UNITED STATES OF AMERICA
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

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ENDOCRINOLOGIC AND METABOLIC DRUGS
ADVISORY COMMITTEE

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MEETING

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WEDNESDAY
SEPTEMBER 25, 2002

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The Advisory Committee met at 8:00 a.m. in the Ballroom of the Hilton Silver Spring, 8727 Colesville Road, Silver Spring, Maryland, Dr. Glenn Braunstein, Chairman, presiding.

PRESENT:

GLENN BRAUNSTEIN, M.D.	Chairman
ERIC ABADIE, M.D.	Guest
THOMAS T. AOKI, M.D.	Consultant
HENRY G. BONE, III, M.D.	Consultant
STEVEN R. CUMMINGS, M.D.	Guest
KENNETH G. FAULKNER, Ph.D.	Guest
MARC C. HOCHBERG, M.D., Ph.D.	Guest
MARIE C. GELATO, M.D., Ph.D.	Member
DEBORAH GRADY, M.D., M.P.H.	Member
SUNDEEP KHOSLA, M.D.	Guest
LYNNE L. LEVITSKY, M.D.	Member
BARBARA P. LUKERT, M.D.	Consultant
ROBERT MARCUS, M.D.	Guest
MICHAEL R. McCLUNG, M.D.	Guest

PRESENT: (CONT.)

RENE RIZZOLI, M.D.	Guest
GIDEON A. RODAN, M.D., Ph.D.	Guest
ALLAN R. SAMPSON, Ph.D.	Consultant
JANET H. SILVERSTEIN, M.D.	Consultant
WILLIAM V. TAMBORLANE, M.D.	Member
CHARLES H. TURNER, Ph.D.	Guest
NELSON WATTS, M.D.	Guest
ERIC COLMAN, M.D.	FDA
David Orloff, M.D.	FDA
BOB MEYER, M.D.	FDA
BOB TEMPLE, M.D.	FDA
NANCY WORCESTER, Ph.D.	Member, Consumer Rep.
ROBERT ZERBE, M.D.	Industry Rep.
KATHLEEN R. REEDY	FDA Executive Sec.

C O N T E N T S

P R O C E E D I N G S

8:07 a.m.

CHAIRMAN BRAUNSTEIN: Welcome to the September 25th, 2002, meeting of the Endocrinologic and Metabolic Drugs Advisory Committee. I'm Glenn Braunstein, Chair. We'll start by going around the room and asking for everybody to make introductions. We'll start with Dr. Marcus.

DR. MARCUS: Good morning. My name is Robert Marcus. I'm Emeritus Professor, at Stanford University. I'm a former member of this Panel, and I'm medical advisor at Eli Lilly and Company.

DR. FAULKNER: Ken Faulkner. I'm currently working at G.E. Medical Systems; also an Associate Adjunct Professor at the University of Wisconsin at Madison.

DR. CUMMINGS: Steve Cummings. I'm a Professor of Medicine Epidemiology and Biostatistics at the University of California at San Francisco.

DR. HOCHBERG: Marc Hochberg. I'm a Professor of Medicine and Epidemiology and Preventive Medicine at the University of Maryland in Baltimore.

DR. TURNER: I'm Charles Turner. I'm a Professor of Orthopedic Surgery and Bioengineering at Indiana University.

DR. RIZZOLI: I'm Rene Rizzoli, Professor of Medicine at the Geneva University of Medicine Hospital in Geneva, Switzerland.

DR. RODAN: I'm Gideon Rodan. I'm the head of Bone Research and Osteoporosis at Merck, and another Adjunct Professor of Pathology at the University of Pennsylvania.

DR. SILVERSTEIN: I'm Janet Silverstein. I'm a Professor in Pediatric Endocrinology at the University of Florida in Gainesville.

DR. ABADIE: I'm Eric Abadie. I'm Director of Therapeutic Evaluation with the French Agency, and I'm also Vice-Chair of the CPMP. The CPMP, for those who don't know, is the licensing body in Europe. And I'm probably here because I was rapporteur for the Osteoporosis Guideline in Europe.

DR. GRADY: Deborah Grady. I'm a Professor of Epidemiology and Biostatistics and of Medicine at the University of California, San

Francisco.

DR. TAMBORLANE: I'm Bill Tamborlane, Professor of Pediatrics at the Yale University School of Medicine.

DR. GELATO: I'm Marie Gelato. I'm Professor of Medicine at the State University of New York at Stonybrook.

CHAIRMAN BRAUNSTEIN: Glenn Braunstein, again. I'm Chairman of the Department of Medicine at the Cedars-Sinai Medical Center and Professor of Medicine at UCLA School of Medicine.

MS. REEDY: Kathleen Reedy, Administrator of this Advisory Committee at the Food and Drug Administration.

DR. AOKI: Tom Aoki, Professor of Medicine, Division of Endocrinology, University of California, Davis.

DR. LUKERT: Barbara Lukert, Professor of Medicine, Division of Endocrinology, University of Kansas.

DR. SAMPSON: Allan Sampson, Professor of Statistics, University of Pittsburgh.

DR. LEVITSKY: Lynne Levitsky, Chief of Pediatric Endocrinology at Mass General Hospital, Associate Professor at Harvard Medical School.

DR. ZERBE: I'm Bob Zerbe, Quatrix Pharmaceuticals, and I'm the Industry Representative.

DR. WORCESTER: Nancy Worcester, an Associate Professor of Women's Studies and Continuing Studies, University of Wisconsin, Madison, and I'm the Consumer Representative on this Panel.

DR. BONE: Henry -- oh, I just needed to hit it a couple times. I'm Henry Bone. I'm Director of the Michigan Bone and Mineral Clinic, and Past Member of this Committee.

DR. WATTS: Nelson Watts, Professor of Medicine at the University of Cincinnati.

DR. McCLUNG: Michael McClung, Associate Professor at the Oregon Health Sciences University in Portland.

DR. KHOSLA: I'm Sundeep Khosla, Professor of Medicine at Mayo Medical School and Mayo Clinic, in Rochester.

DR. COLMAN: I'm Eric Colman, a Medical

Officer in the Division of Metabolic and Endocrine Drugs at the FDA.

DR. ORLOFF: David Orloff, Director of the Division of Metabolic and Endocrine Drug Products, FDA.

DR. MEYER: Bob Meyer, the Director of Office of Drug Evaluation II at FDA.

DR. TEMPLE: Bob Temple, Director of the Office of Medical Policy at FDA.

CHAIRMAN BRAUNSTEIN: Thank you. We'll now turn the podium over to Kathleen Reedy.

MS. REEDY: This is the acknowledgment related to general matters waivers for the Endocrinologic and Metabolic Drugs Advisory Committee, September 25th, 2002. The following announcement addresses the issue of conflict of interest with respect to this meeting, and is made part of the record to preclude even the appearance of such at this meeting.

The Food and Drug Administration has approved general matters waivers for the following special government employees, which permits them to

participate in today's discussions: Dr. Thomas Aoki, Henry Bone, Glenn Braunstein, Deborah Grady, Lynne Levitsky, Barbara Lukert, Allan Sampson, Janet Silverstein and William Tamborlane.

A copy of the waiver statements may be obtained by submitting a written request to the Agency's Freedom of Information Office, Room 12-A-30 of the Parklawn Building. In addition, Drs. Marie Gelato and Nancy Worcester do not have any current financial interests in pharmaceutical companies.

Therefore, they do not require a waiver to participate in today's discussions. The topics of today's meetings are issues of broad applicability. Unlike issues before a committee in which a particular product is discussed, issues of broader applicability involve many industrial sponsors and academic institutions.

The Committee Members and invited guests have been screened for their financial interests, as they may apply to the general topics at hand. Because general topics impact so many institutions, it is not prudent to recite all potential conflicts of interest

as they apply to each participant.

FDA acknowledges that there may be potential conflicts of interest, but because of the general nature of the discussion before the Committee, these potential conflicts are mitigated.

We would also like to note that Drs. Robert Zerbe, Gideon Rodan, Kenneth Faulkner and Dr. Robert Marcus are participating in today's meeting as nonvoting industry representatives. As such, they have not been screened for conflicts of interest.

In the event that the discussions involve any other products or firms not already on the Agenda for which FDA participants have a financial interest, the participants' involvement and their exclusion will be noted for the record.

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

CHAIRMAN BRAUNSTEIN: Thank you. Now, Dr. David Orloff, Director of the Division of Metabolic and Endocrine Drug Products, will give some welcoming

opening comments.

DR. ORLOFF: Good morning. I want to thank everybody in advance for coming. I understand, and I guess everyone knows around the table, that this was intended to be a three-day meeting for the Advisory Committee; has been now foreshortened to one.

And again, we thank you for your understanding. Certainly, in light of busy schedules that's a -- both a sort of unfortunate error and a boon, I suppose. I also want to thank in advance Henry Bone for his invaluable assistance in putting together the Agenda for this meeting.

And I want to recognize and welcome Dr. Braunstein back to the position of Chair of this Committee, which was a position he held back from '91 to '95. So as he said to me earlier, we've taken him out of mothballs, I guess.

But he was -- he served us very well in the past, and we anticipate that it will be repeated here again. Today's meeting is not a typical, I guess, Advisory Committee Meeting, based upon most people's experience. There's no specific drug

application that is the subject of the discussion.

Nevertheless, this is an important issue that we'll be discussing with the potential for great impact on the way we and interested sponsors and investigators proceed in the area of research and development of new therapeutics for osteoporosis.

The title, if you will, of today's meeting -- I don't know that it's specifically written anywhere -- is, "Standards of Evidence for Approval of Drugs for Prevention and Treatment of Osteoporosis." And the purpose, generally, is to frame the issues around the possibility or the consideration of alterations in our -- that is, FDA's -- Guidance to industry on the development of osteoporosis drugs.

