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FOOD AND DRUG ADMINISTRATION

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CENTER FOR DRUG EVALUATION AND RESEARCH

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JOINT MEETING OF THE

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

AND THE

ENDOCRINOLOGIC AND METABOLIC ADVISORY COMMITTEE

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FRIDAY

JULY 14, 2000

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The Committees met at 8:00 a.m. in the Versailles II Room of the Bethesda Holiday Inn, 8120 Wisconsin Avenue, Bethesda, Maryland, Dr. Eric P. Brass, Chairman of the Nonprescription Drugs Advisory Committee, presiding.

PRESENT:

ERIC P. BRASS, M.D., Ph.D., Chairman, NDAC
GEORGE A. BLEWITT, M.D., Non-Voting Industry Liaison
LUTHER T. CLARK, M.D., Guest Expert
JAIME A. DAVIDSON, M.D., Consumer Representative, EMDAC
JANET ELASHOFF, Ph.D., Consultant
MARIE C. GELATO, M.D., Ph.D., EMDAC Member
EDWIN E. GILLIAM, Ph.D., NDAC Member
DEBORAH GRADY, M.D., M.P.H., EMDAC Member
JULIE A. JOHNSON, Pharm.D., NDAC Member

PRESENT:

EDWARD P. KRENZELOK, Pharm.D., NDAC Member
BARBARA P. LUKERT, M.D., EMDAC Member
MARK E. MOLITCH, M.D., EMDAC Member
RICHARD A. NEILL, M.D., NDAC Member
JANET H. SILVERSTEIN, M.D., EMDAC Member
WILLIAM V. TAMBORLANE, M.D., EMDAC Member
SANDRA TITUS, Ph.D., NDAC Executive Secretary
DONALD L. UDEN, Pharm.D., NDAC Member
HENRY W. WILLIAMS, JR., M.D., NDAC Member

FDA REPRESENTATIVES:

ROBERT J. DELAP, M.D.
CHARLES GANLEY, M.D.
JOHN JENKINS, M.D.
LINDA M. KATZ, M.D., M.P.H.
KAREN LECHTER, J.D., Ph.D.
DAVID ORLOFF, M.D.
MARY H. PARKS, M.D.
DAIVA SHETTY, M.D.

SPONSOR REPRESENTATIVES:

RENE BELDER, M.D.
MICHAEL BOTORFF, M.D.
W. VIRGIL BROWN, M.D.
J. JAIME CARO, M.D.C.M.
JEROME D. COHEN, M.D., FACC, FACP
CAROLA P. FRIEDMAN, M.D., FACC
CHARLES HENNEKENS, M.D.
GARY KOCH, Ph.D.
MARK B. KRESTON
PATRICIA A. KRIGER
MARK PFEFFER, M.D.
C. MICHAEL WHITE, Pharm.D.

I-N-D-E-X

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

(8:03 a.m.)

CHAIRMAN BRASS: Welcome to the second day of the Joint Meeting of the Nonprescription Drug Advisory Committee and Endocrinologic and Metabolic Advisory Committee.

I'm Eric Brass, Chair of the Nonprescription Drug Advisory Committee from the Department of Medicine at Harbor-UCLA Medical Center. I think we will begin this morning by just doing a quick circle of the room and letting everybody introduce themselves.

DR. JENKINS: I'm John Jenkins. I'm the Director of the Office of Drug Evaluation II at FDA.

DR. ORLOFF: I'm David Orloff. I'm the Deputy Director of the Division ofMetabolic and Endocrine Drug Products at FDA.

DR. GANLEY: I'm Charlie Ganley, Director of Division of Over-The-Counter Drugs.

DR. KATZ: I'm Linda Katz, Deputy Director for OTC.

DR. WILLIAMS: Yes, I'm Henry Williams, Howard University, Department of Community Health and Family Practice, then with the Nonprescription Formulary Committee.

DR. GELATO: I'm Marie Gelato. I'm a professor of Medicine at the State University of New York at Stonybrook and in the Division of Endocrinology and I'm a member of the Endocrinologic and Metabolic Drug Committee.

DR. KRENZELOK: Good morning. I'm Ed Krenzelok. I'm Director of the Pittsburgh Poison Center and a professor of Pharmacy and Pediatrics at the University of Pittsburgh and a member of NDAC.

DR. DAVIDSON: Good morning. Jaime Davidson, a clinical and associate professor of Medicine, University of Texas Southwestern Medical School and I see patients.

DR. ELASHOFF: Janet Elashoff. Biostatics, Cedar Sinai and UCLA, Consultant to the Committees.

DR. NEILL: Richard Neill. I'm an assistant professor in the Department of Family Practice and Community Medicine at the University of Pennsylvania and a member of NDAC.

DR. TITUS: I'm Sandy Titus. I'm with the FDA's Advisory Committee Staff and I'm the Executive Secretary for NDAC.

DR. JOHNSON: I'm Julie Johnson from University of Florida, Departments of Pharmacy

Practice and Division of Cardiology and I'm a member of NDAC.

DR. SILVERSTEIN: I'm Janet Silverstein, a professor in Pediatric Endocrinology at the University of Florida, also a member of EMDAC.

DR. TAMBORLANE: I'm Bill Tamborlane, professor of Pediatrics at Yale School of Medicine and I'm a member of the Endocrine Committee.

DR. LUKERT: Barbara Lukert, professor of Medicine at the University of Kansas School of Medicine Division of Endocrinology, and I'm with the Endocrinologic and Metabolic Section.

DR. GILLIAM: I'm Eddie Gilliam. I'm a Family Nurse Practitioner from Tucson, Arizona.

DR. MOLITCH: Mark Molitch, professor of Medicine in the Endocrinology Section at Northwestern University Medical School in Chicago. I'm with the Endocrinology and Metabolic Drugs Advisory Committee.

DR. UDEN: I'm Don Uden from the University of Minnesota College of Pharmacy and a member of NDAC.

DR. BLEWITT: George Blewitt, Industry Representative to NDAC.

DR. CLARK: I'm Luther Clark, Chief of Cardiology at SUNY Downstate at Brooklyn, Consultant.

CHAIRMAN BRASS: We did pretty good on the microphones. One was left on and I will again just remind the committee members to please always speak loudly and clearly into the microphone so your remarks can be shared by all. Next may I ask Dr. Titus to read the conflict of interest statement.

DR. TITUS: This is for the July 14th Endo and Metabolic Drugs Advisory Committee and the Nonprescription Drugs Advisory Committee. The following announcement addresses the issue of conflict of interest with regard to this meeting and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda for the meeting and all financial interest reported by the committee participants, it has been determined that all interest in firms regulated by Cedar present no potential for an appearance of a conflict of interest at this meeting with the following exceptions. In accordance with 18 USC 208(b)(3) full waivers have been granted to Dr. Eric Brass, Dr. Barbara Lukert, Dr. Jules Hirsch, Dr. Robert Kreisberg and Dr. Mark Molitch.

A copy of the waiver statements may be obtained by submitting a written request to the

agency's Freedom of Information Office, Room 12A30 of the Parklawn Building. We would also like to note that Dr. Jaime Davidson has interest in Bristol-Meyers Squibb, Warner Lambert and Parke-Davis which are unrelated to Pravachol or its competing products. In addition, we'd like to note that Dr. Barbara Lukert has an interest in Merck, the manufacturer of Mevacor and Zocor, competing products to Pravachol, which is unrelated to the firm's competing products.

Further, Dr. William Tamborlane's employer, the Yale University School of Medicine, has interest in Pfizer and in Parke-Davis, a subsidiary of Pfizer, the manufacturer of the competing product to Pravachol, which are unrelated to the firm's competing product.

Although these interests do not constitute a financial interest in the particular matter within the meaning of 18 USC 208, they could create the appearance of a conflict. However, it has been determined, none withstanding these interests, that it is in the agency's best interest to have Dr. Davidson, Dr. Lukert and Dr. Tamborlane participate in the committee's discussions concerning Pravachol. Further, we would like to note for the record that Dr. George Blewitt is the non-voting industry

representative and is on the committee to represent industry's interest.

As such, he has not been screened for any conflict of interest. With respect to FDA's invited guest, Dr. Luther Clark, has reported interest which we believe should be made public to allow the participants to objectively evaluate his comments. Dr. Clark would like to disclose that he is an investigator for research, has served as an educational consultant and received speaker's fees from Bristol-Meyers Squibb, Merck and Parke-Davis. In the event that the discussions involve any other products or firms not already on the agenda for which an FDA participant has a financial interest, the participants are aware of the need to exclude themselves from such 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 products they may wish to comment upon.

CHAIRMAN BRASS: Thank you. I would now ask Dr. Orloff to provide us an introduction to this morning's session.

DR. ORLOFF: Good morning. In the

interest of time I will make my remarks brief this morning. I think everyone at the table heard the introduction yesterday. And so I'm just going to touch on a few points this morning. Let me begin by thanking again the members of the FDA staff, the review staff, for their hard work and review of the NDA and for, in preparation for this meeting. Again, I'll be touching on the high points, I hope. We have a regulatory standard that guides us in the decisions regarding over-the-counter marketing of drugs.

I won't read it for you, and let me say again, let me say first of all that these slides can be made available to members of the advisory committee, I believe by early this afternoon, if need be, thanks. Critical in this language that guides us are issues, and I don't have a pointer, of methods of use and collateral measures necessary to use, which really makes our judgments in OTC switches, or the marketing of OTC drugs different and sometimes more complex than those for prescription drugs.

Traditional over-the-counter drugs which need to be used without the physician and need to be safe and effective in such use are therefore often are usually for low-risk symptomatic conditions where self-diagnosis is the rule for short term use as

monotherapy or the worsening or persistence of symptoms leave the patient to seek more definitive care.

What we're talking about today is something completely different than that. This is dyslipidemia with atherosclerotic cardiovascular disease risk, which is an asymptomatic disease which has added to it from the standpoint of complexity in mediating an effective therapy by the patient him or herself, the issues that diagnosis and follow-up require blood tests and interpretation. The treatment is reduce the risk of life-threatening or life-altering outcomes and where optimum benefit requires long-term compliance, not just short-term compliance but long-term compliance with drugs, diet and lifestyle.

And where, in many instances, titration, combination therapy, treatment of co-morbidity is an important aspect of follow-up. And finally, where the role of the physician, at least as currently, as care is currently undertaken in vigilance for and in anticipation of clinical coronary disease or cardiovascular disease, is an all-important aspect of effecting optimum benefit in the long run. So what about methods of use and collateral measures of use

that I referred to before?

Clearly, when we contrast Rx cholesterol lowering with the hypothetical OTC cholesterol lowering, this issue of methods of use and collateral measures necessary to use is something that we have to look very carefully at. As I said yesterday, when we approve a drug for prescription use, we make a reasoned database judgment that it will be safe and effective if used according to the labeling. At that point, to a large extent, the role of the FDA stops.

We rely, from that point on, on the learned intermediary, the physician or other healthcare professional, to mediate the safe and effective use in collaboration with the patient. The FDA doesn't regulate the practice of medicine and, for better or worse, we cannot insert ourselves into the doctor's office. There are limitations to this system for the treatment of hypercholesterolemia that I won't go through today. We spoke about them yesterday.

By contrast, when we approve a drug for OTC use, again a databased, reasoned judgment that if used according to the label, it will be safe and effective. But in this instance neither we nor the patient can rely on the physician, learned intermediary, healthcare professional, what have you.

And so we, as regulators in making the decision, have really an additional burden and there's an additional standard of evidence that may be required and is unique in contrast to the Rx situation, whereby we have to examine issues of method of use.

