trying to attempt to find out
16 what the actual dose should be. So it is probably not
17 terribly critical my guess is. But I think we
18 certainly need to have that information before it
19 would be let on the market for the few physicians who
20 might care.

21 CHAIRMAN BONE: The last topic brought up
22 the subject of some different subpopulations which
23 might have special needs for control and also be
24 special cases as far as pharmacokinetics and
25 pharmacodynamics of insulin. That touches on a topic

1 that was mentioned in the draft, which was the
2 possible need for doing clinical trials, and I presume
3 this would mainly be in Type II diabetics, but perhaps
4 for adjunctive therapy in Type I diabetics as well in
5 various population groups. I wondered if anyone had
6 additional comments to make concerning special
7 populations which ought to be studied separately
8 rather than just be included in very large clinical
9 trials. Doctor Davidson?

10 DOCTOR DAVIDSON: I don't necessarily
11 believe that we need to have special clinical trials,
12 but I think that the populations that we are seeing
13 most affected by Type II diabetes are not part of any
14 of the clinical trials. And unless we involve these
15 populations, we cannot claim that the drugs work
16 exactly the same in everybody. And I think instead of
17 having separate clinical trials, I think we need to
18 identify African Americans, Latino Americans, Asian
19 Americans, and other special populations afflicted
20 with more diabetes to be a percentage of those
21 clinical trials.

22 CHAIRMAN BONE: So you are saying that
23 rather than having a separate trial, you would have
24 trials in which sufficient numbers were included for
25 those groups to be analyzed separately?

1 DOCTOR DAVIDSON: To be representative of
2 the U.S. diabetes population.

3 CHAIRMAN BONE: Well, I think there are
4 two separate questions here. One is whether you have
5 got a representative population over all. And another
6 is whether you have got enough people in those
7 subgroups to really look and see if they are different
8 -- if there response to the treatment is different.
9 It seems to me that if you are -- one question has to
10 do with the representativeness of the trial of the
11 whole population. But the other has to -- if you are
12 really concerned about the ethnopharmacology here, the
13 other really implies that you had to have an adequate,
14 well-defined sample size balanced between the
15 treatment groups to be able to actually tell whether
16 there was an ethnopharmacologic variation.

17 DOCTOR DAVIDSON: I agree with you. And
18 if that will require separate clinical trials, that is
19 the way it should be.

20 CHAIRMAN BONE: Doctor Critchlow, would
21 you want to comment on which is the better approach?
22 To have a very large trial with those groups
23 adequately represented or subspecialty trials?

24 DOCTOR CRITCHLOW: Well, I think it is
25 just as you say. If you are interested in the

1 ethnopharmacology and really desire to make separate
2 statements, you either -- I mean, either way you are
3 going to have to have the large number, as you say, to
4 either make -- if you want to make statements that are
5 specific to that group, then it is not going to matter
6 whether you do a separate trial or not. You are still
7 going to need the same number, whether it is part of
8 the trial or not. But if it is a matter of having the
9 representativeness of the group, then that is a much
10 smaller number.

11 CHAIRMAN BONE: If you then --

12 DOCTOR CRITCHLOW: I mean, they would need
13 to be included in the trial if you are going to make
14 specific statements comparing -- making comparative
15 statements as to either relative efficacy or issues
16 along that line. Then you would need them within the
17 trial in sufficient numbers.

18 CHAIRMAN BONE: It will probably require
19 a stratification or balancing procedure as well.

20 DOCTOR CRITCHLOW: If the desire is to
21 make those comparative statements.

22 CHAIRMAN BONE: All right. Any further
23 comment on that topic, which is one that we kind of
24 went by but had been raised?

25 DOCTOR MOLITCH: I think there have

1 certainly been some reports that different groups
2 might have a variant in their degree of insulin
3 resistance, although not everybody has confirmed some
4 of those reports, and therefore the drugs might work
5 differently. And I think that these kinds of studies
6 would be well worthwhile.

7 CHAIRMAN BONE: Okay. All right. I think
8 we have covered the topics that we had on the agenda.
9 Maybe we will just summarize and finish then. We have
10 had a long day and we have talked about a lot of
11 individual topics. I think the overall perspective
12 that Doctor Fleming gave us in the morning was very
13 good. That we want to regard this as part of the
14 process of developing guidance for the development of
15 these drugs, and we have certainly had an interesting
16 and provocative at some points presentation by Doctor
17 Misbin raising some issues that the committee found
18 very interesting to discuss.

19 I think there were some sort of consensus
20 views that didn't require much discussion by the
21 committee about how we would like to see the ultimate
22 document structured as it evolves, and that is to be
23 a little more organized according to the type of
24 diabetes and the phase of development. One subject
25 that wasn't discussed at all was pre-clinical studies,

1 but particularly for novel agents. Obviously pre-
2 clinical studies are very important, and I don't know
3 if we are at the point yet where guidance can be given
4 about this area, but that will be a consideration for
5 the authors as well as we go on.

6 The major part of the discussion had to do
7 with clinical trial organization and endpoints. The
8 document which we discussed as a starting point for
9 today's discussion tended to emphasize Phase III
10 trials, but there were emerging distinctions about how
11 people viewed Phase II and Phase III in development.

12 There was some difference of opinion about
13 the role of placebo-controlled trials in Phase III,
14 although I think there was a general consensus,
15 although perhaps not unanimous, that in Phase II
16 trials, these were extremely important. I took it as
17 the overall view that everyone was concerned that in
18 Phase III trials, which tended to be a relatively long
19 duration of exposure, that they regarded the
20 protection of subjects from increased risk due to
21 deterioration of control of diabetes compared to their
22 pre-study status as being something that needed to be
23 taken into account very seriously by investigators and
24 sponsors.

