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JOINT MEETING OF THE

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE

AND THE

ENDOCRINOLOGIC AND METABOLIC ADVISORY COMMITTEE

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THURSDAY
JULY 13, 2000

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

MEMBERS PRESENT:

ERIC P. BRASS, M.D., Ph.D., Chairman, NDAC
GEORGE A. BLEWITT, M.D.,
Non-Voting Industry Liaison, NDAC
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
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
WILLIAM V. TAMBORLANE, M.D., EMDAC Member
DONALD L. UDEN, Pharm. D., NDAC Member
HENRY W. WILLIAMS, JR., M.D., NDAC Member
SANDRA TITUS, Ph.D., Executive Secretary

MERCK REPRESENTATIVES:

JEFFREY L. ANDERSON, M.D.
POLLY BEERE, M.D., Ph.D.
JOHN COOK, Ph.D.
JOHN W. FARQUHAR, M.D.
EDWIN HEMWALL, Ph.D.
SCOTT KORN, M.D.
STEPHANIE LAROUCHE, M.D.
EVE SLATER, M.D.
JONATHAN TOBERT, M.D, Ph.D.
JOSE VEGA, M.D.

FDA REPRESENTATIVES:

ROBERT J. DELAP, M.D.
CHARLES GANLEY, M.D.
DAVID HOBERMAN, Ph.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.
ANDREA LEONARD SEGAL, M.D.
ROBERT TEMPLE, M.D.

PUBLIC SPEAKERS:

PENNY KRIS ETHERTON, Ph.D., R.D.
JOHN A. GANS, Pharm. D.
SUZANNE HUGHES, R.N.
DEBRA JUDELSON, M.D.
BERNARD L. KASTEN, M.D.
BRETT KAY
WAINE KONG, Ph.D., J.D.
ERNEST C. MADU, M.D.
THOMAS PEARSON, M.D., Ph.D.
WARREN PINCKERT
RENE F. RODRIGUEZ, M.D.
SIDNEY WOLFE, M.D.

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

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

(8:02 a.m.)

CHAIRMAN BRASS: We're going to go ahead and get started. I'd like to welcome you all to this joint meeting of the Nonprescription Drugs Advisory Committee and the Endocrinologic and Metabolic Advisory Committee.

My name is Eric Brass from Harbor-UCLA Medical Center and I appreciate you all getting up at 5 o'clock in the morning for this meeting. I think we will begin by just going around the Committee table and allowing everyone to introduce themselves. This will also serve as microphone practice. You have to press the on button and turn it off again or all your whispered comments will be broadcast throughout the room. Perhaps if we could start at the end and just go around and introduce ourselves.

DR. DELAP: Robert Delap, Director of the Office of Drug Evaluation V at FDA.

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

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

DR. WILLIAMS: Yes, I'm Henry Williams from Howard University and I'm a member of the Committee.

DR. GELATO: I'm Marie Gelato from Stonybrook University, and I'm member of the Committee.

MR. KRENZELOK: I'm Ed Krenzelok. I'm Director of the Pittsburgh Poison Center, a Professor of Pharmacy and Pediatrics at the University of Pittsburgh, and on the NDAC.

DR. DAVIDSON: Jaime Davidson, member of the panel. University of Texas Southwestern Medical School, Clinical Practices.

DR. ELASHOFF: Janet Elashoff, Biostatistics from Cedar-Sinai and UCLA, Consultant.

DR. NEILL: Richard Neill. I'm a Family Physician Faculty member from Family Practice and Community Medicine at the University of Pennsylvania, member of the NDAC Committee.

DR. TITUS: I'm Sandy Titus. I'm the Administrator for the Nonprescription Drugs Advisory Committee.

MS. JOHNSON: Julie Johnson from the University of Florida, Department of Pharmacy Practice and Division of Cardiology, and member of NDAC.

DR. TAMBORLANE: I'm Bill Tamborlane, Chief of Pediatric Endocrinology at Yale, and I'm a member of the Endocrine Committee.

DR. LUKERT: Barbara Lukert, University of Kansas School of Medicine, Division of Endocrinology. I'm on the Endocrine Committee.