Now, so what is the evidence that we would need, or that we do need, to feel, to have assurance that the drug will be safe and effective when used by the patient without the learned intermediary. Well, obviously we need to know about the intrinsic characteristics of the drug that in the simplest fashions speak to its basic safety or elemental safety and efficacy.

But we clearly need more than that. We need information on manner of use, because the overall, the summation of risk and benefit that now addresses the overall impact of this treatment, is going to be a function of the extent to which there is appropriate targeting or capture of patients who are likely to benefit, appropriate exclusion of those who are unlikely to benefit, or otherwise suitable for more definitive therapy because in those instances there may be risk that begins to outweigh benefit, and there has to be some achievement of the ancillary aspects of treatment or we at least need to ascertain

what those are.

As I said before in the case of hypercholesterolemia, that's diet and lifestyle, treatment of co-morbid conditions and follow-up. And we have to have some evidence that people can use it, dosing properly, the proper intervals, and can be aware of any potential drug interactions, for example. I talked to you yesterday about the background in this area. I don't need to go through it again. We're here for the third time in five years to discuss this issue.

There have been changes in the interim, notably a changing landscape and a vast clinical experience with statins and with pravastatin. Here's my take on the sponsors essential rationale for over-the-counter marketing of pravastatin 10 mg., and I'm sure you'll hear this again. Cardiovascular disease is the leading cause of death in the United States.

There's a well-known continuous and grade of relationship between total cholesterol or LDL cholesterol levels and heart disease risk and furthermore, an abundance of trial data support the benefits of cholesterol lowering across the spectrum of levels of cholesterol and levels of risk. There's a perceived therapeutic gap with under-treatment

across the spectrum of risk. There's a changing landscape that we've talked about before. There's the vast experience and, therefore, unrestricted access according to the sponsor for a motivated low-risk population to pravastatin 10 mg. is warranted.

What is the target population that we're talking about today? Men greater than 35, women greater than 45, without coronary disease or diabetes, low-risk, told by the physician to lower their cholesterol but not put on prescription therapy, and with total cholesterols between 200-240 and LDL cholesterols of greater than 130. Let me remind the committee again, the proposed over-the-counter population-- this is a new indication for pravastatin, first of all.

The proposed over-the-counter population is not currently targeted for drug therapy. The heart disease risk, I believe in this population, is something below one percent per year. I can't put my finger on it. We need to address the issue at its most basic of whether this indication, a new indication is supported by data that speak to definitive clinical benefit of the treatment.

And if there are such data and the indication is justified, is over-the-counter access to

prava 10 mg. a safe and effective way to address the unmet medical need in this at-risk population? We have to look at the data presented to us in this package in order to answer these questions. You'll hear presentations as before, but obviously different studies, different designs, on efficacy, from control trials and consumer-use trials that address lipid altering, clinical impact of pravastatin.

You'll hear about safety from the control trial database, from spontaneous reports, from drug metabolism studies or inferred from drug metabolism studies and from consumer-use studies. And you'll hear about label comprehension and consumer behavior specifically with regard to the involvement of the physician, a critical aspect of this treatment paradigm, and appropriate self-selection and -exclusion, clearly something very important in our assessment of whether this can be a safe and effective OTC treatment.

Again, questions. You'll be asked at the end of the day, in effect, regardless of whether we're talking about an OTC drug or an Rx drug, is therapy with pravastatin 10 mg. across the broad target population warranted based upon evidence of clinical benefit, safety and considering the balance of risk

and benefit? Question two, with regard to the OTC appropriateness or applicability, if this treatment is justified in the target population, do we have evidence that benefit can be reaped with an acceptable level of risk across the population in an over-the-counter setting?

This speaks to issues about manner of use, method of use, and collateral measures that determine the sum total of risk and benefit. And finally, is there evidence supported sufficient to support— or presented, excuse me, sufficient to support the expectation of the safe and effective use of pravastatin 10 mg. across the broad target over-the-counter population directed by the consumer without a learned intermediary healthcare professional to assist in safe and effective use?

Thank you. That concludes my remarks.

CHAIRMAN BRASS: Thank you. I will now turn the floor over to Mark Kreston for the sponsor's presentation.

MR. KRESTON: Thank you, Dr. Brass. To members of the Nonprescription Drugs Advisory Committee and members of the Endocrinologic and Metabolic Drugs Advisory Committee, representatives from the Food and Drug Administration, ladies and

gentlemen, good morning.

My name is Mark Kreston and I am President of Worldwide Consumer Medicines for Bristol-Meyers Squibb Company. My colleagues and I come before you today with a unique proposition. We're here to request OTC status for Pravachol 10 mg. which will fill a therapeutic gap and will have a positive impact on cardiovascular health. While we know you entertained an application yesterday for a different cholesterol-lowering proposal, we ask that the committee evaluate the unique characteristics of this specific molecule.

But not only is our molecule different, so too is our entire approach, as you'll see from our consumer-use trials, the level of physician involvement, and our planned post-marketing studies. Indeed, the concerns raised by this panel yesterday will be addressed in our presentation today. I'd like to examine the specific OTC proposition.

Our intended dose is Pravachol 10 mg. once daily in conjunction with diet and exercise to lower cholesterol. For those who have total cholesterol levels between 200-240 mg. per deciliter with LDL over 130 mg. per deciliter. The specific defined populations are men greater than 35 years of age and

women older than 45 years of age. Consumers who were told by their physician that they need to lower their cholesterol levels but who are not on prescription therapy.

These consumers are not at desired levels of cholesterol despite diet modification and exercise. They do not have risk factors such as coronary heart disease or diabetes, and importantly, are likely to reach their end-set goal with this therapy. And finally, it is critically important to this proposition to maintain physician involvement.

So here's the flow of the presentation for today. The background and rationale for OTC Pravachol will be presented by Dr. Jerome Cohen. Dr. Rene Belder will discuss the extensive and well-established safety profile of Pravachol. Dr. Carola Friedman will present the OTC clinical program, and Ms. Patricia Kriger will review the post-launch education and marketing programs, which will ensure appropriate use and compliance.

Lastly, Dr. Friedman will provide a summary and will be pleased to take any questions that you may have. Now we would like to ask the committee members to hold questions until the end and we'll leave plenty of time to have that dialogue. We've

also included for your convenience, in the bottom right-hand corner, slide numbers for ease of reference. Lastly, I would like to acknowledge our panel of distinguished consultants who have worked with us to develop this program and they are available to address questions within their field of expertise. Bristol-Meyers Squibb has conducted more than a decade of research on this molecule, making Pravachol the most widely studied drug of its kind in the world. This unique molecule is very well characterized as a result of this research and our proposal to market Pravachol 10 mg. OTC is a logical outcome of this comprehensive body of research.

Thank you for allowing us the opportunity to have this critically important dialogue today. And with that I would like to introduce our first speaker, which is Dr. Jerome Cohen. Thank you.

DR. COHEN: Thank you very much, Mark. Good morning, ladies and gentlemen, Mr. Chairman, members of the Joint Committee, members of the FDA staff.

My name is Jerry Cohen. I'm a cardiologist on the full-time faculty at St. Louis University. My training and background has been in cardiology, but my interest professionally and

research has been in preventive cardiology, specifically. And I'm pleased to be here today because I've thought about this problem of OTC lipid-lowering therapy for more than five years now and I want to share with you some of the background and rationale for the proposed switch to OTC therapy or as an additional remedy to the problem that I'm going to present to you.

Dr. Orloff gave some of the background and rationale and I think he did a very good job. He also emphasized several points that he wants the committee to consider with regard to this proposal and I want to put the rationale and background in the context— I want to put the context in appropriately with respect to the background and rationale as he addressed it. And so let us begin at the beginning and I know at the risk of some boredom I'm going to show you a slide that you've seen before.

It's a slide that we refer to in brevity as the MRFIT slide, and I show you this with some pride because I am still a member of the MRFIT Executive Committee and we continue to get in data in terms of the National Death Index. And this data is very powerful data when we consider some of the issues that confront us with respect to OTC therapy. And so

let us examine the data more carefully than I think we've done in the past.

What we have is a cohort of 361,662 men, and I'll get to the women's story a bit later, and in this cohort, it's so robust. We have more than 20,000 African Americans. In addition we have a huge Latino base. It's the largest such study of some of these minorities ever conducted and still being done today. And the data are so robust that what I'm going to tell you for the entire group applies as well to some of the subgroups. And what you can see is this graded risk between cholesterol levels, and we looked at total cholesterol in this screening process, and coronary mortality rate. And we know in large groups of people, total cholesterol is really a surrogate for LDL cholesterol.

And what you can see in the left panel is that the higher the cholesterol, the higher the risk. And the lower the cholesterol, the lower the risk. And this is something that is well known to you. But you need to consider it in light of the question before you this morning. And when you look at the right-hand graph, you will see the relative risk, fixing the relative risk at one for a level of 200 mg. per deciliter, which is "normal", and I'll come back

to that normal in a minute.

You can see that as the level goes up to 250 mg. and then to 300 mg., the risk doubles and doubles again. And we recognize that. And I'm happy to say in medicine, over my professional lifetime, we have seen the definition of normal come down. Where was it when I began? 300 mg. per deciliter. 280, 250, 240, and now what do we call "normal"? 200. But I would submit to you is that really normal? When you look up here, what we want to look at, is that associated with the lowest rate? And not how we refer to as ideal, and we should strive for an optimal cholesterol level.

That's really what we should say, because what does a normal American who has a normal cholesterol die from? He or she dies, most likely, from coronary heart disease with that so-called normal cholesterol. And so we have learned from this MRFIT data, a huge amount in terms of population base, and let me tell you that epidemiological data, when conducted in a large scale study properly designed, has never led us astray with regard to the clinical trials that have subsequently followed.

And you'll see some of that evidence in just a few moments. Now another important point to

make apropos to what was said earlier is an asymptomatic condition. Let me show you the next slide. This is the MRFIT data representing the distribution of total cholesterol. The mean is, I'll tell you, is about 206 mg. per deciliter. If you'll look at the proportion of coronary events that come from this target group of 200-240, it represents a substantial proportion of patients who are in that range.

How do they present? Well they present in one of three ways. They present with an acute MI which we can treat very well in hospital today. They present with angina which we can recognize. Or, and this is the key, they present asymptomatically as the first time sudden death. A first event sudden death. My friends, no symptoms whatsoever. Thirty percent.

Thirty percent of people who manifest the disease for the first time have a first event sudden death. How do you get to that guy if he hasn't been seen within the medical care system earlier? Well in fact I think, as you'll see, one of the ways we can get to somebody in this range is through the proposition of having available OTC Pravachol. And so what our target population is here, is this group between 200-240, which represents a substantial risk.

We don't like to use the word low-risk, because they aren't at low-risk. They are at high-risk. They just so happen to be a relatively lower-risk than the upper end of the distribution here. And that's an important notion for you to understand as well.

If you really want to be at low-risk, have your total cholesterol around 150 mg. per deciliter. Now, reference was made yesterday to HDL. Now I think it's important to consider where we are with HDL. The current guidelines, and we have with us this morning one of my colleagues who was a member of the guideline's writing committee, in fact established LDL as the target molecule. It is the molecule at which we aim our therapy and we base our therapeutic considerations.

And in fact HDL is taken into consideration only for risk stratification. And it's used in a dichotomous way. When it's over 60 it's counted as a so-called negative risk factor. When it's less than 35 it's a risk factor that's added to. But it's not used as a means of determining whether or not we should treat somebody because total cholesterol is an independent risk factor as is HDL, and I'll come back to that point a little later, because I think the

panel had some questions relative to HDL. Now I want to go into more of the rational that was touched on a little bit by Dr. Orloff.