By our way of thinking, any consideration of change in that regard must be in light of the accumulated epidemiologic data, of the large and increasing body of clinical trial results, of experience with animal models, of advances in our knowledge of bone molecular physiology and of the pathophysiology of osteoporosis, our understanding of the mechanisms of actions of several existing and

emerging drug classes, and the validity of intermediate measures of efficacy as predictors of true clinical benefit; thus, the panel of experts in the field that we've convened today.

A few days ago I sent a brief memo to the members of the Committee and the invited guests and consultants, and I'd like to share some of the salient points that I raised in that memo with you now.

As you'll hear from our first speaker, Dr. Eric Colman, in a few moments, current FDA Guidance regarding development of drugs for osteoporosis has proposed a weight-of-evidence approach to the demonstration of acceptable safety and efficacy of new treatments.

The approach begins with preclinical or animal data showing bone efficacy and safety, continues through assessment of bone mineral accrual in humans and of bone microscopic morphology in patients, and culminates -- for all drugs but estrogens -- in randomized placebo-controlled trials assessing efficacy in reducing incident fractures.

This last piece in the puzzle has been

required in the final analysis because of concern whether bone mineral density, in conjunction with other studies of markers, can serve as a reliable predictor of bone quality and strength.

As many of you know, in June of this year the National Institutes of Health and the American Society for Bone and Mineral Research convened a meeting to address growing concerns over the appropriateness of placebo-controlled fracture trials, based on ethical constraints against the use of placebo when effective therapies for the target disease already exist.

Participants at that conference did put forward proposals for ways to address the ethical issues around the use of placebos in fracture trials raised by increasing numbers of IRBs and others involved in this field.

Indeed, numerous patients -- papers; excuse me -- have been published since the revisions to the Declaration of Helsinki in 2000, proposing constructs by which to decide on the appropriateness of placebo versus active controls in given instances,

with several references included, I believe, in the Committee's package.

Without passing judgment on the approaches or proposals at the NIH meeting, it is I think fair to say that the future does not appear bright for the routine use of placebos in trials examining the effects of new therapies on fracture incidence in the development of osteoporosis drugs.

It is important to note that the NIHA SBMR meeting did include discussions of non-fracture endpoints as valid surrogates for change in fracture risk, not a new topic. Today -- one that will certainly be central to today's discussion.

A central theme of the NIH meeting, though, appeared to be that demonstration of anti-fracture efficacy would be critical to the wide acceptance of a new therapy. Whether and in what circumstances anti-fracture efficacy should be required for approval is a central question we wish to address in today's meeting.

What may be the preferred, practical or scientifically valid or ethically acceptable route to

a promotable fracture effect is a subject reserved for another discussion. So in sum, the purpose of today's meeting is not to revisit the ethics of placebo controlled fracture trials.

Rather, we feel that the time is right to turn the discussion to the question of whether we -- meaning the regulatory authorities, pharmaceutical sponsors, investigators, doctors and patients -- should reassess what types of clinical and preclinical information should lead us to accept as safe and effective, new drugs for osteoporosis.

What guidance can we offer drug companies -- that is, FDA -- as to requirements for convincing evidence that fracture benefits will accrue, even if in some circumstances we are unable to put a number on that effect size.

As you can see, today's Agenda will begin with a session as necessary background on the U.S. and European guidance documents currently in use. The second session includes discussions of the validity of animal models as predictors of clinical efficacy and safety of the bone.

The third session will address the validity of BMD, bone mineral density, as a marker of fracture risk based on information from observational studies and the results of therapeutic trials.

We will conclude the morning with the open public hearing, and after lunch, we'll turn to trial design issues with the stage set by a presentation of the implications for osteoporosis trial design of the choice of placebo versus active controls.

Finally, the discussion of issues following the formal presentations will, at least at the start, be directed by consideration of four hypothetical new drugs in development. These are a new bisphosphonate, a new estrogen or estrogen agonist on bone, a new mechanistic class antiresorptive agent, and a new bone anabolic agent.

And I'll have more to say before we start that discussion. So for now, I'll say that's all and turn it back over to Dr. Braunstein. Thank you.

CHAIRMAN BRAUNSTEIN: Thank you, Dr. Orloff. We'll start with the history of the U.S. Guidance by Dr. Colman, and after the first three

talks we'll take some time for questions and answers and clarification before going on to the next set of talks.

Dr. Colman.

DR. COLMAN: Good morning. What I plan to do over -- well, what I plan to do is go back one slide now. Okay. What I plan to do over the next 15 minutes or so is discuss three general topics, starting with the regulatory history of estrogens as they relate to osteoporosis, then talk about the non-estrogen compounds, and finish up with some of the highlights of the development of the Agency's Osteoporosis Guidance, which was first issued in 1979.

Before I do that, for those of you who are not familiar with some of the osteoporosis lingo, two abbreviations that you'll frequently see, postmenopausal osteoporosis is usually PMO, and bone mineral density is usually designated BMD. So you'll see that throughout my presentation.

The regulatory history of the estrogens dates quite a bit back in time. In 1942 the FDA approved conjugated estrogens for menopausal symptoms.

It was then some three decades later that the DESI procedure, that stands for drug efficacy study implementation, and involved the National Academy of Sciences.

A group of individuals sat around and discussed what the available data on estrogen and osteoporosis were, and they made the rather undefinitive comment that estrogen was probably effective for selective cases of osteoporosis.

From about '90 onward, the labeling for the estrogen products as they relate to osteoporosis, there's been some changes in the language in the labeling. If you were to look at the PDR for some of the estrogens in 1990, you would see this wording: "The mainstays of prevention and management of osteoporosis are estrogen and calcium."

Management, we really weren't clear what that meant. So in 2000 it has been further simplified to read: "It's indicated for the prevention of osteoporosis or prevention of postmenopausal osteoporosis." We removed "management."

Some people took that to mean that

treatment was rescinded, when in fact, estrogens have never been indicated or approved for the treatment of osteoporosis. It has always been prevention, and in the past, "management" was also in there.

This slide, this gives you a sense of where I think we stand from a regulatory standpoint with estrogen and osteoporosis. There's no question that estrogens increase bone mineral density. They do that in a dose-dependent manner.

The recent publication of the Women's Health Initiative data clearly suggests that estrogen plus progestin -- in this case it was Premarin -- significantly reduced the risk for osteoporotic fracture, including hip fracture, certainly the largest database confirming a favorable effect of estrogen progestin on osteoporotic risk fracture.

However, there's nothing that is free in this world, and the risk versus the benefit of this compound is under close scrutiny and debate right now, and I'm sure it will continue for some time to come. We don't -- I don't personally -- know where estrogen's role in the treatment or prevention of

osteoporosis will fall out in time.

Next month, the NIH will have a meeting to discuss the WHI data. Again, it's -- this is a summary. Estrogen is currently approved for the prevention of PMO, but not the treatment of PMO. I think that'll become a little clearer as we get into this, as to why we chose those words.

Moving on to the non-estrogens, I want to talk a bit about calcitonin, fluoride, the bisphosphonates and the one selective estrogen receptor modulator, SERM, that's approved for osteoporosis; that is, raloxifene or Evista.

Injectable Calcitonin was the first non-estrogen approved for osteoporosis in this country. That was back in 1984. Total body calcium was one of the primary endpoints. The total body -- the total number of subjects taking part in these trials was relatively small, less than 200.

They did have two-year studies. This went to an advisory committee. It was a fairly small committee. There were a couple of members who voiced concern about approving this drug without fracture

data. There were three members, however, who felt that the data that were presented were sufficient for approval.

The drug was approved based on total body calcium data, in part. But the message was clear to the company that you really should do a fracture trial. So the company did embark on a Phase IV Fracture Trial shortly after approval. Due to a number of problems, such as a very high dropout rate, recruitment was very slow. The study, in essence, never materialized and never produced usable, viable, accurate data.

Starting with fluoride, this really marks the 1980s and the early '90s as critical periods for the development of osteoporosis drugs, and in turn, for the regulation of those drugs.

Some studies early in the '80s were published that suggested favorable effects of fluoride on bone density and fracture risk in postmenopausal women. Larger studies were done after the initial studies, and one study in particular certainly demonstrated that the fluoride increases bone mineral

density of the spine by a dramatic amount.

But in that study the rates of vertebral fracture in the fluoride group versus the placebo group was not significantly different. Furthermore, there was some suggestion that fracture rate in some skeletal sites may actually be higher on fluoride than placebo.

So this really wrangled some thinking. It caused people to question the validity of using an increasing BMD as an automatic indicator of reduction in fracture risk. People have pointed out that fluoride is known to cause mineralization defects in animals.

So this is not a complete surprise, to see this association. Nonetheless, it did set the stage for the next drug that was brought to the FDA, and it had a similar unfortunate correlation. Etidronate was the first intravenous bisphosphonate brought to the FDA seeking indication for osteoporosis in 1991.

This did go to an advisory committee, as well. It was known up front that etidronate could cause osteomalacia in animal models. That was a

concern that was certainly sitting in the back of people's minds.

That information, coupled with a rather strange finding in the third year of two American trials, where the BMD and the fracture rates were what you would expect up to the two-year time point, but during the third year while the BMD was maintained, the fracture rate was not maintained and actually was going in the other direction.

There was quite a bit of controversy over how to interpret these data. I don't want to get into that. The point here is to highlight that fluoride and Etidronate caused some people to step back and say, well, how valid is an increase in BMD in terms of predicting a reduction in fracture risk?