DR. GILLIAM: Edwin Gilliam. I'm a Family Nurse Practitioner from Tucson, Arizona, and I'm on the NDAC Committee.

MR. UDEN: I'm Don Uden from the University of Minnesota College of Pharmacy and on the NDAC Committee.

DR. GRADY: I'm Deborah Grady. I'm an internist and epidemiologist from the University from California, San Francisco, and I'm on the Endocrine Committee.

DR. BLEWITT: George Blewitt. I'm Industry Representative to the NDAC.

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

CHAIRMAN BRASS: Thank you. I'll now turn the microphone over to Dr. Titus for the reading of the Conflict of Interest Statement.

DR. TITUS: The following announcement addressed 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 interests reported by the Committee participants, it has been determined that all interests and firms regulated by the Center for Drug Evaluation and Research 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 Doctors Eric Brass, Barbara Lukert, Jules Hirsch, Robert Kreisburg, and 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 12A-30 of the Parklawn Building.

We would also like to note that Dr. Jaime Davidson has interest in Bristol-Myers Squibb, Warner Lambert, and Parke-Davis which are unrelated to Mevacor or its competing products.

In addition, we'd like to note that Dr. Barbara Lukert has an interest in Merck, the manufacture of Mevacor and of Zocor, a competing product to Mevacor which is unrelated to the firm's product or competing product. Further, Dr. William

Tamborlane's employer, The University School of Medicine, has interest in Pfizer and in Parke-Davis, a subsidiary of Pfizer, the manufacturer of a competing product to Mevacor, 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 notwithstanding 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 Mevacor.

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 interests 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 receives speaker's fees from Bristol-Myers 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.

That concludes the official announcement. Now I'd like to just unofficially talk about the Open Public Hearing speakers.

I didn't get to talk to all of you, I talked to some of your staff. There is an expectation before you begin your speaking today to disclose to us what your financial arrangements are in terms of this discussion today.

You need to disclose if you have received money from either of the basic products being looked at today or tomorrow and you need to make a simple statement to the record please. And I won't time that. That will be a free part of your speech.

CHAIRMAN BRASS: I'm not sure I endorse

that not timing part. Thank you Dr. Titus.

We will now move to the Open Public Hearing and I would just like to reinforce the request that disclosure of financial interest be made and particularly request that the five-minute time allocation be adhered to strictly as we have a very full agenda today.

Our first presenter in the Open Public Hearing will be Dr. Rodriguez. Is Dr. Rodriguez here?

Going. Going. Our next speaker, thank you for sticking to the five minutes --

(laughter)

Then our next speaker will be Dr. Kong. And if you could come to the front of the room please.

DR. KONG: Good morning ladies and gentleman. My name is Waine Kong. I am the CEO for the Association of Black Cardiologists. On my left is Dr. Ernest Madu, cardiologist and Assistant Professor at Vanderbilt University. He will be speaking on behalf of the Association of Black Cardiologists today and he will address all the clinical issues involved in this issue.

The Association of Black Cardiologists was founded in 1974. We have 700 members and are committed to the concept that children should know

their grandparents and become great-grandparents themselves, and we are awfully concerned about the high rate of cardiovascular disease in the black community and want to do as much as we can to preserve that.

We've provided packages for everyone. That includes a position paper that was developed by the Cholesterol Committee of the Association of Black Cardiologists and approved by the Board of Directors.

In the package is a copy of our annual report divulging all of our financial relationships and we receive funding from all the major pharmaceutical companies to support our programs. We supported our activity here today out of our own funds.

Now I'd like to introduce Dr. Ernest Madu who will make the formal statement.

DR. MADU: Good morning and thank you for the opportunity to address the panel and the audience today.

We have deliberated on this issue and the Cholesterol Committee of the Association of Black Cardiologists and have come up with a position paper. Catastrophic cardiovascular events occur more commonly in African-Americans and other underserved minority

populations.

Reasons for this disproportionate burden of disease include a high prevalence of cardiovascular risk factors, limited access to healthcare, and underutilization of interventions and medications that could prove lifesaving.