First we have national policies already in place and we must consider that. The national guidelines were developed and the current ones were written in 1992 and published 1993. They are now seven to eight years old. They were written at a time before we had evidence of the statins. They were written at a time when in fact the principal therapy was said to be, and I stated today, bioacid resin binders.

That's the treatment if you go by the current guidelines today. Because it was pre-experience with the megatrials. How it defines optimal levels, and again I don't necessary-- these are desirable levels that actually is determining its use, it's less than 200 and less than 130, and that's where we would like to get the population to. In accordance with that, Healthy People 2010 who recently said that's really a wonderful idea. We've got to move the population down there for reasons of primary prevention and having to do that. You establish a goal of 199 mg. per deciliter. We would like to have that as the mean.

As I mentioned, the current mean is 206. That's 7 mg. per deciliter. It may not sound like a lot to you, but it's a big number when you apply it across the population. It represents a three and a half percent reduction. And what we have available to us today, in terms of the wisdom of our thinking and decision making, is the opportunity to create an option where we have available a tool to help move the population in that direction.

What is appalling to all of us interested in primary prevention is in fact what exists today. And all of us who practice know in fact that the cholesterol is significantly undertreated and a therapeutic gap to which Dr. Orloff referred remains today. What is that gap? Well, we have people with a defined goal of less than 200. It says so in the guidelines.

They should be at less than 200, but yet their cholesterol's are between 200 and 240 and they go to the doctor and what does the doctor say? He says your cholesterol is 220. That's a little above average, not to worry, not too high. 300's high, 280's high, 250's high. And so that's why it's often called the most dangerous cholesterol in America. Why? Because it's not treated. It's not treated,

it's ignored. If his cholesterol was 280 or 300, doc said we gotta get you on a drug. We've gotta lower that cholesterol. And that's the population for which we have real concern. That's where the action is with regard to coronary heart disease. Now in addition to that we have, as Dr. Orloff again said, a changing environment. Things are changing. What's changing? The American people. And I think the manifestation of that is here in this room and the coverage that this whole issue at the public forum two weeks ago. Attitudes have changed. Americans are interested in self-care.

And they're voting with their dollars, 400 million dollars are spent annually on supplements used extensively to lower cholesterol and in fact there is very little data for most of what's bought with regard to the two things that we are most interested in, safety and efficacy. And that's what we need to consider in light of this changing environment. Do we have a tool available with proven safety and proven efficacy that we can give to the American people with knowledge of safety and knowledge that we are going to do benefit and with regard to cholesterol reduction. And that's the questions that I think you'll be addressing. Prescription medications are often seen

by this group as a last resort.

I'm not sick, I'm not ill, I don't need to go the doctor and get a prescription. And this is the group that might be interested in taking such a product where available. And compliance doesn't matter. You say what's long-term compliance? I heard that yesterday. 100 percent? No. 50 percent? Maybe. 40 percent, whatever it is, it's a positive number for people who are not currently being treated. That's the idea to bring people into the system, to get their cholesterols lowered first with safety, which I'll come back to, and that's the idea that we need to consider here this morning. There is this gap. We can narrow that gap by an OTC approach and we have data that you'll see that will promote interaction with a healthcare provider. It doesn't drive people away, it brings them into the system, and you'll see that a bit later.

And it increases access particularly to minority groups and others who may under-utilize medical services and there I think we have an opportunity to really reach out in ways that haven't been done before because the number one cause of death in these minority population groups is in fact coronary heart disease. This isn't the answer,

members of the committee and ladies and gentlemen. This isn't the answer. There isn't the answer to the question.

It is one of the answers to a very large problem and I believe it is a significant answer. And the data support cholesterol lowering across a broad spectrum is huge, and you remember the database, the five megatrials including three that used pravastatin, and the primary prevention study, the West of Scotland, the CARE and LIPID studies, were secondary prevention trials, all of them showing highly significant reductions in event rates. Different population base to be sure, but when we pull the data and in particular looking at safety which we'll talk about in a little bit, it gives us confidence about that particular issue. And so if you look at the megatrials together in terms of randomized clinical trials, we have the spectrum that is pretty broad now, with respect to our knowledge of randomized clinical trials.

No, we do not have a clinical trial, nor does anyone else, with respect to looking at the target population per se. You won't get that. But what you will get is the preponderance of evidence if you step back from the data and look at everything.

Look at the clinical trials, look at the epidemiological data, look at the animal studies, and you will see, ladies and gentlemen, that the preponderance of evidence clearly tells us that the target population will benefit from cholesterol lowering.

Don't look at a single trial. Don't look at two trials or five trials, look at everything we have. And I would submit to you that there's very little that we do in medical practice today, for which we have more proof of efficacy than lowering cholesterol. Let us go on from these trials and address the HDL issue that came up yesterday. Is HDL an independent risk factor? Absolutely. Does it predict or diminish the benefit of lipid-lowering? No.

And that's the important point here. Looking at West of Scotland and looking at baseline HDL levels divided by quintiles, you will see that there's no evidence of attenuation of the benefit of LDL reduction with Pravachol by HDL at baseline. Those who have the highest levels clearly show benefit and the benefit at least is great if not greater relatively than those who have the lowest levels of HDL.

Clearly the absolute risk is lower in those who have HDL, but that isn't the point. The point is that these people benefit regardless of their HDL levels. And the same can be said when we analyze the secondary prevention studies. If you look at the CARE and LIPID studies taken together and draw the line looking at HDL again at baseline and looking at outcomes, you can see at the event rate the benefit that's seen with pravastatin is across all HDL levels. There's no evidence of interaction and there's no evidence that these lines become parallel. Those with high HDL's benefit, those with low HDL's benefit. Let me turn, then, for the indications for Pravachol itself. It's a great story in terms of our ability to lower lipids. When I began many years ago, a couple of— we never dreamed we'd be able to do what we can do today.

Cholesterol lowering was approved in 1991 and the sequence we've seen over the last 10 years, amazing, amazing trials that I showed you that allows them to have approval by the FDA for Pravachol, for primary prevention of coronary events based on the West of Scotland, for secondary prevention based on CARE and LIPID, of total mortality by appropriately reduction in coronary mortality, by reinfarction and

stroke in those who've had a myocardial infarction, and importantly, slowing the rate of progression of atherosclerosis. And why do I say that's important? Because no one here that I've heard in the last two days mentioned the word atherosclerosis. And that's what I am particularly interested in is the disease process.

The distinction sometimes between primary and secondary prevention is blurry and with increased technology is becoming more blurred. We can diagnose subclinical disease now. Does that person have secondary disease or primary disease? And so we can slow the rate of progression by use of pravastat. And when we've considered this at-risk population, this 200-240 target population, by all means some of them, some who may be destined to die tomorrow, have underlying disease that we can slow the progression of.

And what we're asking for, in this current application, in the proposal before you for the year 2000, is in fact an indication for cholesterol lowering, specifically 10 mg. pravastatin cholesterol lowering. Now, let me conclude with this part of the presentation about what we learned in medical school, "primum non nocere". When I began thinking about

this, I thought in order to have a product out there with regard to reducing risk of disease and particularly an asymptomatic disease, what do we need to have? And I kept coming back to this, "primum non nocere". We first must do no harm. And that's where the standard needs to be highest. And I agree with when we say we need a higher standard, not in terms of clinical trials. We'll never have all the i's dotted and the t's crossed there. The higher standards must come from safety. We must protect our population out there. And we're all in agreement with that. That came through loud and clear at the public forum. Now let us look at what we have with Pravachol. As was mentioned, it is the drug that has the largest clinical base experience. More than 100,000 patient years in randomized placebo controlled studies. That's a huge database that you'll see. There is based on those a lack of significant drug interactions which differentiates it from other statins, importantly so. There is no evidence of musculoskeletal events and the rates are similar to what was seen in placebo. The same with hepatobiliary profile, the same in terms of overdose, potential. And trials using 100– 160 mg. have been done without evidence of harm. Finally in terms of pregnancy,

there's no evidence of reproductive risk if taken inadvertently during pregnancy. What we have is a safe compound, as safe as a compound can be. As Janet Woodcock said, there's no such thing as a perfectly safe drug and I would agree. But this is about as safe as we can get in terms of an over-the-counter product. Particularly when we counter-balance it with the 400 million dollars that's being spent for it, in terms of safety and efficacy. OTC Pravachol provides a well-characterized, safe option for individual choice and so what we see is a reduction of LDL cholesterol at average of about 18 percent. This we know will be associated with a significant reduction in risk estimates as we know it from all of the data. We know that consumers are interested in nonprescription options. We have a way that we can close or narrow this therapeutic gap. This option of allowing OTC Pravachol will go a long way at reducing the burden of cardiovascular disease. So in summary, then, we have a compound that is very, very safe, that is effective in terms of LDL reduction, and no matter how you look at this particular ratio, it comes out very favorable when you in fact start with a low safety base. We can talk about the numerator benefit later on if you wish, but in fact you have to come up

with a very favorable benefit risk ratio. And with that I'll conclude my remarks and it gives me pleasure to introduce our next speaker, Dr. Rene Belder, who in fact will emphasize and talk about the safety profile. Rene?

DR. BELDER: Thank you Dr. Cohen. Good morning ladies and gentlemen. My name is Rene Belder. I'm the Executive Director with the cardiovascular clinical research at Bristol-Meyers Squibb. I've been with the company for about 12 years, and all those years I've been working with pravastatin. It's now for my pleasure to introduce to you some of the safety data that has been mentioned earlier. As mentioned before there's an extensive profile safety experience with pravastatin. It has been used in over 200 clinical trials. We started studying it in 1986. It was a well-established safety and efficacy profile. It doses up to 160 mg. per day which is four times the highest prescription dose and 16 times the proposed OTC dose. We've had more than 100,000 patient years of exposure and placebo controlled morbidity and mortality trials of which 50,000 patient years were on pravastatin. Our long-term safety data is in excess of five years and more than 5,000 patients have been exposed to pravastatin for more than five years in

these trials. In addition we have an extensive post-marketing experience. Pravastatin is available in 68 countries for periods up to ten years. And we estimate that there's more than 22 million patient years of exposure. Certain safety considerations are important for the OTC availability of statins. And these are drug interactions, the safety with respect to the musculoskeletal and hepatobiliary system, the risk of overdose and of course, the inadvertent use during pregnancy. I will discuss in the next few slides each of these topics with you. I will demonstrate to you that pravastatin 10 mg. is an appropriate choice for the OTC market. Let's start with the drug interactions. Pravachol has no clinically relevant pharmaco-kinetic drug interactions. It's unique among the statins because it's not significantly metabolized by cytochrome P450. In addition there were no significant interactions in the standard PK studies, for instance, with digoxin, warfarin, and cimetidine. And of course of interest it is to know cimetidine, as you know, is available for the over-the-counter use. However, inhibitors of P glycoprotein may cause small increases of pravastatin levels and I'll show it to you a little bit more about that in the next slide. Based on this

profile we propose for the OTC label that there's no warning for drug interactions. There's a lack of drug interactions with pravastatin and this slide shows you what it means relative to the other statins. As you can see compared to the other statins, there's no significant increase in pravastatin levels when combined with some of the common 3A4 inhibitors, for instance, verapamil, itraconazole, erythromycin, grapefruit juice, and also diltiazem. As said before, inhibitors of P glycoprotein transfer system may increase levels of pravastatin. For instance, erythromycin and clarithromycin have shown about a two-fold increase in pravastatin levels and you show that here, that's shown here. That means that for a 10 mg. proposed OTC dose, the exposure would be similar to a 20 mg. dose, which is still below the highest prescription dose available. Furthermore with cyclosporine we have seen about four to five-fold increase in personal levels. We do not think that these increases are clinically relevant and I would like to refer to you the extensive literature that's available about the use of pravastatin in transplant patients. Doses of 20 and 40 mg. have been used and have been shown to be safe and effective in these patients. In conclusion, pravastatin— In conclusion,