If you add animal data to that equation, I think you have a better sense that we certainly knew that fluoride and Etidronate could cause mineralization defects in animals, and that added to the complexity of interpreting these two development programs. But they did have a big effect on drug development and regulation.

Calcitonin nasal spray was approved in 1995, again, based primarily on bone mineral density. There was still no definitive fracture data. There was -- the proof trial was underway, a five-year, 1,000-woman trial.

The Committee Members felt that it was reasonable to approve this formulation without definitive fracture data, as long as this Phase IV study is ongoing. Then along came alendronate in '95, and the development program for Alendronate really took into account what happened with Etidronate and fluoride.

The company conducted three-year fracture trials. It showed in these trials that the lumbar spine BMD increased by a significant amount, and that that increase was associated with a significant reduction in vertebral fracture risk.

So there was no discrepancy here between increases in BMD and reduction in fracture risk. That's what you would expect. Animal data also did not suggest there were any problems with mineralization. So the preclinical data looked good.

Having the fracture data with the BMD that confirmed this association, the company then was able to get a prevention-of-PMO indication by studying early postmenopausal women who were osteopenic for a two-year period, comparing it to placebo, and that was based solely on BMD, although we did have the knowledge that in a older group of women the increases in BMD were associated with a reduction in fracture risk.

So the -- what we learned here was applied to this population, although BMD was the primary endpoint for the prevention indication. And again, the correlation between increases of BMD and decreases in vertebral fracture risk, this again was resurrected as a reasonable surrogate.

Let me quickly just run over -- the only SERM that's approved in this country is Raloxifene, approved in 1997. It was deemed an estrogen from a regulatory standpoint back then. So the company was able to secure a prevention-of-PMO indication based solely on BMD, because it was viewed as a estrogen.

Shortly thereafter this approval they had

a long-term fracture study ongoing done primarily to satisfy a European regulatory request. So we shortly learned that, in fact, that the modest increases in BMD did translate into a modest reduction in vertebral fracture risk.

But this was a development plan that differed from the non-estrogens and the estrogens, to some extent. Risedronate was the second bisphosphonate; again, followed the very similar program to that for Alendronate.

This is just to quickly highlight some of the points of the last 60 years. Because of their age, they've been around in regulatory parlance for 60 years. Estrogens and non-estrogens have been treated, regulated, developed along slightly different pathways.

The clinical trials have become enormous. If you'll recall, the Calcitonin trials in the early '80s had about 200 patients. The risedronate database in the mid-'90s had nearly 15,000 patients. BMD was -- took a bit of a beating with fluoride and Etidronate.

I think BMD has again risen up to its proper place as a reasonable surrogate for fracture, as long as animal data support that. You'll note that all of the primary, pivotal, long-term big trials for osteoporosis have been placebo-controlled, although the option to do active control has always been there for them.

And what we have, after years of this investigation, is -- we have a number of drugs that we know reduce the risk for vertebral fracture, and in some cases, nonvertebral fracture over a three-year period.

Let me finish up quickly with some highlights of the development of the FDA's Guidance document, first issued in '79, updated in '84 and '94. You can see from the very beginning in the late '70s, people thought that it was going to take a fair amount of time to study these drugs before they were approved.

This had to do with the relative weakness of the drugs at hand. The technology to measure bone mass was fairly rude and crude and insensitive. So

from the beginning these were envisioned to be long-term trials.

This was some of the technique that was available. Single photon absorptiometry allowed you to measure mass in the forearm but not the spine; again, crude techniques. Evaluating fractures. From the beginning fractures have always been important.

The Guidance said that they're highly desirable to get fracture rate. In the same breath it also said, well, it may also be quite difficult to do that because of the large sample size. And again, back here a large sample size was 300 patients.

So they did -- the Guidance did articulate a middle ground, which in essence said, if you can demonstrate that the bone you form with your drug is normal, then a measure of bone mass would be an adequate surrogate for approval.

If, however, there's any evidence that the normal -- the bone is not normal that you form, you're going to have to do a fracture trial to prove that the drug reduces the risk for fracture. In '84, there were a few changes made to the Guidance, nothing too

significant.

Prevention studies were now discussed. You could take early postmenopausal women, expose them two years to drug versus placebo, and use BMD as a primary endpoint. Dual photon absorptiometry now allowed measurement of -- major screw-up.

Anyway, the techniques became better at that time to measure lumbar spine BMD, and calcium and Vitamin D supplementation was recommended for all trial participants. And then we move on to the updates in the 1994 Guidance.

And the '94 Guidance, you will see, has incorporated many of the lessons learned from the Etidronate and fluoride experiences. Okay. Here we go. In the '94 issue, there was a clear delineation between what estrogens needed to do versus what non-estrogens needed to do to garner osteoporosis indications.

Preclinical data became very important, again, because of what happened with Etidronate and fluoride, in that you could pick up abnormal bone histology with those studies. DEXA was available.

You could do skeletal assessment at various sites. It was a fairly accurate technique, lower radiation.

Fracture assessment at this time was also becoming more refined. The techniques were improving to allow assessment of vertebral fracture, which was the primary endpoint for most trials in the '90s.

This is taken verbatim from the '94 Guidance, and it pretty much -- very clearly lays out what a company needs to do to get a drug approved for the treatment of PMO, approval of treatment of PMO based on three-year clinical data.

The third year, I believe, is a direct result of what happened with Etidronate between the second and the third years. The third year puzzle, I think, led to -- let's go to at least three years to look at this.

You could follow this path if you could demonstrate in animal models that the bone quality is normal, histology's normal, bone strength is normal. Again, that was an issue that was raised with Etidronate and fluoride. If you studied those, you would see problems.

We also had to have at least a positive trend in three-year fracture data. You had to have a subset of patients in the trials that had a bone biopsy, and those biopsies also had to show normal bone.

The BMD had to increase by a statistically and clinically significant amount, and the fracture study must continue to five years or until a definitive benefit is shown. In practice, most of these studies were designed to go to three years, not five years.

This gives you a quick glimpse of what the current regulatory policy has been in the past few years. It differs from what's written in the '94 Guidance. Clearly, estrogens have all along been getting prevention-of-PMO indications from two-year BMD studies.

Treatment of PMO, unlike what is voiced in the '94 Guidance, we would like to see large prospective databases to -- before we would approve an estrogen for a treatment of PMO indication. The SERMs have actually drifted towards the non-estrogens with

respect to what is required before approval.

Prevention of PMO can be based primarily on BMD if we have some fracture data that indicates the drug is effective at reducing fracture risk. And as always, a treatment of PMO requires a fracture.

Now, hopefully, at the end of the day, I won't look like this when people continue to ask me what's going to happen with the future Guidance, because I think most of us in the Division don't know exactly which direction things are going to take.

CHAIRMAN BRAUNSTEIN: Thank you, Dr. Colman.

Move on to a discussion of the evolution of the European Guidance. Dr. Abadie.

DR. ABADIE: Okay. Thank you very much and good morning, everybody. It's a great pleasure and a great honor for me to be here. I would like just to say before starting that I'm not a specialist, you know.

I'm only rapporteur of the EU Guideline and the translation, the EU, I would say, translation of the rapporteur is that we work as a coordinator,

but we are surrounded by many experts.

And I think that what I'm going to present to you today is more or less the reflection of the EU experts in this field, and I think that, broadly speaking, most of the experts, EU experts, agree with that.

Every good development starts with labeling. There are two types of indications that could be sought by an applicant. The first one is the treatment of osteoporosis, and the second one is the prevention of osteoporosis.

Let's start with the treatment, and that is something which clearly differentiate today the EU and the FDA Guidance. We need -- we need fractures at the initial stage of registration. We need fractures and we need new fractures.

And if we think about the primary endpoints, we would like to see the percentage of patients with new incidents of fractures. That is, the patient sees the sample unique. We are not interested as primary endpoint with the worsening of fracture.

Therefore, the percentage of patients with new vertebral fracture will be the primary endpoint. Another very important issue which didn't appear in the -- I would say the first briefing book that you have, because you have the former EU Guidance in your first briefing book and in the new one, you have the new EU Guidance.

And there was a major difference between those former and new EU Guidances, that we now require both spinal and femoral fracture as co-primary endpoints in a Phase III trial. This Phase III trial could be the only one, and therefore, there will be some stratification between spinal and femoral.

Or you may have two Phase III pivotal trial, the first one being aimed at the spinal and the second one being aimed at the femoral. And I think it makes sense because the population, broadly speaking, between spinal and femoral is totally different.

The indication will be granted only if the antifracture efficacy has been demonstrated at one site, and there is no deleterious effect at the other sites. And at the end of the day the results will be

specified in the labeling, for instance, treatment of postmenopausal osteoporosis to reduce spinal vertebral or vertebral fracture. The effect has been also shown in hip fracture, or the effect has not been shown in hip fracture.

So the results of the pivotal trial will be mentioned in the labeling. The prevention of osteoporosis is something which is more straightforward. It's clear that the aim of prevention is to maintain or increase bone mass and strength in order to avoid the occurrence of fracture.

But it's clear that the prevention will come afterwards and after the treatment. We, again, I repeat that we need fracture as the initial stage of registration. That's quite a preclinical package for us. It's probably, probably less sensible than in -- for our U.S. colleague.

Obviously, a robust preclinical package would show, first, no adverse effect on bone quality through histomophometry or histology data and the increase in bone mass and strength. There are probably specialists in the room. I will not dwell on

that.

However -- and I think it's important -- the impact of the preclinical package will not be very important on the burden of proof required in fracture study. That is, again, we need fracture in order to get the first approval for an antiosteoporotic drug.

The clinical trials indication treatment, it's relatively straightforward. The minus 2.5 standard deviation on the spine and/or with or without fracture, and obviously there will be stratification. It's the indication treatment, and in the indication prevention.