25 There were some various strategies

1 discussed, some of which had to do with using positive
2 comparator trials, and others having to do with
3 continuing to use placebo-controlled trials in Phase
4 III, but with some mechanisms introduced to make sure
5 that patients who were previously well-controlled were
6 not allowed to go badly out of control for a long
7 time.

8 We had quite a lot of discussion about the
9 interpretation of hemoglobin A_{1c} as a primary endpoint
10 for clinical trials. It seems to be the consensus
11 that that remains our major endpoint, largely on the
12 basis of the DCCT experience and the correlations that
13 that has provided, although this does not preclude the
14 emergency of other perspectives as we go along,
15 particularly in Type II diabetes. But for the moment,
16 glycosylated hemoglobin seems to be the most important
17 primary endpoint.

18 The interpretation of this was enhanced
19 considerably by the discussion about the importance of
20 looking at the relative change in glycosylated
21 hemoglobin as opposed to the absolute change in
22 glycosylated hemoglobin percent, because this seemed
23 to be so nicely related to relative risk reduction for
24 each different complication, although of course the
25 proportional reduction varied from complication to

1 complication.

2 There was a fair amount of discussion
3 about what the minimum hypoglycemic effect might be
4 that would be regarded as therapeutically meaningful.
5 And I think the committee did not reach any -- or even
6 attempt to reach any view as to what a minimum
7 magnitude of effect might be. The point was
8 repeatedly made that very small effects appeared to at
9 least have measurable consequences for risk in the
10 DCCT study. So no one wanted to enunciate the
11 threshold. But I think there was also a view that as
12 the hypoglycemic benefit of a therapy would be
13 smaller, the weight given to end-organ effects -- the
14 therapeutic benefit on end-organ effects might be
15 given considerable weight, and that would have to be,
16 of course, very well demonstrated by a sponsor, but
17 that there could be some offset there where this would
18 in a sense help a drug with only a modest effect on
19 glycosylated hemoglobin, although a beneficial effect
20 would still be expected.

21 There was some discussion about drugs
22 which acted on the end-organ effects of diabetes
23 independent of a hypoglycemic effect, and I think
24 these were regarded as special and specific
25 indications that would not be part of what we were

1 talking about generally here today.

2 There was quite a little bit of discussion
3 about the issue of drugs which reduce body fat and
4 thereby improve glycemic control. That, I think, is
5 going to be an ongoing subject of discussion. But
6 there was some support for recognition of these as
7 anti-diabetic agents as well as agents strictly for
8 obesity. But I think there are a number of
9 distinctions that would have to be made about
10 mechanism of action, scope of studies, and so forth
11 before this were codified.

12 The subject of hypoglycemias was another
13 one about which there was a substantive discussion,
14 and I think that we were left with the somewhat
15 frustrating view that the only events that we could
16 really count in a reliable way were the relatively
17 severe hypoglycemic episodes identified and recognized
18 in the DCCT, which were those that essentially
19 resulted in neurologic impairment such that the
20 patient required assistance or had a seizure or became
21 unconscious. This is somewhat frustrating because
22 everyone recognized the importance of lesser degrees
23 of hypoglycemia. The problem is a technical one
24 really that measuring the blood sugar under the
25 conditions when it would need to be measured is

1 problematic if the subject has to do it. It was
2 advocated that techniques be employed which would
3 allow securing of a sample that might be analyzed at
4 a central laboratory for this purpose, and that was
5 given some weight and interest, although I don't think
6 anyone advocated that that be a required part of all
7 studies, but merely something that would be of
8 interest and could be employed.

9 We have had some specific discussion about
10 some specific topics such as the emerging problem of
11 Type II diabetes in the pediatric and adolescent
12 population, concerns related to pregnancy and
13 gestational diabetes, and some discussions about
14 patient populations and trial designs as well as what
15 I think I could put together as some very limited
16 discussion of technical issues related to insulin
17 analogues and mixtures.

18 So I think the committee has found this an
19 interesting discussion and one in which we hope we
20 have provided some useful perspective for the Agency
21 as the Division goes forward to develop guidance. One
22 topic or one idea that came up in actually an informal
23 conversation that Doctor Fleming and I had, and others
24 seemed to be interested in the idea, is that there may
25 be a role for some specifically designed workshops to

1 address some of the particular issues in more detail.
2 A number of these might be imagined. I think we have
3 found the discussion, for example, of the risk/benefit
4 analysis and how we saw sort of a first glimpse of how
5 we might quantify or at least begin to think about
6 quantifying that analysis a little better was a very
7 interesting one. And it may well be that the
8 development of this very complicated guidance over a
9 period of time, even if it turns out to be a couple of
10 separate guidances for different types of diabetes,
11 would benefit from that sort of more focused
12 discussion with really an expert panel on a much
13 narrower set of topics.

14 In conclusion, I think the committee hopes
15 that our contribution has been useful and also that we
16 will be looking forward to seeing the next addition.
17 Doctor Misbin?

18 DOCTOR MISBIN: You didn't mention the
19 issue -- I think you just omitted the issue of
20 duration of trials.

21 CHAIRMAN BONE: Yes. I think there was
22 little quarrel with the suggestion of the one-year
23 trial. There had been some controversy about that, I
24 gather, but it didn't seem to be a controversial
25 subject for the committee. But there was quite a lot

1 of support for longer term trials where we were
2 talking about essentially co-treatment of obesity and
3 diabetes mellitus, and there was some discussion about
4 other ways in which longer term data could be obtained
5 on new drugs, for example, in extension studies,
6 either open label or positive controlled blinded
7 extension studies.

8 So with those points having been made, I
9 will adjourn the 69th meeting of this committee.

10 (Whereupon, at 4:19 p.m., the meeting was
11 adjourned.)

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