there's a lack of drug interactions with pravastatin and we do not think that a warning on the label is necessary. Let's move on to safety considerations with respect to the musculoskeletal system. I would like to in particular discuss with you rhabdomyolysis. This has been discussed yesterday and rhabdomyolysis is a serious condition. It's defined with a clinical diagnosis of rhabdomyolysis combined with a CK level in excess of 10,000 units. As you know there are multiple risk factors known for rhabdomyolysis and in patients who present with rhabdomyolysis, often multiple of these risk factors are present. That makes the attribution of a case of rhabdomyolysis to a specific factor often very difficult. In addition, the background rate is unknown. However, rare cases have been associated with pravastatin--, with statin use in general. I will show you the cases which have been associated with pravastatin, but before I do that I would like to mention that due to the lack of direct drug interactions with pravastatin and due to its hydrophilic nature and its active transport into hepatocytes and virtually no uptake by nonhepatic cells, we would not expect that rhabdomyolysis is a particular concern with pravastatin use. And these are the data that we have. There are no cases of

confirmed rhabdomyolysis in our clinical trial experience. In the CARE study, one investigator reported one case of rhabdomyolysis, however, the peak CK level was less than two times the upper limit of normal. Serious musculoskeletal events in our clinical trial database were similar to placebo with an incidence of .2 percent in each treatment group. Our post-marketing surveillance database will attempt a 40 mg. dose use show there are very rare cases of rhabdomyolysis, .3 cases per 100,000 years of patient experience. And as a total of 74 cases that we counted, 57 cases met a definition, in 17 cases there was a CK level that was unknown, however, were conservatively incorporated. Most cases, 47, had confirming factors. In 15 cases there was an association also with a fibrate. In two cases it was clofibrate, in two cases gemfibrozil, in 11 cases was bezafibrate, a compound that is not available at the U.S. market. FDA review showed a preponderance of cases at the 10 mg. dose and also a preponderance of cases at the Japanese population, posing the question whether or not there would be a dose relationship or perhaps a specific vulnerability of the Japanese population to rhabdomyolysis. Since most of the sales of pravastatin occurs in Japan, where the 10 mg. dose

is used most likely, we did another analysis whereby we normalized the cases of rhabdomyolysis and divided it by the number of tablets distributed. And you see that on these two panels here. On the left-hand panel distribution by dose, on the right-hand panel distribution by country. And as you can see when we look at the dose distribution, there's no apparent dose relationship with respect to the risk of rhabdomyolysis.

I would like to point out that at a 40 mg. dose there were only four cases reported and therefore their confidence intervals around this estimate. Similarly when we look at the distribution by country, there's a very similar rate reported in the United States, Japan and France, which is about 85 percent of total pravastatin sales. And again, there's no evidence of a specific vulnerability of the Japanese population. In summary, the cases of rhabdomyolysis reported with pravastatin are very rare, there are many confounding risk factors, the background incidence is unknown, there's no apparent relationship by dose or country, and there's no increased risk to be expected due to the lack of drug interactions. The proposed OTC label nevertheless will contain the appropriate warnings. In summary, there's a wide

safety margin for pravastatin and we do not expect rhabdomyolysis to be of a particular concern. Let's now look at the unique safety profile with pravastatin in the hepatobiliary system. This slide gives you an historical overview of the LFT requirements of the liver function testing requirements with pravastatin over the years. We started in 1991 with a class labeling, and here you see the frequency of liver function testing that was required. Over the years we gained experience with pravastatin and in '96 on the basis of the results of the West of Scotland study, we had a requirement for liver function testing approved by the FDA, but only a baseline and a testing or any time when the dose is elevated.

At this moment based on the polled analysis of the three prevention studies, we believe that the data supports elimination of all liver function testing. And I will show you some of the results of this analysis. In the interest of time, I will only show you the results on ALT. We have similar results for AST. This shows you the incidents of post-baseline market formalities more than three times the upper limit of normal in the pravastatin and the placebo group. As you can see there were more than 9,000 patients in the pravastatin group compared

to more than 9,000 patients in the placebo group and this was based on more than 250,000 liver function assays, and there's no difference between the placebo and the pravastatin group in the incidents of marked abnormalities. The question was asked yesterday, what if a patient has a baseline abnormality to begin with? And we had 317 patients in the pravastatin group who had an abnormal level before they start— got into the study. And there was between one and three times the upper limit of normal. In the placebo group we had 262 patients and again, as you can see, there is no difference in the risk for subsequent abnormalities between the placebo and pravastatin group. We therefore conclude that there is no necessity for liver function testing with the use of pravastatin. In summary, a clinical trial database does not have any signal of drug or dose related hepatotoxicity. A post-marketing surveillance shows that there are only very rare cases of liver failure, less than one per one million years of exposure. Most of these cases were confounded by predisposing conditions and multiple concomitant medications. As I said before we do not think that liver function testing is necessary during the use of pravastatin. Finally, the safety considerations with respect to the risk of overdose

and the risk of inadvertent use during pregnancy. As said before, in a clinical trial, pravastatin has been shown to be well-tolerated and safe in a trial in 48 patients of six weeks duration, is four times high as prescription dose and, of course, 16 times the proposed OTC dose. In our post-marketing surveillance database we had 14 cases of overdose. One resulted in death, it was attempted suicide, and 13 cases recovered without sequelae. However, the proposed OTC label of course will contain warnings with respect to overdose and use in children, or at least a warning that it should be kept out of reach of children. Finally, pregnancy. Of course, we do not advocate that pravastatin is being used by pregnant women. However, I will show you the data that is relevant to the risk when used inadvertently by a pregnant woman. Pravastatin was not teratogenic at doses with a 20 fault or a 240 fault greater exposure than humans, based on the surface calculation and 40 mg. dose. There was no evidence of impaired organogenesis and the offspring had normal birthweight. Our post-marketing surveillance database has 43 cases of pregnancy reported. Of 29 cases, the outcome was known, and there was no evidence of teratogenicity. So our pre-clinical data and the experience with

exposure during pregnancy do not demonstrate it an increased risk for congenital malformations. The proposed OTC label will of course contain a warning to seek medical attention in case there is a pregnancy. In conclusion, these are the issues that we discussed and Dr. Cohen had mentioned them before as well, there's a lack of significant drug interactions, serious musculoskeletal events were similar to placebo in our controlled clinical trials, cases of rhabdomyolysis are very rarely reported in post-marketing surveillance, the hepatobiliary safety profile is similar to placebo and supports elimination of liver function testing, and there's a wide margin of safety demonstrated and thus minimizing the risk of overdose, and there's no evidence of reproductive risk if taken inadvertently by pregnant women. We therefore think that pravastatin 10 mg. is safe for the use in the OTC setting. Thank you for your attention. I would like now to hand over to Dr. Carola Friedman.

DR. FRIEDMAN: Thank you. Good morning. I'm Dr. Carola Friedman. I'm an Executive Medical Director at Bristol-Meyers Squibb and I'm very pleased to be here today to present to you the OTC development program that we put forward to support OTC status for

Pravachol 10 mg. I'd like to remind you again who is the OTC population. These are men who are 35 years or greater and women who are over 45 years. They have been told by their physician to lower cholesterol, and they are not at a desirable level, despite having pursued diet and exercise, and yet they are not taking prescription therapy. That puts them in cholesterol ranges of total cholesterol of 200-240 and an LDL cholesterol of greater than 130 mg. per deciliter. This is a primary prevention population. These people do not have established vascular disease or diabetes. And these people, as you will see, are very likely to reach their NCEP goal with a moderate reduction in LDL cholesterol that will be achieved with 10 mg. of Pravachol. Now the points that we thought about as we developed the program are points that have been discussed before in these last couple of days as well as points that we talked about with these committees in our previous meetings as we thought about OTC lipid-lowering therapy, and we discussed with FDA the kinds of issues that we needed to consider. And they're listed here. First, will the product be used by the appropriate people? Will the OTC defined population in fact be the ones to go to this product? A very important consideration of OTC therapy is that

it will benefit and not destruct. And that means that the physician needs to be maintained--, physician involvement needs to be maintained, both initially when thinking about using the product and over time as cardiovascular risk factors will evolve and change. Will compliance in the OTC environment provide a similar profile of biologic activity that is LDL reduction? And importantly will use in a less supervised environment result in the similar profile of safety that you've just heard about? The program that we put together to address this is listed here. First, a label comprehension and then two consumer-use trials, PREDICT and OPTIONS. The objectives of this program are listed here. First we wanted to develop a label that consumers could understand and then test it with a special attention to illiteracy. In the label comprehension trial, as well as all of the consumer-use trials, we use the REALM test to assess literacy in everyone who entered. In the consumer-use trial, we wanted to really allow everyone to come in so it would be as much as possible if the product were available for purchase in a store in an OTC environment. And that would include people for whom this was inappropriate to see if they would make the right decisions. And then we wanted to assess their

behavior in these environments that were as natural as possible and allow them the myriad of behavior options that do occur in the real world with a minimal intrusion of the study architecture. We wanted the data to be generalizable and that meant to include enough numbers of populations that we could do meaningful subanalyses, and we wanted it to be reliable. And importantly we recognized and we heard from this committee the last time that one trial cannot answer every question. So we devised, we designed two trials with very different study designs to see if the results would be concordant. In PREDICT, we created OTC and prescription environments to assess comparability, so that the prescription group would act as, if you will, as a control group. In OPTIONS, we captured a real-world setting. Now in the interest of time, I'm just going to spend a couple of slides on the results of label comprehension. This study involved 612 people, 27 percent of whom read below ninth grade level. This was a mall-intercept study. There was in no way prior knowledge of or interest in cholesterol required. People were shown the package and then asked a series of questions. Importantly as you can see here, people understood the key messages, whether they read below ninth grade or

above ninth grade. Importantly they understood that they should see the doctor and get their level checked, they shouldn't use if they've had heart disease or diabetes, and if they had the adverse symptoms of muscle pain, they should see the doctor and stop the medication. Now there has been a question raised in the FDA review as to whether the rel--, as to the relevance of the label comprehension test, given the fact that the label tested was not exactly the same as the label that was submitted. This slide summarizes the differences in the label tested versus the label that has been submitted to the application that you have. As you can see here, the changes primarily reflect the evolution and requirements of Drug Facts format. We have attempted to incorporate all of the key messages. We have kept the readability level at the same level. The label tested read at a seven and a half grade reading label and the Drug Facts format label is at about an eighth grade reading label, so that the number of the "see your doctor" messages are the same, and we have added additional information based on our learnings. First we have included the LDL greater than 130 mg. per deciliter and we have tried to highlight the importance of the total cholesterol level, 200-240 by

a graphic. The other changes that we have made is the age for women has been changed to greater than 45 years and the erythromycin warning was eliminated based on the pharmacokinetic data. I'm going to spend the rest of my time now talking about the consumer-use studies that we conducted, first starting with PREDICT. The objective of this study was to allow very diverse populations to participate, to randomize everyone as they came in to two kinds of environments, not two kinds of therapies but two kinds of environments. First, an OTC and then prescription, before we knew anything about them, and allow them to do the behavior that would exist in those environments. The prescription environment served as a control group. Once they came in they were left alone to behave as they would in the real world for six months. What we assessed here was whether they would consult a physician if they purchased the product in the OTC environment. And the secondary objectives were comparative between OTC and prescription to see if utilization of the healthcare system would remain similar and whether the reduction in LDL cholesterol and safety profile would also be similar. Turning now to how we recruited these people, we again wanted to try to capture a broad