It's also interesting to see that we have in the last version defined two populations, the first one within the five years after menopause and the other one more than five years after menopause, because more or less I think most of us believe in the transience.

And therefore, we think that there are two populations, within and after five years. And therefore, the risk factors for these two populations are either the BMD plus other risk factors for the

population within five years, while we will concentrate on the BMD that is the definition of osteopenia according to WHO; that is, between minus 1 and minus 2.5 in a patient after five years of menopause.

But in Phase II, due to the complexity of the study, we will not require any BMD data before recruiting those patients in Phase II for the prevention trials. The endpoints, very rapidly as I said before, the fracture is the first endpoint in Phase III in the indication treatment.

It would be the incidence of patients with new fracture with the serial x-ray once a year at the minimum, and a BMD would be the first endpoint in Phase II and in Phase III for the indication prevention.

But we think today that BMD is overall -- and I repeat overall -- not an appropriate surrogate for fractures. And if you see these charts, it shows that in fact the relationship between the percentage of reduction in vertebral fracture risk on the Y axis versus percentage increasing BMD on the X axis is not

marvelous, and you have all the data on the right-hand side of this slide -- Calcitonin, Raloxifene, Etidronate and Alendronate.

Now, I don't mean that there are not differences between bisphosphonate and the others. It's clear that -- and I think we will have this point to be discussed in the future in -- later on -- but it's clear that the relationship is more convincing for bisphosphonate overall than for the others.

Nevertheless, nevertheless, overall -- and we wrote down the Guideline for the whole class of pharmacological -- pharmacological class of antiosteoporotic guidelines, overall the relationship is not marvelous.

Regarding the endpoint, the biochemical markers, again, it was interesting probably to have those markers, indicators of bone resorption as co-primary endpoint in Phase II with the BMD, while for the stimulator of bone formation, the situation is for us a little bit unclear today.

Criteria of safety, it's important especially for those intermittent -- intermittent --

treatment. With the new bisphosphonate it will be important to have the serum level of PTH and 25 OH determined, because if there is a large increase in PTH with a corresponding hypoglycemia, it will be very important for this type of drug to know that and to monitor that from the beginning.

And finally, connective bone histomorphometry, which will obviously depend on the particular preclinical testing, it's not, I would say, very pleasant for the patient to have a bone biopsy. So it's clear that we will be more demanding on the data about bone biopsy in the patient, depending on the results of the preclinical testing.

So there is here now probably the most important and the most, I would say, innovative in the near future, which is the problems of the placebo and the comparator.

It's clear that today we would like to see a placebo controlled trial, and/or a non inferiority trial versus a comparator of three years duration, with calcium and vitamin D supplementation, which is clearly recommended that I would like to point out

here, that we are more or less in the kind of add-on trial since all those patients are already treated by calcium and vitamin D.

And finally, the problem, the major problem, the question about the placebo, is it desirable and is it feasible? About the placebo controlled trials -- and I will not dwell on that because, again, there are people in the room which are much more competent than me -- but let's say that about the placebo, it's the most efficient tool to assess efficacy and safety of a test, few number of patients and easier to interpret when you have a statistically significant difference.

However, the ethical concern is absolutely obvious. And if had a mother or aunt with osteoporosis with a fracture, a prevalent fracture, I wouldn't like her to be treated by the placebo, that's for sure.

Should ethical concern be the same in all population? That is, I think, a very important and interesting issue that we will discuss just later on. About the active control trial, you should know that

it's a common requirement.

I would say overall in the EU, we are fond of active controlled trials, which means that we would like to see first the placebo, and I'm not talking here specifically on osteoporosis, but we do like to see a placebo and also an active controlled trial, and the advantage of this active controlled trial is of use.

You can make a relative benefit/risk comparison to other therapeutic strategy, which will give you the possibility to place the compound in the therapeutic armamentarium. However, it's absolutely obvious that there are some drawbacks of noninferiority trial, and I would like to refer you back to a very good document, which is called the ICH Guideline E10, "Choice of Control Group," which clearly explains the situation of noninferiority trial.

It applies a number of assumptions which are difficult to verify, and finally, the choice of the delta is critical, especially with the osteoporosis topic. For the prevention, no major

difficulties.

If you use with the prevention the same formulation and the same dose as the treatment, you will have the indication or the company will have the indication, with a placebo control trial with a BMD, as first endpoint in a two-year study.

And if you have a new dose, a new route or a new formulation, that will be a three-arm study with a placebo. Those are formulation which have been shown effective in reducing incidence of fracture, plus the new dose, new route or new formulation, so a three-arm trial.

The first conclusion is that I think the main difference between the FDA and the CPMP rests on the role of the BMD and the preclinical safety, which is probably more important in the U.S. than in the EU, where we will concentrate more on the fracture rate for initial drug registration.

However, it's of use that we will have to cope in the very near future with a difficult problem, which is the design of confirmatory trials in the treatment indication, and there are, at least for me,

maybe not two but three alternatives which may not be mutually exclusive, to use placebo in a certain category of patients, to shorten the duration of confirmatory trials and/or to modify the endpoint, and finally also, probably to use the add-on design.

So I will take, if you'll allow me, Mr. Chairman, the last five minutes to try to elaborate on the future. And I will immediately put a disclaimer saying that we have discussed that, but informally, in Europe.

And again, what I will -- going to present you first -- will probably overlap with the future description. That's why I will be extremely brief, but there is something which has not been confirmed at the EU level.

So coming back to the placebo, I think that the placebo could be feasible in certain circumstances. First, the placebo in osteoporosis without fracture; secondly, the placebo in trials of shorter duration; and third, the placebo in add-on trials with patients already treated by an agent of a different class than the test.

I will go directly on the third indent, first to tell you that that is something which may be interesting. We had this example recently in the scientific advice at the EU level. So we won't talk about that especially, for reasons of confidentiality.

But it is an interesting issue that could be debated. The major problem that I see as far as the EU is concerned is the labeling -- is the labeling. And I think in the labeling -- and also for the prescriber in its clinical practice -- we will have to recognize that the patients before taking the test have been treated by another drug, and that may not be totally -- I would say -- the will of the applicant when you submit the dose here.

But I think that as far as we are concerned in the EU, the results of the clinical trials should mimic the clinical practice. The results and the design and the population of patient should mimic the clinical practice.

We have here a table which is interesting and which tried to -- maybe to elaborate a little bit more on the problem of low risk and potential

extrapolation from low-risk to high-risk patients.

And here it's interesting because you see that -- in this table which has been borrowed from Pierre Delmas in the recent paper that he published in The Lancet -- it's clear that you see that for Alendronate, for instance, in the low- and high-risk profile, on the right-hand side the relative risk is relatively similar in both populations.

The same holds true for Raloxifene, on the one hand, with the low population and the high population -- high-risk population where you see that the results are relatively consistent. And if we take the vertebral U.S. and the vertebral multinational regarding Risedronate, we have also -- broadly speaking -- some consistent results.

So the question is, could we use placebo in osteoporosis without fracture, knowing that broadly speaking the relative risk may not be totally different from the high risk, which raises a difficulty if you use the placebo.

Before -- I think that it's a matter for debate. I think the use of placebo in low-risk

patients is legitimate for these reasons that I've just stated, and also for the fact that the risk, as you saw, is low, that the patients, at least in Europe, are not systematically treated when they have only an osteoporosis based on BMD, and finally, that they have to sign an informed consent under the GCP recommendation, which are more today recommendation, which has an obligation.

And so for these three reasons, I think that at the very least we could discuss that, so there will be pros the solution, which would tell you -- or the extrapolation -- which would tell you that the relative risk is broadly similar between high and low risk, so we could extrapolate.

But there are cons who could say, the relative risk is the same or nearly the same, but the absolute magnitude of treatment effect -- that is, the number needed to treat -- is totally different between both situations -- that's for sure -- since the baseline is different.

And so the question that we should raise is, is regulatory extrapolation of low risk to high

risk possible? Now, I will skip very rapidly the concept of sustained versus unsustained efficacy. For the Risedronate, you know that between the first year and between the years thereafter there are no major difference, again.

In the vertebral multinational, in the vertebral U.S., for the PTH we have exactly the same profile, not very different from the beginning until the end of the trial. For the Raloxifene we have also exactly the same picture.

For the strontium ranelate, which is a compound which has not been submit today, either in the EU or in the U.S., but which will be submitted in the future, the problem is similar. The issue is similar. The first versus the third, you have approximately the same results.

So my first conclusion is, is it possible again to shorten the duration of confirmatory trial, but the ethical concern may persist with respect to placebo? And secondly, it is possible or it could be possible to extrapolate from low to high risk.

If we think that the regulatory

extrapolation is not possible, therefore, we should go along with non-inferiority trial in high-risk patients, which would remain the only option. And therefore, we have tried to work on this alternative scenario, but it's clear that we came out with a choice of data of 20 percent, with a realistic sample size.

If you want to shorten or to narrow the data to ten percent, we would have some sample size which would be probably unrealistic, but colleagues dealing with the statistics in the metallurgy would probably confirm that.

And so -- it will be my last slide -- if the extrapolation is permitted. It could be -- if it's the placebo control trials in low-risk patients with the endpoint vertebral and hip. And if no other, it's the noninferiority trial with the vertebral or the hip -- but let's say the vertebral -- as the first endpoint. Or an in-between solution, which could be the placebo control trial in low-risk patients, and an active control trial in high-risk patient with an endpoint, which could potentially be BMD, which would

probably ease the realization and the achievement of those trials.

So that is something that I think will be the topic for the future discussion. Thank you very much.