One such class of lifesaving medications is the HMG-CoA reductase inhibitor class, commonly referred to as statins. The past decade has produced overwhelming evidence that cholesterol-lowering therapy with statins leads to a striking reduction in coronary events, cerebrovascular events, and total mortality. These improved outcomes have been seen in both primary and secondary prevention trials.

African-Americans are at a high baseline risk of potentially having cardiovascular or cerebrovascular events and stand to gain enormously from statin medications should these be available over the counter.

Despite the documented benefit of statins, however, many high-risk patients fail to receive them, often times because of limited access. Failure to receive these medications, in our opinion, may contribute to the continued disproportion in the problems of cardiovascular and cerebrovascular illness

in African-American and other underserved minority populations.

The mission of the Association of Black Cardiologists is to make exemplary healthcare available and affordable to all in need. Given this charge, the Association of Black Cardiologists is continually seeking ways to improve patient's access to beneficial therapies such as statins.

One potential way to increase the accessibility of statins is through over-the-counter dispensing of this product. The Association therefore endorses the proposition that statins should be available for over-the-counter dispensing under certain circumstances and with specific guidelines in place. We base these recommendations on several premises.

One is the unique safety profile of satins. Secondly, we believe there is a large body of evidence, the most rating the overwhelming safety and efficacy of this product class. At the present time we do not have evidence to suggest that there are differences of safety among the class of the entire statin family.

We also believe that over-the-counter statins will be appropriate only for lower-risk,

primary-prevention patients and that SART should only be targeted to this population. Also, in order to ensure safety, routine monitoring procedures must be clearly specified in the product literature and package insert.

Finally, the Association of Black Cardiologists wishes to emphasize that endorsement of over-the-counter dispensing of statins is based on an overwhelming body of evidence demonstrating the unique safety and efficacy of this class of medications and should not be generalized to other medications for the treatment of chronic asymptomatic conditions. Thank you.

CHAIRMAN BRASS: Thank you very much. I understand that Dr. Rodriguez is now here? Yes, if you could come to the front please.

Since you missed the opening comments, if you could identify any financial support that contributed to your visit today.

DR. RODRIGUEZ: Good morning. My name is Rene Rodriguez. I am an orthopedic surgeon and President of an organization of Hispanic physicians based here in Washington, DC.

We have received financial assistance, no assistance, but we get some financial from

pharmaceutical membership, but I have not been paid for being here and our organization doesn't receive any remuneration for myself being here today.

As a national organization representing over 39,000 health professionals in the Hispanic community, the ICPS's, the Inter-American College of Physicians and Surgeons, primary goal is to strengthen the health service delivered to Hispanic community. We believe that offering this reductase inhibitor over the counter is an important step in the direction to providing greater access to a clinically proven therapy for treating elevated cholesterol.

Today, cardiovascular disease remains the leading cause of death for Hispanics in the United States, representing 26.9 percent and 33 percent of total deaths for males and females respectively in 1996. Moreover, Hispanics who are less likely to have access to health insurance and adequate preventive medical care, suffer a greater incidence of cardiovascular disease than the general population.

For example, 39 percent of Mexican-American men and 38 percent of Mexican-American women, age 20 and older, have LDH-C greater than 130 milligrams.

The problem of elevated cholesterol

requires additional treatment options to reinforce ongoing efforts and we believe that offering the statins over the counter will provide patients with greater access to a proven therapy for treating elevated cholesterol.

Numerous randomized placebo-controlled trials have shown that statins dramatically reduced the degrees of heart disease, even for patients who showed no signs of heart disease. Statin products have a long history of safe use and minimal side effects and could be used safely and responsibly in an OTC setting.

For people who continue to struggle with elevated cholesterol levels despite healthy diet and exercise, OTC statin will provide a new safe and effective treatment option approved by the FDA.

Today, consumers want and deserve statin products over the counter. There is an increasing trend in self-care among consumers. Functional foods, dietary supplements, and other alternative therapies claiming to lower cholesterol are already used extensively, even though the jury is still out there on this.

OTC statin will provide a clinically proven alternative approved by the FDA. In addition,

OTC products advertised in educational information will increase awareness about this serious public health threat. The Inter-American College of Physicians and Surgeons believes that making the statins available over the counter is a significant step in the battle against heart disease. Thank you very much.