spectrum of the population. The study was conducted and advertised in 20 geographically diverse areas. We were very careful to characterize the demographics of the radio and print media to make sure that that mirrored the demographics of the community and we did augment advertising by placement on Hispanic and gospel stations and minority magazines. The key communication messages of the advertising, whether this is a nonprescription medicine for people to lower their cholesterol. For people who are generally healthy and had total cholesterols between 200 and 240. Importantly the ad had no mention of age or other medical conditions and was really quite general. This is how people came into the study. Reflecting interest in our prescription therapies, over 11,000 people responded to the ad by calling a call center within six months. Now we were very careful at the call center not to do any screening so that the call center operators had a script that allowed them only to give directions to the site and the hours of operation to the site to the callers, except for screening out women of child-bearing potential. The study did exclude women of child-bearing potential because it was started prior to the submission of the pregnancy data that you heard to the FDA. This

exclusion counted for about five percent of the calls. There were 3,888 people who decided to visit the retail sites, 80 percent of whom responded to the ad, 20 percent by a walk-through. Importantly, of the people who decided to come, the vast majority, 3,872, almost everyone, was ultimately randomized to one of the two environments. I'm going to spend a few minutes talking about the retail sites because this is so different from a clinical trial. This is actually one of the retail sites where people went, and we really wanted to try to make this accessible to everyone, so we placed it in neighborhoods that had access to public transportation, minority populations, populations of low literacy. And again this is where people were randomized, before we knew anything about their medical conditions or their cholesterol levels. Now we also wanted to make this as much as being in a store as possible so there were no medical personnel. As you can see it was dissociated from the clinics. There was no screening performed, and there were minimal exclusion criteria. Anyone could purchase the product if they were above the age of consent, if they had not been in a research study in the last 30 days, or if they weren't women of child-bearing potential. At this point, OTC participants could purchase the

product in a prototypical package that we would expect to be available in the real world. And once they did and left the site, there was no contact made with them for six months. If they wanted to come back to the site to re-purchase, they could, but no contact was made to anyone. I'm going to spend a couple of minutes talking about how people flowed through this study because it is so different from a usual clinical trial. And I think that's very important as we consider the analyses of the different patient populations. As you see here this is the OTC and the prescription group, and this is how it would flow if it were a real or usual clinical trial that we're used to in evaluating drug applications. First, people are randomized to the environment, and you can see the numbers flow down here. And then if they want to, they would consult the physician. Then the physician would make a decision of whether their therapy was appropriate. And then the subject would make a decision of whether they wanted to take it, and this would be the qualified and treated group. And that's of course if everything went according to the protocol. But we know in the real world that that doesn't happen. What are the options that the prescription had? Well, really they had to come in

and they had to see the doctor if they wanted to get a prescription and really their only option, or the only thing that they could do, is decide whether or not to fill that prescription, and we see that about 50 people decided not to. But really, they had to make this decision and then they came into this qualified and treated group. On the other hand, the OTC purchasers had many other options. Once they were randomized, they could go and purchase, they could decide to consult first and then purchase, they could find out if it was right for them and then purchase, they could find out it was not right for them, the physician could recommend that this was not a good idea, but they could still purchase. So they could really purchase at all these different places. They had so many other things they could do. And then of course, once they purchased, they could decide whether or not they wanted to take it. So these different activities help us characterize or place people in the appropriate analyses. To characterize the people who are interested in this kind of a OTC proposition, we really wanted to look at everybody before there were any of these biases either by the subjects themselves or by the physician as they came in. So this is the randomized population which we used to characterize

the people who are interested. The primary objective of the study was to see whether OTC purchasers in fact consulted the doctor. In terms of tolerability, in order to compare the OTC and prescription group, we used the qualified and treated population because this is really where the two groups had converged and where they had the equal choices and options. And of course, for safety, we looked at everyone who took any medication at all. I'm going to show you now the results of the characteristics of the people who were interested in OTC therapies, really who is coming in to purchase an OTC product. It's a middle-aged population, few people below the age of 35 or greater than 75. Again, because we excluded women of child-bearing potential in this study, there were a preponderance of men. Eight percent of this 3,872 people were black, five percent were Hispanic, eight percent read below ninth grade literacy. In terms of their healthcare status, this was a population with access to healthcare who are still seeking nonprescription options. 85 percent of them had a doctor. 83 percent saw that doctor annually, a quarter specifically for cholesterol. A quarter knew that they had high cholesterol for more than five years. There are no impediments to taking

prescription therapy. Three-quarters of the population had prescription coverage. And interestingly, this is actually the characteristics of the U.S. population, where about 85 percent of people do have a doctor, see the doctor annually, and about three-quarters of the population do have prescription coverage. This was a motivated group of people. Using the MEDFICTS tool, which is a validated tool proposed by the NCEP, 80 percent were already following an American Heart Association diet. But twice as many people were using nonprescription therapies to lower their cholesterol compared to prescription therapies. 18 percent taking nonprescription therapies to lower their cholesterol versus nine percent who are taking prescription therapies. Here's what people would do if they decided to see the doctor. The physician saw both OTC and prescription patients so that there would be no bias in the clinic visits or recommendations. The visits were intended to mimic a typical practice where people would have a lipid evaluation and then a therapy recommendation according to study guidelines. If the therapy was appropriate for people, the doctor would recommend that they come back in eight weeks, but again it was up to the participant to make an

appointment to come back. At six months we contacted everybody, whether they purchased, whether they saw the doctor, we really wanted to see what happened to everybody at the completion of the study and we did a cholesterol questionnaire, a lipid profile and a dietary assessment. And in order to have an assessment of longer-term compliance over the course of an entire year, we invited people who were on therapy for six months to continue into a six month extension. I'm going to talk now about the behavior of the OTC consumer. 1,924 people were randomized to the OTC environment. Of those, 720 ultimately decided to purchase. I think it's important to spend a couple of minutes looking at why people decided not to purchase. 47 percent wanted to consult the doctor. 18 percent recognized from the label that it wasn't right for them. 15 percent cited cost, because as you know in this study people were required to pay for medication out of pocket. Now what are the characteristics of people interested in purchasing the therapy? This was a primary prevention population free of heart disease and diabetes. These people knew that a healthy total cholesterol was below 200 mg. per deciliter, 80 percent. 91 percent had been told they had high cholesterol and they were right. 87 percent

had total cholesterols greater than 200 and three-quarters had LDL cholesterols above their desirable levels. This slide depicts the behavior of what people did when they purchased the product. The primary objective of the study was to see the percentage of people who would see the doctor within two months of taking the product. And you can see here that 77 percent of people fulfilled that primary objective. An additional 8 percent of people didn't consult the doctor but at the end of the six months returned their medication unused indicating that they never took it and just didn't follow on with the proposition. An additional five percent of people consulted but outside our predefined two month window, leaving 90 percent of people behaving appropriately and 10 percent who took and never consulted. Now what is the profile of that population? Here we look at the people who took without consulting, there were 72 of them. Interestingly 88 percent of them had discussed their cholesterol with a doctor in the last six months. This was still a primary prevention population. And importantly there was no evidence of increased risk here. Only two people reported adverse events, one of myalgia and one patient underwent prostate surgery. 90 percent of these people did not

go on to repurchase. I'm going to turn now to the secondary objectives where we look at the OTC environment versus the prescription environment and look at comparability. Here we look at the people for whom the doctor said this is a good idea, take it and come and see me again in eight weeks. We can see for the OTC group in yellow, prescription in blue, follow-up after that initial consultation was comparable and very good in both, indicating that because the product is OTC doesn't necessarily mean lack of involvement in the healthcare system. Now another aspect we really wanted to look at carefully was whether OTC availability would distract people from their prescription therapy. Would this be adding people into the system or actually taking people perhaps down from a therapy that was already benefiting them? And how we assessed this was by looking at the people who were randomized to the OTC environment— remember everyone who came in was randomized, whether or not it was appropriate for them, there was no screening done. And when we looked at all the people who were randomized, there were 183 people who were already taking prescription therapy when they answered the ad, and when we looked at them at the end of six months, only two percent had actually shifted down to the OTC

therapy option. Now there's been some discussion about whether OTC availability would lead people to abandon lifestyle modification and that was an issue that has been brought up in the past and one that we wanted to look at very carefully. As I mentioned we used the MEDFICTS tool to assess AHA diet status and as I mentioned coming into the study about 80 percent of people were already following an American Heart Association diet. When we looked at what they did at six months, the vast majority had not changed. About ten percent had actually improved, and a small number had worsened. But interestingly, more people in the prescription group had worsened compared to OTC, indicating that the OTC availability was not something that would lead people to fall off their diet any more than prescription. Now can there be other benefits to an OTC program? I think we can perhaps see some of them here. At entry when people came into the study and saw the doctor, by NCEP criteria, there were 321 people who needed a higher dose prescription therapy because they were at high risk. And in this study the doctor said you're really not appropriate for this therapy. You need a prescription. You should go talk about it with your personal doctor. When we contacted these people at the end of six months, 46 percent in

fact had gone on to see their personal physician, and now 29 percent had started taking prescription therapy, whereas of course none of them was started, had been that six months ago. In addition, new medical conditions were diagnosed in the work-up of high cholesterol, including hypertension, diabetes and thyroid disease. Importantly and of course not surprisingly given the very good safety profile that we've heard about this drug, the safety profile in the OTC environment was excellent. There were no doubts or serious adverse events related to Pravachol, and the overall incidents of adverse events was similar to the prescription experience. The most common reason people discontinued was for myalgia or headache, occurring in one percent of both the OTC and prescription group. Now there has been some discussion in the FDA briefing book about the tolerability and compliance in OTC and prescription environments, and I want to address that on the next slide. When we look here at the reasons for discontinuation of medication, and again going back to what is the appropriate population to look at? We think that's a qualified and treated population, the people who the doctor said this was right, and then went on to take medication. That's really where the

OTC and prescription group had that equal right, equal choice, and where we can compare apples to apples. When we look at the reasons for discontinuing medication, there's no difference statistically between OTC and prescription overall, for adverse events, or for any of the other reasons that people gave. Now of course the benefit of allowing Pravachol 10 mg. OTC is the LDL reduction that it can afford. And we used as our benchmark the LDL reduction that has been seen in the placebo-controlled dose response trials that initially supported the NDA. What we can see here is a summary of those results with about an 18 percent reduction in LDL cholesterol. That was highly statistically significant compared to placebo, and this was the benchmark that we gave ourselves to see if we could achieve in the OTC environment. What did we see and predict? In the OTC subjects we saw a meeting of that benchmark at eight weeks and sustaining for six months. And importantly in this lower-risk population, this reduction brought 83 percent of the OTC subjects to their NCEP goal. Now I want to spend a couple of minutes talking about the longer-term compliance because this issue was discussed quite a bit yesterday. This data is based on the extension protocol which was filed to our four-

month safety update. What we see here is a summary of the OTC and prescription group who qualified for therapy at the beginning of the study. At one year about 50 percent of both groups equal were on drug. Importantly, when we look at the LDL reduction achieved in this population, it was very significant. This was a really compliant group of people. We looked at them eight weeks, six months, one year, 22 percent reduction in LDL cholesterol achieved and maintained. Then we also wanted to see if people remained involved in the healthcare system over this longer period of time. It's important to remember that in this study people did not have the prompts that would occur in the real OTC world. There was none of the advertising or education programs, or any of the media that would accompany a real OTC situation. People could choose to enroll in a Pravachol Partners program, but that was really the extent of the reinforcement messages. So what did people do at the end of a year? As you can see, the vast majority of people who started on, who came in, completed therapy and consulted the doctor at a year, there's a small number who discontinued before that year, but consulted the doctor prior to discontinuation. There were some people who