CHAIRMAN BRAUNSTEIN: Thank you. Our next speaker is Dr. Henry Bone, who will talk about the rationale and durability of the U.S. Guidance.

DR. BONE: Thank you, Dr. Braunstein. I guess one of the reasons I was asked to talk about this is because I can actually remember when we went through the previous drafts of these things, as it -- I guess that's an advantage of advancing age. Hope it's correlated with some wisdom or insight.

I'm going to talk a little bit about what the reasoning is. I think Dr. Colman has given an excellent resume of the history, and a lot of the rationale was incorporated into that history. I'm going to try to emphasize a few points that are especially pertinent to today's discussion.

The first thing I would like to do is remind everyone that there are a wide spectrum of

disorders that could be considered osteoporosis. On this slide we see the ones that have been recognized, by and large, as indications of proof by major regulatory agencies.

And by far, as you see, most of the emphasis has been on postmenopausal osteoporosis. This is where the Guidance documents have been most extensively developed.

We also have had some registrations for glucocorticosteroid exposure, and there's a disorder that's been described or an indication of male osteoporosis, which obviously is just osteoporosis in men and doesn't really specify any particular pathophysiology.

Numerically, as well, the postmenopausal osteoporosis is of course by far the most prevalent. But one of the important points to remember here is that there is a very wide spectrum of severity within the scope of the term "postmenopausal osteoporosis."

This ranges from women with low bone density to women who are in very impaired health as a result of osteoporosis. And this -- while this

spectrum has common features of pathophysiology, and as Dr. Abadie has said, a fairly consistent response to certain interventions, the spectrum of the disease clinically is extremely wide.

There are some other examples -- which in this list is not comprehensive -- of osteoporosis, mainly ones we might think of as accelerated osteoporoses, which are not being currently addressed by sponsors or regulatory authorities to any great degree, but which have some certainly common features with regard to histology, fragility and perhaps even interventions.

There are three main Guidance documents, and the Committee Members I think have received copies of all these. The earliest to be developed, as Dr. Colman has described, was the FDA Guidance, which has gone through three iterations now.

There was also a WHO Working Group Guidance which has, of course, no regulatory authority, but which has been published as what I hope would be something more than an academic exercise, at least from the standpoint of providing a rationale for

an approach to this.

And of course, there's the EU CPMP Guidance that Dr. Abadie has just described. There are a number of similarities between these documents. The main differences involve the role of bone density as opposed to direct assessment of the effect on fracture for the initial registration.

Now, Dr. Colman has told you about some of the experiences leading to the U.S. Guidelines revision in 1993 and 1994. Prior to that revision the Guidance had said that if bone quality remains normal, then increasing bone density is adequate indication of a favorable therapeutic effect, and this is simply applying the laws of physics.

It's clear: the increase in the mass of a structure, as long as its architecture and material properties are not altered, will increase its strength. This is not an opinion. It's an inevitable fact of engineering and physics.

And I don't think anyone thought that the laws of physics had been revoked when the Guidance was revised. But there was some recent experience in --

as has been mentioned with drugs that appeared to increase the bone mass, but didn't necessarily appear to decrease fracture rates or to produce a sustained improvement.

These two drugs, the two drugs that were a particular concern, were fluoride and Etidronate. Both of these drugs were well known for a long time to cause histologic and biomechanical abnormalities in preclinical studies.

Neither of these qualified under the Guidance, the previous Guidance and certainly not under the present Guidance, for registration under -- on a BMD endpoint full stop.

What I think the major effect, however, of this recent experience was on the revision of the Guidance that we carried out in 1993 and 1994 was that the Guidance became much more specific about the requirements for preclinical testing. so that this wasn't a fuzzy gray area vaguely referring to normal bone quality, but the requirements were enumerated for evaluating this.

We also had the failed trial with

subcutaneous salmon Calcitonin. So the issues that were being addressed at that point were the meaning of bone quality in -- as it affected the relationship between mass and strength.

What emerged was a document that says that -- it doesn't actually underline or use the word "robust," but that's the point -- robust preclinical testing can identify drugs that cause a disparity between mass and strength.

However, at the time of the writing of that Guidance it was -- we had relatively little actual experience with drugs that had been successful. A lot of our experience was with identifying the problems.

So it was considered that a "belted braces" approach was probably a prudent idea. And the Guidance said that drugs that did not harm bone quality with a thorough preclinical testing could be approved, based on a primary BMD endpoint in the Phase III trials provided that an ongoing fracture endpoint trial showed a confirmatory trend, as Dr. Colman has told you, and these trials had to be completed.

It put the FDA in a different position from that which they had encountered with the salmon Calcitonin subcutaneous situation. In that Phase IV trial, there was really no way of being sure that the trial would be successful as a trial, irrespective of the outcome of the evaluation.

Whereas, in this situation if it -- obviously, if a trial is fully enrolled and it's far along, enough along for an interim analysis -- the agency could be quite confident that it -- that this sort of Phase 3.5 trial would be successful in at least adequately evaluating the effects.

It was clear that drugs that caused abnormalities in preclinical testing could not be evaluated on this basis, but if the sponsor did carry through a trial -- for example, as we've seen with anabolic agents now -- that a fracture rate was the only acceptable endpoint.

One of the issues that was a little muddy, I think, in some people's minds that -- when you go back and look at the transcripts and remember the discussion in the previous Guidance Advisory Hearing -

- was that model systems actually have several purposes, and we're going to hear about model systems from experts on model systems and that.

But -- and it's important not to confound the points that are made by different kinds of investigations using model systems. You can model a disease and its response to therapy. You can use models to detect specific adverse effects.

You might very well look at model systems to detect a mineralization defect, for example, in a system that might not be particularly informative about efficacy of a drug or pathophysiology of a drug. So it's a question of which model system answers which question.

And I think it's extremely important to understand the ability of our model systems to detect effects of drugs that might alter the relationship between mass and strength. You certainly can use model systems to evaluate specific pharmacokinetic or pharmacodynamic phenomena, but of course, we're all familiar with species variations and so on in this area. So this is a general issue in drug development

at an early stage.

Again, the point that emerged was that the preclinical testing was generally probably reliable, but it was felt that -- at the time of the development of the Guidance -- that these results required clinical confirmation.

And I think that's -- at some level of evidence that's always the case. We would never approve a drug for human use without, you know, a certain amount of clinical information.

With respect to the specific issue that pertains today, the role of preclinical testing is complimentary to toxicology, and in fact, it could be considered a highly specialized form of toxicology.

The ability of the preclinical testing to identify situations in which a problematic divergence between bone mass and bone strength might occur is crucial. The Guidance is quite specific about -- and thorough about -- the studies that are required to evaluate the architecture, mass and strength of the bone, and this will be discussed.

More limited requirements were indicated

for estrogen because of the physiologic nature of the agents and because the experience prior to the Guidance had been supportive of the safety from a skeletal standpoint, and the efficacy of long-term treatment with estrogen.

We do not have specifications in the Guidance -- and this might be a point for discussion -- about when is a SERM an estrogen in the bone. For example, what is the skeletal definition of an estrogen? I think this is -- will be an important point because as Dr. Colman mentioned earlier, Raloxifene was evaluated as an estrogen. We've been in a little bit different mode subsequently.

There's some back and forth on this point, and if we had a very clear understanding of when the appropriate evaluation would -- in the clinic would resemble that for an estrogen or when it might not -- that would be extremely helpful in terms of future clarification.

But the primary objective, clearly, is to make sure that we don't have some undermining of the effect. There was an extension of what had been a

two-year observation period to three years. And there were really two reasons for this, two specific reasons.

The one -- the first reason had to do with the bone mass effect of a drug. The subcutaneous Calcitonin trial was two years long, and the numerical, total body calcium estimate at 24 months was lower than it was at 18 months.

And while this was not a statistically significant decline, it was pretty obvious on all the graphs. The total effect was actually small in the first place. The increase in total body calcium by the neutron activation analysis was only about two percent.

There was concern that the biomechanical regulation of bone mass might actually result in a re-equilibration at the original bone mass. This is a plausible concept, particularly at the time, and that what we -- there was concern that what was being seen was just a transient antiresorptive effect that then would be re-equilibrated back to baseline by the -- what's now known as -- by some of us as the

mechanistat, following Harold Frost's terminology.

And the other reason, as mentioned, for the three-year observation period on fractures was a concern that if you had a drug that had an antiresorptive effect that might transiently increase bone strength and bone mass by its transient effects on bone remodeling, but nevertheless have some adverse effect, such as a mineralization defect, that this might not be detected in the early phases of the trial, so that the on-treatment observation period was felt to be -- needed to be at least three years.

At that time there was no discussion about whether the placebo phase of that study needed to be quite that long, however. I think the emerging concept was reminiscent of a previous approach to arms control, which was "trust but verify."

It was considered important to confirm the qualitative effects in humans by evaluating the fracture rate. This allowed just -- us to determine whether both vertebral and nonvertebral fracture rates were improved, and it helped to support specific claims.

Part of this has to do with initial registration, if the -- when we look at the minimum requirements for initial registration -- and part of this has to do with: what do doctors actually have to know as a practical matter about their drug?

If we have drugs that are registered with less information than practicing physicians actually need, then we're going to have to get that information with additional studies, and those claims that result from those studies will still have to be registered in order for the information to be disseminated in the marketplace.

One of the questions that has come up repeatedly is whether fracture studies need to be repeated for every single additional indication. If our major concern is the possibility that a drug might induce a discrepancy between bone quality -- or between bone strength and bone mass -- is it reasonable or plausible to suppose that this is going to be different in every sub-indication?

In other words, if the drug doesn't cause a qualitative abnormality in women, is it likely to do

so in men? Is there likely to be a qualitative abnormality caused by the drug in steroid-induced osteoporosis, if it's not in postmenopausal osteoporosis? And this has been, let's say, a thorny point in the evaluation of drugs until now.