CHAIRMAN BRASS: Thank you. Our next speaker will be Dr. Judelson.

DR. JUDELSON: Thank you. My name is Dr. Debra Judelson. I'm an internist and cardiologist with Cardiovascular Medical Group of Southern California, and I'm Medical Director of their Women's Heart Institute.

As past president of the American Medical Women's Association, or AMWA, and the creator of our education project on coronary heart disease in women, I'd like to speak to you today on the issue of the FDA's interest and the approval over-the-counter drugs.

My disclosure statement: I am a speaker and receive honorarium for a variety of pharmaceutical companies. I receive less than one-half of one percent of my income from Bristol-Myers Quibb or Merck. For the organization AMWA, in addition to its

membership dues, it also receives funds from a variety of foundations, government, and industry sponsors. Less than one-half of one percent of our annual budget come from Bristol-Myers Squibb or Merck pharmaceuticals.

I'm with a national organization of 10,000 women physicians and medical students dedicated to promoting women's health. A cornerstone of our efforts has been raising awareness about heart disease in women. Our education project stressed the under-recognition and undertreatment of risk factors for heart disease and their symptoms that we've identified.

We feel the wide availability of drugs to lower cholesterol for the prevention of heart disease and the regulation are cornerstones to women's health. AMWA is in favor of the concept of over-the-counter drug product use for elevated cholesterol levels when the drugs are shown to be safe and efficacious in unmonitored situations.

Our reason: Heart disease is the number one killer of American women as well as men and the risk factor of LDL cholesterol elevation is well known and recognized. Numerous studies and articles have been published detailing the gender disparity in

cardiac risk evaluation and treatment including the undertreatment of LDL cholesterol leading to unnecessary mortality, especially in the underuse of statin drugs. The disparity is unwielding. We cannot live with this.

Women with known heart disease already get adequate treatment; however, it's the woman without heart disease or the asymptomatic woman with a modest or moderately elevated cholesterol who is not being offered these proven therapies.

The primary therapy is lifestyle modification. We follow this, but when we talk about medication use, the most effective medication that is being promulgated by physicians for postmenopausal women is the use of hormone replacement; however, we have had recent studies that have identified some problems with this and until these are clarified, we're not sure what to do.

Even more problematic, is the fact that risk factors in premenopausal women are often not even addressed by physicians who mistakenly believe that these women are not at risk for the development of heart disease. We have proven benefits of lower LDL cholesterol for all levels of cardiac risk, including in asymptomatic women with modest to moderate LDL

cholesterol elevations with the use of the statin drugs.

We feel FDA approval will give women the options they need to improve their health and healthcare. I'm not going to address safety and monitoring of efficacy issues because I'd like to focus predominantly on the barriers to care.

Women want to use self-help therapies to improve their personal risk factors and improve their personal health risks. Women need options. We must acknowledge that every patient does not have the opportunity to fully discuss all of their perceived risk factors and all of their fears and concerns with their health with a professional on a regular basis.

Very often our healthcare situations occur in an acute setting with an acute problem. This may be due in part to the failure of most insurance plans to cover the cost of well visits and general health screening.

This may be due in part to the lack of recognition by healthcare professionals of an individual's risk or of their willingness to be evaluated or treated for asymptomatic conditions. This may also be due to the willingness of many women to acknowledge their own health risks and concerns to

busy professionals, or to take time out of their own lives to come in for asymptomatic conditions.

But most seriously, it may also be due to the unwillingness on the part of certain healthcare professionals to make treatment available to women patients because of their own biases or misinformation.

AMWA is addressing the biases and misinformation of primary care physicians with our education project on coronary heart disease in women; however, our efforts and the efforts of so many other groups to raise awareness have not been able to improve the knowledge deficit of every primary care physician. Women who want to improve their health or face these barriers need options.

In conclusion, because of AMWA's interest in improving women's health and our belief that the statin class of medications may be safely and efficaciously used in the over-the-counter setting by individuals with an awareness of their LDL cholesterol level, who discern their personal risk factors, and especially those who face barriers, or perceive they face barriers, to getting care from their physician, the American Medical Women's Association endorses the concept of over-the-counter LDL cholesterol-lowering

medications and urges the FDA to proceed with the appropriate evaluation of those that may be safely and efficaciously used in the over-the-counter setting.