discontinued on their own, but actually came back and saw the doctor at their annual visit, leaving only about eight or seven percent who neither consulted the doctor at a year or prior to stopping the therapy on their own. So what do we think PREDICT can tell us about behavior in an OTC environment? We can see that of the 1,924 people who were exposed to OTC Pravachol, about 25 percent decided to buy and take the drug. 83 percent of those people talked to a doctor and adjusted their behavior accordingly. For people in whom the doctor thought OTC Pravachol 10 was appropriate, 52 percent were still on drug at 48 weeks and they achieved meaningful LDL reduction comparable to an Rx group. I'm going to turn now to the second consumer-use study that we did, OPTIONS. And this was a study that we wanted to create real-world environments. We conducted this in 20 communities in six states and allowed people to purchase Pravachol 10 in their own pharmacies and observe their behavior for three months. Now of course when we did this we had to be able to verify that what they said they did, they in fact did. So to do that we chose OTC pop--, we chose HMO populations so that we would have access to the patient charts, the doctor could verify that data in this real-world setting. What we wanted to do

was assess whether people saw the doctor within two months of using the product, and again because the doctor had access to the charts and we could see if people would self-select appropriately whether or not they saw the doctor. And we had a pre-specified definition of self-selection in the protocol that was really to be sure that people weren't distracted, that the high-risk people were not using the therapy. So that the definition of appropriate self-selection were people who had no heart disease, diabetes, liver disease or pregnancy, were not currently taking prescription lipid-lowering therapies. We obviously also wanted to assess safety. Here's how the study was conducted. We again placed the sites that would be accessible to diverse population and we sent advertising like this to a non-targeted big sample of the HMO. As you can see this was one of the pharmacies that used. We had floor stands and posters to attract walk-through. The advertising was very commercial-looking as much as possible in a clinical trial, and again, participants could purchase and once they did there was no contact made with them for three months. We wanted very minimal exclusion criteria, so that people again had to be above the age of consent and could not have participated in a

research study within 30 days. They needed to have been an HMO member for six months so we would have some relevant data in the chart and we did exclude women who were pregnant or breastfeeding. Here is the results of the characteristics of people responding to the ad. 161,000 people received this mass mailer. AS would be expected with a mass mailer, very few people were interested, about one or two percent ultimately came to the pharmacies, 2,202. And when they saw the package and the floor stand, 782 people were interested enough to enroll in the study. This was about equally divided between walk-through and the mailer. Looking at the demographics of the people responding to the advertisement, again, mean age of about 51, few people below the age of 35 or above the age of 75, about equal of men and women, 21 percent of the people were black, five percent Hispanic, 12 percent read below ninth grade level. Here is their healthcare status and cholesterol option. Not unexpectedly in an HMO population, 96 percent saw the doctor yearly. Nearly a third of the people had seen their doctor specifically for cholesterol. 70 percent had seen the doctor for cholesterol in the last--, or had discussed cholesterol with the doctor in the last six months. And just like PREDICT about a quarter of

these people knew they had high cholesterol for at least five years. But also similar to PREDICT despite having access to prescription coverage, fewer people taking prescription therapy, 16 percent, compared to 26 percent paying money out of pocket for nonprescription therapies. Now if a person decided to go to the doctor in the study, they had to make an appointment with the doctor as they would in the real world and they saw their own primary care physician. There were no research physicians in the study. And this HMO setting, like I said, allowed the physicians to verify the risk factor profile that the participant reported as well as of course whether a person did what they said they did and consulted. And here's the results of the consumer behavior. Of the 782 people who enrolled, 404 decided to purchase. The reasons for non-purchase again were very similar to what we saw in PREDICT. 47 percent wanted to talk to the doctor first, 20 percent recognized warnings on the label indicating that the product wasn't right for them. Of those who purchased, again most people--, this was a primary prevention population, and of the people who had lab values in the chart, 89 percent had total cholesterols greater than 200, 79 percent had an LDL cholesterol greater than 130 mg. per deciliter.

Here's the behaviors of the purchase population. Here again our primary objective was consultation within two months. 44 percent of the people achieved that objective. Another five percent consulted, but outside of our predefined two month window. 12 percent purchased the medication but didn't take it within this three month period either because they weren't interested or hadn't yet had time to make the appointment with their physician. And again because in this study we could assess appropriate self-selection by looking at the charts behind the scenes, we could see that an additional 32 percent, although they didn't consult, did appropriately self-select by these predefined definitions of not being at high-risk, leaving only seven percent of people who didn't consult and did not appropriately self-select. Well, let's look at the profile of these people who didn't consult. There were 157 of them and as I mentioned, 82 percent self-selected appropriately and that they were not at high-risk. Three-quarters of these people had discussed the doctor in the last six months and 90 percent of them had a total cholesterol greater than 200. Importantly the incidents of adverse events in this group was similar to those who did consult. In OPTIONS a safety profile was maintained, and I think

the safety in the OTC environment was also demonstrated. Again we could see of the people who came into the study who were already taking prescription therapy, 11 percent shifted to the OTC option. So how can we summarize the consumer program that we put forward to address whether Pravachol 10 mg. can be used appropriately in an OTC setting? First, comprehension of the label was evaluated with special attention to the low-literacy population. The identification of the OTC consumer and evaluation of that behavior was assessed at large in varied populations by very different study designs that allowed real world behavior. And of course we do recognize that no matter how natural we try to make these studies, nothing can truly mimic the real world completely, and we are committed to monitoring a real world environment after launch and that program will be discussed by Ms. Kriger in the subsequent presentation. I think we can also conclude that the characteristics of people who are interested in purchasing OTCs are remarkably consistent across the studies. Over 90 percent have been told they have high cholesterol and about 90 percent in fact have cholesterol levels above desirable levels. Three-quarters have LDL above desirable levels. And

importantly this is a group of people who are interested in taking nonprescription therapies. The people who purchased OTC Pravachol, about a quarter were taking nonprescription therapies, two to three times as many who were taking prescription therapies to lower their cholesterol. And yet this a doctor-involved population. The vast majority see their doctor at least annually. From the data that I have shown you I think we can conclude that Pravachol 10 mg. can be used appropriately in the OTC environment. Consumers can understand the label communication. The physician does remain involved both initially and over time. The safety profile, and by a profile of biologic activity, has been demonstrated to be maintained. OTC availability does not significantly shift people down from prescription therapy. And in fact we think that OTC availability can serve as a gateway for increased utilization of appropriate therapy by many people. Thank you for your attention. I would now like to turn the presentation over to Ms. Kriger who will discuss with you the education and marketing programs that we would want to put forward with a launch of this product.

MS. KRIGER: Thank you Dr. Friedman, and good morning. I am Patricia Kriger, Senior Director

of Rx-to-OTC Marketing at Bristol-Meyers Squibb. I am very pleased to be with you this morning to review the education and marketing program that would accompany the OTC launch of Pravachol 10, as well as the post-marketing surveillance program we have planned. As outlined earlier, our data demonstrates that consumers could safely use and would derive benefit from Pravachol 10 even in the absence of physician involvement. However, we strongly believe that the benefit would be maximized by keeping the physician involved. Therefore, we have developed a comprehensive, educational campaign that emphasizes the importance of keeping the doctor in the loop. The key goals of our plan are first to deliver a responsible education and marketing program that will complement, and not supplant, current efforts to reduce cardiovascular risk in the United States. Second, to provide all the tools that consumers and healthcare providers will need to ensure appropriate use in an OTC setting. We feel confident that the program as proposed will allow us to translate the very positive results we saw in the consumer-use trials into a real world setting. In fact, we will have many more opportunities available to us to communicate and reinforce key messages in an OTC

environment than we had in the consumer-use trials. In an OTC setting we will surround consumers with multiple messages, including cholesterol awareness initiatives, healthcare provider programs, retailer programs, as well as consumer advertising. To maximize their effectiveness, these programs must be designed with the consumer in mind. So who is the likely OTC user and what is likely to motivate him or her? The profile of the likely OTC use that has emerged from our extensive consumer research is remarkably consistent. Those most interested in OTC options are concerned about cholesterol, proactive and prevention oriented, are already using diet and exercise to help control cholesterol, and they are doctor involved. In fact, more than 80 percent have discussed their cholesterol with their doctor in the past year. And importantly for both epidemiologic as well as attitudinal reasons they are not ready for Rx medicines. There has been discussion about whether the therapeutic gap can best be addressed by simply lowering the Rx treatment guidelines to include those with cholesterol in the 200-240 range. It is evident from how consumers perceive Rx and OTC medicines that this is not the total answer. As we look at how cholesterol concerned consumers view Rx versus OTC

options, this becomes even clearer. As demonstrated here, the vast majority of consumers regard Rx as only for people with severely elevated cholesterol and something to be avoided for as long as possible. Specifically, 78 percent of consumers agree Rx medicines are for people with severe cholesterol problems, while only six percent agree this is true for OTC medicines. Consistent with this, 58 percent agree that Rx medicines are something they would avoid for as long as possible, while only 13 percent think this applies to OTC options. Conversely, OTC is seen as the preferred option if cholesterol is only mildly elevated and is viewed as something to prevent versus treat disease. As a result, OTCs can complement currently available options by providing a more accessible and less intimidating way into therapy for many low-risk individuals. With this in mind, let's move to the education and marketing program itself, starting with the key objectives. First, to raise cholesterol awareness and foster a productive dialogue between consumers and healthcare professionals. This will help close the therapeutic gap highlighted earlier by providing greater access and providing a more acceptable treatment option for many consumers. The second objective is to ensure that consumers can

appropriately self-select, and third, to encourage responsible, ongoing use. Let's turn now to the program elements designed to encourage awareness and dialogue. First is consumer advertising, which will serve to increase awareness broadly and generate physician contacts. In addition we'll reach consumers broadly through community outreach and work-site programs to increase awareness of cardiovascular risk and to encourage cholesterol awareness, intervention and screening. In this way, we hope to broaden access to minority and underserved populations who may be less likely to engage in the traditional medical system. To further facilitate the dialogue between consumers and healthcare providers, we'll also provide tear-off pads at the retail shelf with questions consumers should discuss with their doctor. Pravachol 10 labeling will also play a key role in encouraging interaction between consumers and healthcare providers. Prominently displayed on the end flaps of the carton is the message that consumers should see their doctor. This message reinforces to the consumer the importance of knowing their cholesterol profile as well as other risks for cardiovascular disease. Inside the carton right on each blister card is a message that serves as a daily reminder that consumers

should keep the doctor involved in their ongoing management of disease. In order to facilitate a productive two-way dialogue, we plan a comprehensive education program directed to healthcare providers. We'll focus on those healthcare professionals who are most likely to interface with OTC users-- primary care physicians, nurses, physicians assistants, as well as pharmacists. Our objective is to broaden education about cardiovascular risk, behavior modification and how OTC options fit into the spectrum of cholesterol management. The tools we'll employ include a professionally staffed 800 number, new product bulletins, continuing education programs and materials to provide to the patients. For the second objective, appropriate self-selection, the labeling will again play a critical role. As outlined earlier, consumers clearly understand the label and higher-risk individuals understand this product is not for them. In addition our program will include a toll-free 800 number and interactive web site. The 800 number will provide answers to frequently asked questions as well as access to live operators. Consumers will be able to request Spanish language package inserts as well as bilingual audiocassettes. When people contact the 800 number, they will be reminded to contact their

physician if they have not already done so. Through the web site, consumers can access up-to-date health information, risk assessment tools, get tips on diet and exercise, and can easily link to other related healthcare sites. Let's move now to the third objective, encouraging responsible use. This begins when consumers first purchase the product. The starter kit will provide a month's supply of product in a calendar pack format to establish the routine of daily use. It will also include free enrollment in Pravachol Partners, a user-friendly package insert and educational brochure, as well as incentives for future purchase and cholesterol testing. We will also work with cholesterol testing companies and retailers to make cholesterol testing more accessible and affordable. This will be an integral part of our program since we know how important positive reinforcement is to ongoing compliance. Pravachol Partners is one of the key elements of the compliance program. The cornerstone of the program is a series of postcards and newsletters with messages tailored to coincide with key points in the adoption curve. This type of program has been shown to be very effective in improving compliance and should be particularly effective in this information hungry OTC audience.