One of the points that I would like to personally suggest we take into account is how we evaluate multiple endpoints or anatomical sites. Is it really necessary to do multiplicity adjustments, for example, when we are showing that the second or third or fourth anatomical site behaves the same way as the first one that we tested? Or does it make more sense to take into account the prior supportive information of antifracture efficacy, allowing us to reduce the sample size required to achieve that information?

When we contrast the WHO, FDA and CPMP Guidances, we see that there are similar preclinical testing recommendations.

They're really quite consistent, and the Phase II requirements are quite consistent, as well, for the indication of osteoporosis treatment, with the

use of biochemical markers being taken into account for dose finding and mechanistic studies, but a consistent requirement for one-year bone density studies for the primary endpoint for Phase II-B.

In other words, we're going to Phase III, based on drugs that have had a full year of bone density evaluation. Efforts to short circuit this have come to grief in most cases in drug development.

The main differences are that the WHO Guidance would recommend registration with no fracture trial at all, if the preclinical testing is robust and satisfactory. The CPMP, as you have heard, requires definitive anti-fracture efficacy for initial registration. And as I mentioned and as Dr. Colman has mentioned, the FDA has required confirmatory fracture information, but not necessarily definitive efficacy at the time of initial registration -- taking into account that during the review period most of those trials that have had the interim analysis of the biopsy will be completed.

This slide is another way of summarizing the same point. Mind you, preclinical testing is

done, as I said, in much the same manner as toxicology. In fact, it's really properly regarded as a part of the toxicology program, in my opinion.

And this means that excess dosing is required. Five times the expected clinical dose or its equivalent is specified in the U.S. Guidance, and the European Guidance is a bit less specific, but generally consistent with this.

If there are no problems, as I mentioned, the approaches in the clinical trials on the left are permitted in the U.S. -- well, are possible. In yellow, I've highlighted the current U.S. approach, amongst the other three.

Now, what happens if you have a drug that causes a histological abnormality? We know, for example, that parathyroid hormone changes the histological appearance of bone if you give five times more than the therapeutic dose, and so will many other drugs that might be considered as we go forward.

This certainly would, I think, diminish confidence in the bone density endpoint to the -- and under the current Guidance that is not an option. If

so, if a company has a drug or a sponsor has a drug that does produce abnormalities under this testing scheme at the high dose, they can do a fracture trial, or they can quit, under the current situation. We haven't really thought through or developed the experience with some of these drugs yet, to see if there's another way.

Now, when the Guidance -- the current Guidance was developed -- there were fewer therapeutic options, and they certainly weren't as thoroughly tested as the ones that we have available now.

We'd had the recent experiences that have been mentioned, and we've had relatively little experience with everything working very well. We've had more recent drugs tested where the premise of the Guidance has been validated repeatedly in an affirmative way, rather than just showing that preclinical testing could detect problems.

There have been some changes in the last ten years, and I'd like to just review how a few of those might interact -- might verge on today's discussion. We certainly have a lot more experience

with drugs in classes that were not ones we'd used extensively at the time of those previous deliberations.

We have had advances in the technology of evaluating bone density and in the ability to evaluate very subtle fractures. And as you will learn, some of what we call fractures are deformities that don't have a clinical correlate, but give very similar information to those -- to clinically apparent fractures.

We've had additional experience in relating the preclinical and clinical measurements, and we have much more information now about what the risk estimates for events are in the clinical trials. There's been an interaction between the Guidance documents, as Eric Colman mentioned, and I think this has had important consequences.

Alendronate and Raloxifene were both registered under the Guidance, pretty much as it was written. But the subsequent registration packages have been designed to simultaneously file in both the U.S. and Europe, or more or less simultaneously file

in both the U.S. and Europe.

So in the instances where the U.S. might not have rigidly required fracture data and the CPMP has required those data, the -- obviously, the sponsors have applied under the -- with the strictest interpretation in order to have the project done as expeditiously as possible.

So a lot of the change in what we have been seeing in development plans has been actually this idea of making essentially the same submission to both regulatory agencies.

Clinically, we've had some evolution, as well. We now have several drugs approved that are about 30 to 50 percent effective in reducing the risk of -- the relative risk of fracture. Fracture rate reduction has become the clinical outcome that is widely accepted as an efficacy measure.

This is what the people who do efficacy reviews, this is what the people who do evidence-based medicine analyses use as the target or the indicator of how well drugs work. And this is considered to be the closest to the practical, clinical implications of

drugs for effectiveness measurements.

The prevailing standard of care is no care at all. The vast majority of patients in the United States, Canada, U.K. and Europe don't -- even those who could be identified by bone densitometry if the patient's had bone densitometry -- do not take even calcium and Vitamin D.

And we have seen several studies indicating that even after clinically serious fractures, a tiny fraction of patients actually receive pharmacotherapy. Even in those situations the majority of patients probably don't even receive calcium or Vitamin D supplements.

So the standard of care has changed in a way that I think is minimally -- and it's been a source of disappointment, I would say, but it's a fact -- the standard of care for the great majority of patients that's prevailing is no care at all.

As we go forward in the development of new drugs for osteoporosis, we want to look at novel mechanisms -- particularly those that might be capable of increasing bone mass substantially. We are looking

at alternative regimens which will improve convenience and adherence, and make treatment more attractive for physicians and patients.

And we'll undoubtedly be wanting to look at combination therapy with complementary mechanisms. Now, a point -- as it was raised earlier -- was the question of the add-on trial. We're really doing add-on trials now.

And as I'll mention in a moment, it's a little bit of a misnomer when we refer to our present approach as a true placebo. But one of the problems that we have if we do add-on trials is, that if we are using an antiresorptive agent and superimpose it on another antiresorptive agent that is potent, we may very well undermine the efficacy.

There is a theoretical concern about the possible adverse affects of such a combination. It might be worse than either one alone, and this is a problem. So the -- we should be -- we have to be a little careful about talking about add-on therapy here, because of the characteristics of our benchmark therapies that are in general use.

We want to limit the risk to participants for participating in studies, obviously. There are several kinds of risks to participants. And we want to keep the development costs and time in a range that does not prohibit development.

Now, an issue that's been mentioned already a couple of times -- and will be undoubtedly a part of the background, even if it's not the foreground, if I can put it that way -- for today's discussion, is the question of the so-called placebo controlled trials with fracture endpoints.

Please keep in mind that in essentially all trials that anybody's going to be discussing, background calcium and Vitamin D are included for all subjects, regardless of their treatment assignment.

When we refer to placebo in our parlance, we're talking about a placebo tablet being used or a placebo infusion or a placebo injection or a placebo nasal spray being used to mask the treatment assignment that that -- for the active patients.

There's a current view that such trials are now acceptable in patients with relatively low

risk, but not in patients at high risk, that is to say, patients with prior fracture experience, and you'll hear more about this. This has a lot of implications for trial design.

As we then want to look at the reevaluation of endpoints, we want to ask the questions, what do we need to know and when do we need to know it? What do regulators need to register a drug as safe and effective, and what do physicians need to know in order to make good clinical decisions, bearing in mind that the FDA is responsible for both the initial registration and subsequent claims? -- this was a distinction that was made earlier in the charge to the Committee -- and recalling that if less information is required early in the course of development, we may need to do more later.

We're specifically going to want to look at the relationship between preclinical testing and registration requirements, clinical trial endpoints to look at both these kinds of problems, and the question of how we analyze the data, and particularly this question of multiple indications.

Dr. Abadie has talked about the spine and hip both being evaluated, and I think this is something that will come up in our discussions as we go along. With that, I'd like to conclude and I believe, Dr. Braunstein, you're going to have discussion now or --

CHAIRMAN BRAUNSTEIN: No. Actually, in order to try to stay to the schedule I think we'll just move ahead with some of the additional talks. And either later on this morning, if we have time, or early in the afternoon we'll have time to question the speakers.

Our next speaker is Dr. Rodan, who will be discussing the preclinical models of drug efficacy and skeletal toxicity.

DR. RODAN: Dr. Braunstein, esteemed guests, members of the Panel, thank you for the opportunity and I would like to thank my colleagues at Merck for their input and to Dr. Dave Thompson at Pfizer.

My task is to discuss the contribution of preclinical studies to the evaluation of osteoporosis

therapy. The use of animal testing is a cornerstone of drug development, especially for establishing the safety of future therapy.

It's not perfect, but it's the only thing -- the best thing we have, and it works most of the time. This can be expanded to establishing the safety of therapeutic agents to bone, as already mentioned here. We have now excellent models for postmenopausal osteoporosis in various species, and can get an idea about future efficacy of agents in humans by evaluating their effect in those models.

And last but not least, preclinical studies. And that's probably the major, potentially the only way, to study the mechanism of agents, not only for their pharmacodynamic effect, but also for their potential adverse effects, because this can provide shortcuts to studying the side effects and their potential impact on safety in general and in bone, as well.

As already mentioned, this has been very well covered over the last few talks. The change in the Guidelines in 1994 was driven primarily by the

experience with Etidronate, which in the third year did not decrease fractures.

And this was a primary motive at that time -- I was at that meeting -- to extend the prior two-year requirement to a third year, and the experience with fluoride, which although it increased BMD, it did not decrease fracture incidents and may have increased it.

And I'll illustrate how preclinical studies actually, with relatively little costs compared to clinical trials, could have preempted the experience which was obtained in the clinical studies. So let's start with Etidronate.

With Etidronate, actually, mechanistically it was known that there is a risk of osteomalacia. And it is preclinically a very good way to study osteomalacia.