I thank you for your time and attention.

CHAIRMAN BRASS: Thank you. Our next speaker will be Suzanne Hughes.

MS. HUGHES: Good morning. I'm Suzie Hughes, I'm a nurse clinician in the Department of Preventive Cardiology at the Cleveland Clinic Foundation. But I'm here today representing the Board of Directors of the Preventive Cardiovascular Nurses Association, formerly the Lipid Nurse Task Force.

We are a 1500-member national organization of professional nurses whose daily work is cardiovascular risk reduction. We are supported by our membership dues and by our pharmaceutical round table. My time and travel here today has not been underwritten either of the sponsors or anyone in the pharmaceutical industry.

Because our membership is on the front lines in the battle against death and disability due to cardiovascular disease, our Board felt strongly that we should go on record here today in support of the consideration of certain cholesterol-lowering medications being made available over the counter.

One of the more difficult fronts in this battle is that of primary prevention. The National Cholesterol Education program, Adult Treatment Panel 2, defines desirable total cholesterol as less than 200 milligrams per deciliter. It is estimated that only 15 percent of those eligible for lipid-lowering therapy as secondary prevention receive it. This falls to less than 5 percent who qualify for lipid-lowering treatment as in primary prevention who actually receive therapy.

In the first 16 years of the Framingham Heart Study, 40 percent of those who sustained myocardial infarction had cholesterol levels between 200 and 250 milligrams per deciliter. We all know the sad fact the first symptom of cardiovascular disease is tragically often sudden cardiac death. We has healthcare professionals do not get a shot at seeing whether we might perform better at secondary prevention for those in that group.

My fellow Board members and colleagues average 25 years experience in cardiovascular nursing. Our roles as patient educators and advocates is constantly changing. In an ever-increasing number of cases, our patients do not come to us with a blank slate eager for the healthcare professional to

dispense information and advice.

In the year 2000, they come instead with information, along with a great deal of misinformation, that they've obtained from the print and broadcast media and more recently from the internet. They now arrive bearing lists of over-the-counter herbal remedies, vitamins, and concoctions, the ingredients of which are often mysterious and unknown, the safety and efficacy even more so.

We believe that this trend toward self-care is only like to grow. The availability of low-dose statins that are effective not only in lowering total cholesterol and LDL, but in preventing first coronary events, has the power to save lives.

It's critical that the sponsors of these statin agents proposing the switch to OTC demonstrate the following: One, that the appropriate population will utilize these agents in the appropriate dose. Number two, that those who choose to use these OTC products will initiate dialog with their healthcare providers. Three, that those who use these agents will not abandon hygienic measures, diet, exercise, and smoking avoidance, when these agents are employed.

Four, that the labeling is understandable. Five, that the marketing efforts are target toward the

appropriate consumer. Six, that the majority who use these agents in the OTC setting will reach and set goals.

If the above criteria are met, we support the OTC availability of such agents with full agreement that this action will not be a panacea for the entire underscreening and undertreatment gap. We feel that it constitutes an important adjunct in increasing death and disability from cardiovascular disease in the United States.

Thank you for your consideration.

CHAIRMAN BRASS: Thank you. Our next speaker will be Dr. Etherton.

Okay, I've been told we are going to temporarily skip over to Dr. Gans if Dr. Gans is available. Is Dr. Gans here? Yes, thank you.

DR. GANS: Good morning. Thank you for the opportunity to present the views of the American Pharmaceutical Association, the National Professional Society of Pharmacists. I am Dr. John A. Gans, Vice President of the Association.

APhA's more than 53,000 members include pharmacy practitioners, pharmaceutical scientists, and pharmacy students. Pharmacists help consumers manage and improve medication use, including the selection of

nonprescription drugs.

It is in the interest of full disclosure that the APhA frequently partners with federal agencies, consumer groups, the pharmaceutical industries, and others to develop educational tools for pharmacists and consumers. Some of the research I will describe today was supported by the pharmaceutical industry, but without influence as to outcome.