These education and marketing programs reflect extensive learning from our consumer-use trials and we feel confident that they will address the specific needs of consumers and healthcare providers. At the same time we also recognize that no consumer-use trial, no matter how well designed, can answer all questions or anticipate all possible outcomes. As a result, we are committed to rigorous post-marketing surveillance, including conducting a Phase IV study. This will allow us to characterize the range of real world behavior and modify our education and marketing program if warranted. The three areas we'll be most interested in evaluating will be safety in an OTC setting, how OTC availability will impact cholesterol awareness and action amongst the general U.S. population, and the specific behaviors of OTC statin users. The primary mechanisms for evaluation include monitoring of adverse events, which will of course be reported periodically to the agency, 800 number contacts from consumers and healthcare providers, and most important, a Phase IV study. The design I will share with you represents a proposal only. Clearly, the final protocol would be discussed and finalized with the agency before implementation. As planned, the Phase IV study will be conducted in three waves--

one baseline reading prior to distribution and two post-launch waves, six and twelve months following the start of advertising. Each phase would include a naturally projectible sample of 10,000 adults and 1,000 OTC statin users. We would also augment to include a readable sample of important demographic subgroups. The key objective of the study would be the characterization of cholesterol-related beliefs and behaviors, including awareness, cholesterol testing, OTC utilization and physician interaction. The study would be sufficiently powered to allow us to identify the scope and nature of any unanticipated behavior so that we could modify our program as warranted. In closing, I would like to reiterate our commitment to continuous improvement of our education and marketing program based on learning from post-marketing surveillance to support cholesterol education efforts amongst consumers and healthcare providers and to amplify important labeling messages, to encouraging ongoing dialogue between consumers and healthcare providers and to encourage appropriate behavior and compliance. I thank you for your time and would like now to turn the podium back to Dr. Friedman for a few closing remarks.

DR. FRIEDMAN: Thank you very much.

Before I entertain any questions that you may have, I'd just like to conclude with these thoughts. First, heart disease is a very important issue in this country. Since we began this meeting this morning, 100 people have died of coronary heart disease in this country. We also know that people are very interested in pursuing self-care options. I think you've seen demonstrated that Pravachol 10 mg. has an appropriate profile of both safety and efficacy for OTC use. We therefore conclude that OTC Pravachol 10 mg. is an appropriate option for the lower-risk individuals who are choosing to lower their cholesterol. It will bring more people on to appropriate therapy and it will provide an additional approach to treat a major modifiable risk factor for heart disease and be a part of the solution to help close the therapeutic gap. Thanks very much. I'd be happy to entertain any questions that you may have.

CHAIRMAN BRASS: We're not going to do the questions until after the FDA presentation today.

DR. FRIEDMAN: Okay.

CHAIRMAN BRASS: Before we take a short break, I just want to remind the committee members that we will have a number of important votes this afternoon and if anybody has flight arrangements, I

hope they don't interfere with that. Those of you who will need to leave early, I would appreciate knowing about it during this break so we can plan accordingly. At this point we'll take a break until 10:05. Thank you.

(Whereupon, the foregoing matter went off the record at 9:53 a.m. and went back on the record at 10:08 a.m.)

CHAIRMAN BRASS: We will continue the morning session with the FDA presentations and I'll turn the microphone over the Dr. Parks to begin that presentation.

DR. PARKS: Thank you Dr. Brass. Good morning. Today you'll be hearing several presentations given by reviewers at the FDA on Bristol-Meyers Squibb application for the Rx-to-OTC switch of pravastatin 10 mg. I'm Mary Parks. I'm a medical officer in the Division of Metabolic and Endocrine Drug Products. I will first be presenting the clinical efficacy and safety review of this application. Following me will be Dr. Daiva Shetty from the Division of Over-the-Counter Drug Products and she will be discussing the actual use trials. And finally Dr. Karen Lechter from the Division of Drug Marketing, Advertising and Communications will be

discussing the label comprehension studies. Dr. Brass, members of Joint Advisory Committee, I would like to present to you today the clinical review of Bristol-Meyers Squibb application for the nonprescription availability of pravastatin 10 mg. My presentation will be focused on the following. First I will discuss the sponsor's rationale for nonprescription pravastatin and who in the population should be using this product. I will then present the studies reviewed in this division and the results of these studies followed by the safety of pravastatin and finally, I will conclude the presentation by highlighting the relevant findings in this review with respect to the potential risk relationship of nonprescription pravastatin. The sponsor's rationale for nonprescription pravastatin is, first, the relationship between total cholesterol levels and the risk of dying from heart disease. You've certainly seen this slide now a couple of times, so I just want to emphasize that this relationship is continuous and great at one with the risk increasing considerably in those individuals whose total cholesterol levels are greater than 240. The second point in the sponsor's rationale for nonprescription pravastatin is based on clinical trials in which drug therapy used to lower

cholesterol level has been able to demonstrate reduction in cardiovascular events, and this has been observed in both the primary and secondary prevention population and across a broad range of cholesterol levels. Now despite these findings, these points, the sponsor contends that there remains a substantial number of individuals in the population who are inadequately treated to the NCEP goals. These goals you're all familiar with. At this point, I just want to highlight that it's based on the presence or absence of a cardiovascular disease and in the absence of cardiovascular disease, it's dependent on the risk factor present and that would determine the LDL cholesterol treatment goal for each of the subgroups. Interestingly, despite the inadequate treatment of dyslipidemia in the population, the sponsor states that there are consumers who are greatly interested in improving their cholesterol levels by buying dietary--, diet foods and dietary supplements. And their proposal is to, by making pravastatin available as a nonprescription drug, this would provide many individuals in the population an additional means for lowering cholesterol level. And who are the people that they are targeting? The sponsor's definition for the OTC target population include those who have been

told by their physician to lower their cholesterol level, but have not been placed on drug therapy. The total cholesterol level should be between 200-240 and the LDL cholesterol is greater than 130. Those who should not use nonprescription pravastatin include those who have established heart disease or diabetes, are currently on prescription lipid-lowering therapy, or children or pregnant women. Several studies were submitted to support the nonprescription proposal and these were reviewed in this division. The 10 and 40 mg. placebo-controlled studies were actually studies that had been previously submitted to the agency, reviewed by the agency and the original NDA. Two new studies were conducted in the OTC clinical development program. The first is PREDICT, the Pravachol Experience in a Documented Consumer-Use Trial. This was a 24-week open label trial in which after consumers reviewed a product label they were randomized to receive pravastatin either as a prescription drug or as a nonprescription drug, and response, lipid response to treatment was evaluated in this trial. The second actual-use study was OPTIONS, and it stands for OTC Pravachol in an Observed Naturalistic Setting. This was a 12-week open label uncontrolled study in which nonprescription

pravastatin was made available to enrollees in an HMO setting. Response to cholesterol lowering--, to pravastatin treatment was not evaluated with respect to LDL cholesterol reduction in this trial. The issues addressed in this review included whether pravastatin would significantly lower LDL cholesterol in the OTC population, what is the role of the healthcare professional in the management of this condition, and what is the concerns of here as to drug treatment for this chronic asymptomatic condition, whether or not treatment with pravastatin in this population will confer clinical benefit, and then finally safety, safety in the clinical trial setting and safety in the post-marketing setting. LDL cholesterol reduction was evaluated first and three placebo-controlled studies, again these studies were previously submitted to the agency and the original NDA and they were about eight to twelve weeks in duration. There was diet reinforcement throughout the treatment duration, and although it was not in the OTC target population, these studies did demonstrate that pravastatin 10 mg. taken daily reduces LDL cholesterol by about 18 to 22 percent compared to placebo. In the over-the-counter population, at least in a clinical trial setting, the LDL cholesterol reduction was

evaluated in PREDICT, but it wasn't evaluated in the PREDICT cohort, it was evaluated in a subgroup of the PREDICT population, and that subgroup was called the qualified and treated subgroup. And how an individual came to be part of this subgroup is through this algorithm. After being randomized to either OTC or Rx, the individual or the consumer at his or her own will, could see the study physician and at this point a baseline physical exam would be performed, lipid profile would be obtained, and also assessments of cardiovascular risk factor. And based on those findings, a set of protocol and post-treatment guidelines would be applied in order to determine if the individual was qualified for treatment. In the Rx population it would be the initiation of treatment, and in the OTC population, as Dr. Friedman had mentioned earlier this morning, it really would either be continuation treatment if they already started treatment, or initiation treatment if they had not started treatment. The end result or the bottom line here is that LDL cholesterol reduction was summarized in the subgroup of which was only 15 percent of the OTC population and about 19 percent of the Rx population because of careful selection by the study physician after applying this set of treatment

guidelines. Now these treatment guidelines were meant to assist the study physician in uniformly deciding who should be initiated on therapy. And after being initiated on therapy, who should have their dose titrated to either a 20 or 40 mg. dose in order to achieve a particular goal. The determination of qualification for treatment in this trial was based on the individual's baseline risk factors for heart disease and also their baseline LDL cholesterol. I wanted to point out that these guidelines are unique to the PREDICT protocol. They're not part of the proposed product label, because in the proposed product label there isn't mention for the consumer to treat themselves to a particular goal. So in some ways this treatment approach in PREDICT is not representative of what we might see in the nonprescription use of this product. Regardless, LDL cholesterol was summarized in this population, or this subgroup, of which 18 percent required their dose titrated to the 20 or 40 mg. dose in order to achieve their NCEP goals. And as you heard earlier again this morning, there was about a 17 to 18 percent reduction in LDL cholesterol, and this was observed in both the OTC and Rx patients of this subgroup. From these findings, the sponsor concludes that the response, the

lipid response to treatment in the adherent individual will be the same in the prescription setting as in the nonprescription setting. And really this is not surprising. We really don't expect the LDL-lowering efficacy of pravastatin 10 mg. to be any different in an individual who takes that drug as obtained from his or her physician as a prescription drug, compared to that same individual who takes that same drug bought over the counter. But what we don't know from these results is really what the lipid response is to treatment in the OTC population. And the reason why is because we wouldn't expect the OTC population who takes any amount of drug to be comprised only of this qualified and treated subgroup. And we don't expect that because PREDICT didn't show it. PREDICT allowed, in the OTC population of PREDICT, allowed consumers to purchase up to two months of drug without having to see a study physician. So it really gave us an opportunity to observe who would actually buy and use this product without the physician. And as a result there were 499 people who purchased the medication and used the medication, and about ten percent of them did not consult a physician. The remainder who consulted a physician, some of them-- the treatment guidelines I had mentioned earlier were at that point applied,

and some of them were disqualified from treatment because they did not meet eligibility for treatment based on those treatment guidelines. And of those who were qualified, some of them may not have returned for follow-up. So the end result here is that LDL cholesterol reduction as summarized in this subgroup here was only representing about half of the OTC-treated population. And that's what I mean by we really don't know what the LDL response is in the actual OTC population. We don't know how the rest of the population, the 49.3 percent who took amount of drug and excluded from this analysis, how they did. In contrast in the Rx population, because the individual had to see the study physician in order to get medication as a prescription, it's not surprising to find that 355 of those who took any amount of drug, almost 100 percent of them were considered qualified and actually considered in the LDL cholesterol analysis. So we have a fairly good estimate of lipid response in the Rx treated population. There are some other points I want to make from this slide here. The conclusion that the OTC population achieved their NCEP goal in 83 percent of them again was limited only to those qualified and treated population. So indeed we don't know if the other half achieved their NCEP goals