The risk was known from preclinical studies which were conducted, actually, by the sponsors, in dogs, and which showed that Etidronate treatment, albeit at very high doses, produced fractures in dogs.

And other studies, also at a multiple of the therapeutic dose, impaired fracture healing in dogs, and this was the background when we studied Alendronate and we knew that osteomalacia is the problem.

And osteomalacia can be very rapidly studied in animals by looking at the accumulation of nonmineralized osteoid in the growth of a long bone. This was described by a Swiss gentleman maybe 30 years ago.

And this is a bone. In blue here you see bone and in red you see nonmineralized bone, and today there are very good ways to measure the quantity of bone in blue, and of nonmineralized bone in red. This can be automated, actually.

And when you look at the effect of Alendronate you can quantify how much bone is retained. This is due to inhibition of bone destruction or resorption, and how much osteoid is present here in red due to a matrix which has to be mineralized. If you have osteomalacia, you have more of the red stuff.

And you can see this with Etidronate and you can quantify that. So this is shown here. You can do a dose response, you increase the doses of the drug to real multiples of the therapeutic dose, and you measure the blue and you measure the red.

The blue is a measure of efficacy because you accumulate bone, and the red is a measure of toxicity because you accumulate nonmineralized bone. And all the bisphosphonates actually inhibit mineralization and keep the accumulation of nonmineralized bone approximately at the same dose, which is about six milligrams phosphorus per kilogram, and so does Etidronate.

The problem with Etidronate is that this happens at a dose which is very close to the effective dose in this model because of the low efficacy of this drug. The new amino bisphosphonates have a much larger window between efficacy and safety risk. This is shown here.

So with Etidronate you get exactly the same place, accumulation of osteoid, but you get also approximately at the same place, accumulation of bone,

so that this exaggerates sort of the problem by showing that the window is very narrow.

So this type of study, when you know the mechanism of action of a side effect, this study takes only about ten days and it's recommended for any agent that has the potential of causing mineralization defects. So understanding of the mechanism of the side effect can be approached head on in preclinical studies, as an example.

Now, you can detect this in a less specific manner if you look at the relationship between the amount of bone, which is measured here by bone mineral density, the way it's measured in the clinic, and the strength of that bone.

These are very simple mechanical principles that are going to be expanded on by Dr. Turner, but it's almost intuitively obvious that if the bone is normal, when you have more bone, you should have a stronger amount of bone.

But this is for the same -- this is an engineered, fixed volume which contains more bone, so as the amount is larger, the strength is larger. And

this follows a certain curve which was scientifically shown to be the third power of the amount of material, based on engineering principles.

And this study can be conducted, actually, with any kind of future therapy to see if the accumulation of bone, which is the purpose of many therapies, is actually going hand in hand with the increased strength of that bone. Because if the accumulated bone is not normal, then the strength should not increase in proportion.

Then on the background of etidronate and fluoride -- when alendronate was developed, we did these studies -- I think this was the first time it was done for drug development -- and did it in many, many species for many periods of time and found that, indeed, when you retain bone as a result of bisphosphonate treatment, the retained bone generates increased strength, commensurate with the amount of bone retained.

Now, to show that this actually works, I'll show you that with fluoride this is not the case. It was actually reported way before, in 1987 by

Mosekilde, that the strength did not increase with bone mass. And much later it was shown that this is due to a defect in mineralization.

But this can actually be detected with the type of study I have illustrated, and this is shown here. We did a head to head comparison between the effect of fluoride and the effect of Alendronate on mini pig bone, and with Alendronate, as previously shown, you see the expected increase.

However, with fluoride you get an increase in the pigs in the amount of bone, measured here histologically as bone volume, but you do not get the expected increase in bone strength. This should have gone in a line which is parallel to this one.

But, actually, the largest increases in bone mass were those which had the largest proportional decreases in bone strength. And when we measured the fluoride content of these bones, the strength decreased with fluoride content, which actually illustrates in an animal study that increases in bone which are filled with fluoride may not lead to increased strength, and therefore, would project a

lack of proportionality between BMD and fracture risk in these patients.

So the preclinical models for safety -- and I agree with Dr. Bone that this could be looked at in an extension of the safety study. By doing bone measurements; histology, which gives you quite a bit of information on the structure of the bone; and measurement of strength, as illustrated, which Dr. Turner will expand on, in animal models with multiples of the dose, like five times because this is a toxicological study, one can detect -- one actually did detect the deleterious effect of Etidronate and fluoride, and this could be a sensitive method to evaluate the safety of future therapy.

Now, the studies I illustrated were of relatively long duration. The pigs were studied for a year. The monkeys were studied for two years and rats were studied for a year or so. In order to realize some savings one could add these measurement of bone properties to regular toxicology studies.

There are toxicology studies, for example, for carcinogenicity, which have to be conducted for

two years, and these could include the toxicology for bone. And there are other studies which may take six months or so. And so this could be incorporated as a toxicology study for agents which are aimed at the treatment of bone.

Now, moving to efficacy studies, we have really very good models of estrogen deficiency bone loss, and this loss occurs more rapidly in cancellous bone, which is the interior of the bone, than in the envelope of the bone, which is called cortical, and occurs actually in most mammals.

It's very pronounced in humans after menopause. It's seen in rodents. It's seen in primates. It's also seen in other species, but because it's driven by a reproductive hormone, usually estrogen, it's dependent on the reproductive cycle.

And some species where the cycle is seasonal show this phenomenon in a seasonal manner, and one can pay attention to that. For example, sheep, dogs and more recently, rabbits, also have estrogen deficiency bone loss in a seasonal pattern and could be used to evaluate estrogen deficiency bone

loss and its prevention or correction by agents which are developed for osteoporosis.

Now, agents that increase bone mineral density and bone strength, as illustrated in those models, and have been tested clinically have been shown to reduce fractures. And now we have quite a database: it's bisphosphonates; estrogen, just published a few weeks ago for the first time in a placebo controlled prospective study; the SERMs do it; PTH is not yet approved, but they did it as well.

However, the quantitative relationship between the effects in animal species and in humans can probably not be easily projected. So for the quantitative relationship the human data are most likely necessary.

Now, I'll just summarize. With certain principles which -- the '94 Guidelines are extremely specific in outlining what studies to do for what duration and so on, and maybe a committee can work on that.

But I'll just list the principles that can be followed for providing the maximum information from

preclinical studies for the development of antiosteoporotic therapy. The first one is to use adult animals to eliminate the confounding effects of growth.

I think that any species that loses bone as a result of estrogen deficiency can be used, because the science that has accrued over the last ten years or so shows that there's really mechanistically no significant difference in the way this happens.

One should deal with several parameters, histology, densitometry, now micro CTs are being developed, mechanical testing, biochemical markers. And there should be internal consistency between the outcomes of these different measures in order to provide further confidence in their validity.

And also mentioned by Dr. Abadie, several doses should be used. Excuse me. For prevention, one should have prevention studies. For treatment, one should document in their own species, and this can be done, that you can actually reverse or restore bone that had been lost, and follow what happens in both cases after cessation of therapy, because this may be

predictive of what might be happening in humans.

For mechanism study, I mentioned already that they provide important insights for both understanding the safety of agents when the side effects actually can be identified. And in many cases this is today possible.

One can identify from histology the type of bone. Dr. Bone mentioned PTH effects on histology. We looked for lamellar bone, which can be easily identified. You can look for ectopic ossification for bone formation agents.

And efficacy. There's actually, at the tissue level, no difference in the way the inhibitors of resorption work. From estrogens to amino bisphosphonate and anything else, at the tissue level, they work through the same mechanism, suppression of bone turnover and they reverse the negative bone balance.

So suppression of bone turnover leads to a positive bone balance and accumulation of bone. So from the tissue-level mechanism point of view, we do not detect differences between the various resorption

inhibitors.

And we know, from a very nice article by Profitt published two years ago, the mechanism for destruction of the cancellous bone or destruction of the cortical bone are the same. So inhibition of resorption of cancellous bone and the inhibition of cortical bone are following the same path.

The Guidelines stipulate that different species should be used for those two; this may not be essential. So inhibitors of bone resorption retain existing bone, which is normal because these are patients that lose normal bone, and produce a positive balance.

And as already mentioned, unless there is an effect on the bone mineral or some other problem, the bone that is retained by inhibitors of resorption should be normal bone. Formation stimulators, on the other hands, generate new bone and this bone should be examined for its so-called quality, histologically and by any other means available now, micro radiography, micro CT and so on.

So, in summary, preclinical studies can

evaluate bone safety -- the way they evaluate safety in general -- of osteoporosis therapeutic agents and examine if increases in bone mass mineral content, which is clinically measured either as BMD or BMC, are associated with increases in bone strength.

And if they are, then they strongly suggest that the bone accumulated is normal. Preclinical studies can test the efficacy of prospective therapeutic agents in animal models of estrogen deficiency bone loss and potentially other types of bone loss mentioned by Dr. Bone and provide some indication for the future efficacy in patients these models are actually trying to mimic. They can provide mechanistic insights into the mode of action, also with respect to side effects, and with respect to the pharmacodynamic action of these new agents.

And if something in the preclinical studies should be considered and reviewed, as already mentioned, the need for multiple species should be evaluated and the duration of efficacy studies. Efficacy can sometimes be determined in relatively short-term studies, but safety requires several

turnovers of the skeleton, which in different species takes different durations. And this could be an add-on to the toxicology studies conducted for longer times, anyhow.

And maybe one should define different criteria for preclinical studies aimed at approving resorption inhibitors, which act through the same mechanism at the tissue level.

So I don't know if one should actually differentiate between them. This could be a topic of discussion later on. So thank you for your attention.

CHAIRMAN BRAUNSTEIN: Thank you. Our next speaker is Dr. Rizzoli.

DR. RIZZOLI: Mr. Chairman, ladies and gentlemen. I'm a little bit confused. I'm a MacIntosh user, and this one is not my most favorite instrument.

(Pause)

DR. RIZZOLI: Okay. Mr. Chairman, ladies and gentlemen, I feel very honored to be here, being a non-European and non-U.S. representative, and despite the fact that my group is a WHO collaborating

center, I will not speak on behalf of this organization, nor of the group who set the guidelines in '98.

So my thrust today will be to discuss a little bit what we could do with preclinical studies in terms of the developmental strategy of new drugs for osteoporosis.

Now, if we look at the three main guidelines you have in your handout, in the objectives, something is very common. Everybody is interested to look at the strengths of bone under the different conditions. So it's very similar from one guideline to the other. And in terms of safety, as well, everybody's interested to look at if a new drug could be potentially harmful to bone.

But what differs a little bit is one of the objectives proposed by the WHO Working Group to look at mechanisms beside bone strength or safety. And, finally -- and probably this is related to safety -- there is a need to look at the effect of an intervention during fracture repair, since we will be probably at risk of giving this new drug to a patient

already with a fracture who will experience a new fracture during therapy.

So now, if we look at the different details, and we will not go into, as pointed out before by Gideon, by Henry Bone, the different working groups have set very strict, precise conditions to investigate drugs at the preclinical level in terms of species, in terms of design, in terms of duration, in terms of scheduled dose and the different variables to look at.

And if we consider the different drugs which have been now registered and how the clinical outcome has been predicted by preclinical data, we will notice that it's relatively or extremely good, since many of the outcomes we have collected in large, randomized, placebo-controlled trials could be foreseen by looking at the preclinical file.

And just to give you a few examples, you know the data with Alendronate. The left-hand side has been presented already by Gideon. An increase in BMD is associated with an increase in bone stress and this, in clinical trial, is ending in a reduction in

fracture rate.

The same is true for Risedronate. Before it was in baboons, here in mini pigs: better strengths, lower incidence of fracture rate. And now, if we look at another category of compound, the SERM, once again, in ovariectomized rats, Raloxifene is associated with an increase in bone strength in the vertebral body, and this has been done by the next speaker.

And if you look at the clinical trial, everything is going in the same direction. And even for a bone forming agent like PTH, you see that you can detect -- in the lab with animal data, you can detect the increase in bone strengths and then you can detect the same effect, favorable effect on bone by looking at the incidence of fracture.

So if we summarize that all together, there's a good relationship. Now, the issue of fluoride, and the issue of fluoride is perfectly supporting this aspect, since if we are to take into consideration the preclinical data, maybe we would have saved a lot of time and money and, ethically

speaking, some problems with the patients since none of the preclinical trials were in favor of a positive effect on bone strength, and most of them were even in favor of a deleterious effect.

I'm sorry. I forgot one of the initial references. So if we summarize all together, we have a good relationship between the effect on one side, BMD, bone strengths in preclinical trial, and then a good relationship with what happened in humans in terms of BMD and also in terms of fracture reduction.

And as mentioned previously by Dr. Abadie, the recent data with strontium ranelate goes in exactly the same direction. It has been recently reported that this compound is reducing the incidence of vertebral fracture and probably also of hip fracture, and this was associated in animals with an increase of bone strengths.

So having said that, now the question is how the three guidelines are taking into consideration these values. And there there is some discrepancy because for the FDA document, for instance, the complete file should be submitted at the end of the

Phase III.

On the other hand, the CPMP suggests that this could provide some information to the development of the Phase II trial, and most strongly, the WHO document relies on that to design a good Phase III trial, and then it will integrate this data in the overall analysis of the outcome.

Now, if we put that also together, you see here the details. There will be some information about quality, bone abnormality, and this will be integrated in terms of the final convincing procedure to see whether or not we will be convinced by the quality of the file.

However, there are some issues which are not exactly solved at the present time, and we should probably take into consideration for further assessment of drugs in preclinical trials.

First of all, is the relationship between bone mass -- and when I write bone mass, it's bone density, either volumetric or area bone density, so the amount of bone, irrespective of the type of expression -- and bone strength.

And the idea would be what could we foresee to detect the exception to the nice relationship. And despite Gideon before emphasizing the point that for a category of drug at the tissue level the expression should be the same, if you would look at this recently published data in which, in a face-to-face trial in ovariectomized rats, we gave either SERM or bisphosphonate at doses leading to exactly the same increase of bone strengths, you see that there was some small discrepancy in terms of area bone density on the left side, and volumetric or trabecular bone content at the middle.

And then in terms of bone turnover, for the same increase in bone strength, there were some small differences in the same category, but not in the same class of compound. So this should be considered in all the determinants of bone strength.

Then another possibility is the heterogeneity of action within a direct category. We know, for instance, for the class of SERMs, they are triggering so many different genes.

And if we look now at one recent poster

presented two days ago in San Antonio, you see here with one SERM in which the vertebral strength was measured at the maximal effective doses, and compare -- this new SERM is in yellow -- compared to Raloxifene, there was a small difference in terms of bone strength, and this was associated maybe with another mechanism of action, since measuring IGF-1 in these rats, it turned out that the level was increased.

So it has been already pointed out that the safety window should be considered. For instance, with anabolic agents or even with a new antiresorbents with a new mechanism of action, maybe this dose, proposed at five times the effective dose, maybe we could end up in some nonphysiological or even the toxicological side of bone.

And, finally -- and this has been drastically proposed by the WHO document -- the integration of preclinical studies in the drug development strategy, taking into account that both approaches are complementary, could help in the definition of study design, including the endpoints,

the type of population. And you have in the document of the WHO a very boring table, but this table tries to synthesize, to summarize this complementary approach, this synthesis between the preclinical part, which would help you to define the endpoint and the population to study, and the different outcome to organize in a Phase II and a Phase III trial.

So with this table that I invite you to carefully analyze, I'm finished, Mr. Chairman. I thank you.

CHAIRMAN BRAUNSTEIN: Thank you very much. Our last speaker on the topic will be Dr. Charles Turner.

DR. TURNER: Thank you, Mr. Chairman, and members of the Committee. My topic today is this term "bone quality" that's come up several times previously. And this has been used as an explanation when bone mineral density doesn't necessarily explain changes in fracture risk.

And what I'd like to do or try to do is show some different aspects of bone quality and what we currently know about the different effects of drugs

on this. Now, I'm picking several examples of therapies. We've already heard about fluoride, and you probably understand why I picked it. And I'd also like to address antiresorptives, with bisphosphonates as the paradigm there, and anabolics with the parathyroid hormone fragment as a paradigm.

And the reason that we're very interested in fluoride is that this has been the most famous failure in osteoporosis therapy. You see, this is from the Mayo Clinic trial where nonvertebral fractures were actually increased threefold after the therapy, even though there were tremendous increases in bone mineral density in the vertebral bodies.

So this clearly is a serious problem that this therapy caused, and what was subsequently shown is that it was a problem in the mineralization of the bone.

Here we see what should be healthy bone in the light color and this undermineralized bone throughout this biopsy sample. Now, if I can get this to forward. I've lost control.

(Pause)

AUDIO-VISUAL ASSISTANT: Why don't you go ahead and keep talking. I'll fix it. It doesn't like your presentation.

DR. TURNER: Apparently not.

(Pause)

CHAIRMAN BRAUNSTEIN: Well, why don't we take our ten-minute break now.

DR. TURNER: Yes.

(Laughter)

CHAIRMAN BRAUNSTEIN: And when we come back the technical difficulties will hopefully be resolved.

(Whereupon, the foregoing Meeting went off the record at 10:13 a.m. and went back on the record at 10:27 a.m.)

CHAIRMAN BRAUNSTEIN: I'd like to ask everybody to take their seats, please. Okay. We were unable to fix the glitch in Dr. Turner's PowerPoint presentation, and so he's going to give a five-minute overview of what he was going to show, and then we'll take about 15 minutes or so for questions from the panel and the guests to the initial six speakers.

DR. TURNER: Okay. Very well. Welcome back. It doesn't look like we're going to get to -- be able to get to the histological slides because that's where it hung up, and really the focus of the presentation was on some of the microstructural details that occur with different treatments.

And I think you'll have to take my word for this, but I will explain what we've learned from the histology and the different types of bone quality changes that have been seen in preclinical studies.

Just to summarize, there have been two incidences or two observations where a drug treatment has actually caused more fractures than it prevented, and one was with fluoride treatment and this was done in clinics. And the example, the main example was the Riggs study, published over ten years ago.

The other example was in dogs with high-dose etidronate that Dr. Rodan referred to, and this study also caused multiple spontaneous fractures in these dogs. And there were a number of theories on how etidronate caused fractures in these dogs, because the histology showed that the fractures were

associated with very low bone turnover.

And there was one theory proposed by Michael Profitt and some others that this was due to the lack of repair, of turnover of the tissue so it was not able to repair accumulation of micro damage, and therefore, the micro damage caused the fractures.

We've subsequently shown in studies with David Burr in our laboratory that that's not indeed the case. The major problem with Etidronate therapy was exactly what Dr. Rodan illustrated. It's a problem with mineralization in that although there is an accumulation of micro damage when bone remodeling is reduced -- and this would apply to all bisphosphonate therapies -- this is a minor change in bone quality and not the major effect.

And we've seen with anabolic therapies, or at least with the currently investigated anabolic therapies; that is, the full-length peptide PTH and the PTH fragment 1 to 34, that the gain in bone mass occurs alongside a rapid increase in bone turnover rate and a rapid increase in bone porosity.

So the question there was whether or not