because they were not looked at. And then, finally, I'm not really certain how representative this subgroup is of the sponsor's targeted population and I'm not certain how representative it is because the mean total cholesterol--, or the median, excuse me, the median total cholesterol level in the subgroup was 245, and that exceeds the total cholesterol range of the targeted population on their product label. The other issue that was addressed in this review was that of the role of the healthcare professional. Certainly this is important in entertaining a nonprescription product because, at least for a chronic asymptomatic condition. And to get a better appreciation for the role of the physician or the healthcare professional, let's look first at the reasons why people were discontinued from their study medication. As I've mentioned there were 499 individuals in the OTC group who took any amount of drug, the treated population, of which more than half discontinued medication. About 25 percent of these individuals were discontinued because of a study physician telling them to discontinue their medication. In contrast in the Rx group, the patients who took any amount of drug, only about a fifth of them discontinued. The primary reason was protocol violation, but interestingly, only

three were told to discontinue the medication by a study physician. So clearly there's quite a contrast here with respect to a physician telling an individual to stop their medication, so in order to appreciate the role of the healthcare physician, let's examine these numbers a little bit more closely. And that's what summarized here in this slide. If you look in the OTC group, of the 123 who were told to stop their medication by the study physician, half of them were told to stop because of this reason: normal cholesterol, therefore really not warranting drug therapy. About 25 percent were told to stop their medication because their cholesterol or risk factor was too high and perhaps warranting more aggressive therapy. And then there were some who were told to discontinue because it was not appropriate or because they were already on lipid-lowering drug. Unfortunately for our three patients here in the Rx group we don't have a specific reason for why the physician told them to stop their medication; however, I think it's really quite evident from this slide that for individuals who received drug in a prescription setting, they have a lower likelihood of being inappropriately initiated on therapy as opposed to those in the OTC group where they have an opportunity

to self-select and use the medication without the healthcare professional involvement in the very beginning. So this does raise a question that the role of the healthcare professional, at least in this study, is not only important in the management of dyslipidemia with respect to treatment of an individual to goal or consideration of dose titration, but it seems apparent that the healthcare professionals should be involved in the very early stages, in the decision-making process, and assisting the individual in terms of whether or not drug therapy should or should not be initiated. Because certainly from PREDICT, in the OTC population, those who self-selected to use were at risk of over-treatment because they had normal cholesterol levels, under-treatment because they had baseline cholesterol levels that were too high, or perhaps high-risk factors, or inappropriate treatment. The next issue to address is adherence to therapy and, as I mentioned yesterday, adherence to therapy is important because this condition, dyslipidemia, is a chronic asymptomatic condition and so to its management requires long-term adherence to any form of treatment including that of nonprescription pravastatin. In the PREDICT study which was 24 weeks long, the study drug

discontinuation rate was 58.3 percent, and as I mentioned earlier, the primary reason, 25 percent of them was due to the physician recommending them to stop the medication. In OPTIONS, the other actual use study, if you recall this was an open labeled, uncontrolled study, in which nonprescription pravastatin was made available to enrollees in an HMO setting. It was a 12 week study and 51.4 percent were told to discontinue their med--, I'm sorry, not told to discontinue their medication. 51.4 percent actually discontinued their medication and the main reason that they discontinued their medication was because of non-compliance. As a matter of fact, 41 percent of these discontinued medication because of reports of non-compliance. Now if you'll look individually at the reasons listed as non-compliance, it included things such as, too busy, inconvenient hours, not interested, so it really was quite a lot of reasons as being listed as non-compliance. But certainly this suggests that adherence to therapy for treatment of this chronic condition does not appear ideal With respect to clinical cardiovascular benefit, the question that we're asking here is whether or not treatment with pravastatin 10 mg. in this targeted population will result in a reduction of

cardiovascular mortality and morbidity, and certainly you've already heard from Dr. Cohen that it hasn't been demonstrated in not only this drug, but other medications, not demonstrated in this target population, not for this product at this dose, and certainly not in an actual use or actual nonprescription setting. So in the absence of clinical benefit we have to ask what are the risks of drug treatment and the risk was evaluated in the safety review, and first we looked at the safety in the clinical trial setting. At the 10 mg. dose, we did not notice, we do not note any cases of rhabdomyolysis, myoglobinuria or liver toxicity. The incidents of myalgia was low and is similar to that in the placebo group. Similarly, the incidents of liver enzyme elevation was the same between pravastatin and placebo. Interestingly the discontinuation of medication due to reported adverse events was slightly higher in the OTC group versus that in the Rx group in PREDICT, but we don't really know the reasons for this and it may speak to the poor adherence to drug therapy as observed in the actual use studies. The safety of pravastatin at the 40 mg. dose was evaluated in three large placebo-controlled trials previously submitted to the agency and these trials were about five years

in duration. And the consecutive elevations in liver enzyme to more than three times upper limit of normal was less than one percent for pravastatin and it wasn't significantly different to that of placebo. There were no cases of liver failure, and although there was one case of reported rhabdo, on closer examination, as mentioned earlier this morning by the sponsor, this didn't really meet the definition of clinical rhabdomyolysis because of the CK elevations. However, we acknowledge that there are limitations to safety assessment in the clinical trial setting, and these limitations are related primarily to the exclusion of high-risk individuals, exclusion of patients on interacting medications, exclusion of patients with co-morbid medical conditions, and certainly in a clinical trial setting, there are scheduled visits and close safety monitoring such that at the earliest sign of trouble, an individual is asked to discontinue the medication or to stop or to interrupt medication. So sometimes safety assessments in the clinical trials are not predictive of what we would expect in the real world use of a product. So to get a better grasp on the safety of a product in the real world we often looked at the post-marketing spontaneous reports and in collaboration with the

office of post-marketing drug risk assessment, we looked at the following safety concerns for pravastatin, primarily liver failure and rhabdomyolysis. For liver failure we looked at the following case definition. We looked at cases of liver failure stated by the reporter or if the individual received a liver transplant and the reporting time period was that for marketing until recently this year, about nine years. There were 13 cases of liver failure reported meeting this case definition, eight of them domestic, five foreign, and our safety evaluators looked at these carefully to pull out the confounding cases. There were only ten unconfounded cases and if we use the domestic unconfounded cases, we get a reporting rate which when we compare then to the background rate of idiopathic liver failure and we found that there was no increase over the background rate of idiopathic liver failure. So although there have been pravastatin-associated cases of liver failure, it's exceedingly rare, and often it's certainly not increase of the background rate, and often is complicated by certain medical conditions and medication views, which makes it difficult to assign any degree of any causality to drug. The other safety concern was that of

rhabdomyolysis and, again, this is not unique to pravastatin, as seen in all the statins. The case definition here used is that of a clinical diagnosis of rhabdo with a CPK elevation of greater than 10,000. The reporting time period here again was marketing until recently this year, and of note, the background rate is not known for this adverse event. And given this case definition we found 35 cases which were broken down here into the foreign and U.S. reports. And I don't want to give the committee the impression here that we are making the conclusion that there is a dose relation or relation to country; this is just merely reporting it, or describing it. It's interesting we do see some cases in the 10 mg. dose, but these are more in the foreign cases, and I do believe that that's probably has something to do with the use of that particular dose more in the country. We don't have access as the sponsor has to the usage data in the foreign countries. Most of this was in Japan and, actually, you probably saw that this morning already. We do have access to usage or, not usage, but prescriptions written in the United States and from IMS HEALTH, we see that indeed the 10 mg. dose is the least prescribed dose across the dosage formulation for pravastatin. Again I want to

emphasize that the number here is number of prescriptions written, not number of individuals using it, so we cannot calculate incidence rates for adverse events obtained from spontaneous reports. So in conclusion for rhabdomyolysis, the true incidence rate is not known, but the risk exists. I think this risk is small, but surprisingly we even see it at the 10 mg. dose, although more in the foreign cases. There might be a potential increase in risk if it's concomitantly used with certain medications. The fibrates and cyclosporine is another concern. As mentioned earlier, it may be through the inhibition of P glycoprotein, and certain co-morbid medical conditions may increase this risk. So in conclusion for safety review, there are very rare but serious safety concerns that relate to pravastatin and primarily that of the muscle toxicity. So again in an over-the-counter setting, the safety concern for a drug is dependent again on the consumer's comprehension of the label, the consumer's ability to follow the label instructions so that there would be no self-titration and no use by high-risk individuals. In conclusion, in evaluating the prescription to nonprescription switch of pravastatin 10 mg., we ask the question what is the balance of benefit versus

risk of nonprescription pravastatin and I'd like to address that question by summarizing the findings or the issues addressed in this review with respect to the benefit side of the equation, we talk about LDL cholesterol reduction and as we saw in the placebo-controlled trials in the original submissions, that pravastatin does lower LDL cholesterol. However, as observed in both OPTIONS and PREDICT, it seems like the poor adherence to drug treatment may reduce the effectiveness of this lipid-lowering in the population. Again clinical cardiovascular benefit has not been established for this drug in this population and certainly the healthcare professional involvement here appears to reduce the inappropriate self-selection as observed in PREDICT. That might actually fall into the risk side of the equation, also. And then finally on the risk side of the equation for safety, there are very rare but serious adverse events which may be compounded by an unmonitored, unsupervised use in a nonprescription setting. So with that, that concludes my presentation. I would now like to introduce Dr. Shetty. Thank you very much for your attention.

DR. SHETTY: Good morning. My name is Daiva Shetty and I am a medical officer in the Division of

Over-the-Counter Drug Products. I am going to present some highlights of the data submitted by the sponsor about consumer actual use and behavior. There are several actual use issues for Pravachol nonprescription use. And first of all, are consumers able to self-diagnose hypercholesterolemia? Do they know their own cholesterol values, and do they understand serum cholesterol values? Are consumers able to self-select appropriately? Can they identify their risk factors for coronary heart disease? And do they understand how many of those risk factors they should or they should not have prior to their drug therapy? Are consumers able to self-treat hypercholesterolemia? Do they know when to start, and are they able to follow label directions for dosing and duration of use? Are they able to understand the treatment goal and what is the goal to lower cholesterol or to reduce the risk factors for coronary heart disease? In the interest of time, I'm not going to talk about the design of the studies, so you can skip through those slides that you have copies. The actual use trials were submitted to the NDA, PREDICT and OPTIONS. First study, PREDICT, stands for the Pravachol Experience Documented in a Consumer Trial. And I would like to make few comments about the label

used in this study. It stated that this product is indicated for those whose total cholesterol is between 200 and 240, and LDL cholesterol above 130 mg. per deciliter. There was no HDL cholesterol value on the label. No specific age requirements listed on the label either. Only do-not-use section that those who are less than eighteen years of age should not use this product. The primary objective of this study was to determine the proportion of the OTC randomized subjects who have purchased OTC Pravachol, consult a physician within two months of using medication. 11,065 subjects called the call center. 3,888 were screened at the screening site. Of those, 3,872 were enrolled into the study and randomized into two groups, OTC and Rx. Those two groups were similar in terms of demographics and the number of subjects enrolled. I would like to make a comment about the call center. The call center served as a screening site for premenopausal and childbearing potential women, and if the subject who called was a woman of childbearing potential, she was not given directions to go to the enrollment site. 119 subjects were found to be ineligible to participate, and half of them, or 61, were women of childbearing age. This two percent comes from the enrolled population only of 3,872 and