The association did not receive funding to participate in today's meeting, but it did cost me $2500 to fly here, so I'll take any kind of contributions that you like. Times are changing. And the views I am presenting are solely those of the association and its membership.

Over the next two days you will hear how hyperlipidemia affects 50 million Americans. In most cases, the first approach to lowering cholesterol levels is through lifestyle changes; however, most of us aren't able to sustain such lifestyle changes over the long term. Making more effective drug therapy more readily available to consumers would facilitate improvements in managing this very costly problem. Making antihyperlipidemic products available over the counter may contribute a solution.

There are two salient questions we would like to address today. One, can consumers select the appropriate therapy to treat their elevated cholesterol? And two, can these products be used safely and effectively in an OTC setting?

APhA offers the following recommendations regarding the ability of consumers to choose the therapy. The determination of whether a product should be switched from prescription to OTC status should include, in our minds, a review of all existing therapies in the self-care market. If existing options for self-care raise questions of safety, effectiveness, or product quality, the relative safety of the switch candidate increases in our minds and the risk-benefit analysis shifts in favor of OTC availability.

Today's consumer self-care options for cholesterol management are limited to diet, exercise, and dietary supplements. Dietary supplements such as garlic and other preparations are marketed as self-care aids to maintain healthy cholesterol levels which have not been yet subject to the rigors of FDA review of safety and efficacy.

Further studies have documented problems with product content and the release of active

ingredients in some dietary supplements. Therefore, consumer self-care options are currently limited to products whose content may not match the claims on the label and whose value has not been shown through rigorous testing.

In contrast, the statin drugs to be presented over the next two days have been studied as prescription products in rigorous scientific trials, post-marketing surveillance, and now as potential OTC products. These would provide the consumer with well-documented, well-studied clinically proven products as a self-care option.

Pharmacists can assist by identifying untreated patients, referring consumers to the healthcare system when their cholesterol level requires medical care, by aiding in the selection of appropriate agents, and by supporting consumer self-care behaviors.

At the recent Part 15 hearing, a distinction was drawn very clearly between the treatment of signs such as elevated cholesterol and high blood pressure, and the treatment of symptoms. As mentioned at the hearing, however, this distinction is changing as consumers now have increasing access to tools to check their signs. Consumers want to know

their numbers and more are taking advantage of this technology to determine their health status.

Pharmacists are ready to increase access by providing tools to monitor these in their pharmacies and are conducting point-of-care screening as I speak today.

Increased access to tools to monitor are now changing the distinction between signs and symptoms. This increased consumer access to management tools supports the management of signs by self-care and as self-care expands, consumers will recognize and self-treat with OTC drugs. To do this well, they must have safe and efficacious products.

Regarding the second question, I'd just like to briefly mention that we completed a study called Project ImPACT: Hyperlipidemia. APhA prepared pharmacists in 25 community pharmacy settings. They were focusing on discussing the health status and treatment and by obtaining lipid profiles by a finger-stick method each month.

The results of this program were dramatic. Persistence and compliance increased significantly when patients were empowered and educated. Almost 400 patients were studied over a two-year period. Persistence was measured at 93 and compliance at 90

percent respectively. These results were better than what was seen in the best studies at 40 percent over just 12 months.

More importantly, 62.5 percent of the patients achieved NCEP goals which are seen typically in the range of 8 to 33 percent. While you won't find this practice in every community pharmacy, it's expanding and Project ImPACT demonstrates the potential of this system. Further, it demonstrates that pharmacists can help raise awareness and understanding that high cholesterol is a modified risk.

In summation, as I have described, OTC availability of drug therapy would provide consumers a valuable tool in managing hyperlipidemia. We encourage the FDA to work with manufacturers of OTC hyperlipidemia products to develop the proper consumer education materials and directed messages to encourage consumers, pharmacists, and physicians to work together on primary prevention.

Product labeling should reinforce these messages and we believe that the availability of statin products directly to the consumer would provide another important avenue to help manage high cholesterol and heart disease.

As the nation's pharmacists, we will do our part has health professionals to work with consumers, physicians, and other healthcare providers to provide and become a valuable partner in OTC drug therapy. Thank you very much for this opportunity this morning.

CHAIRMAN BRASS: Dr. Etherton.

DR. ETHERTON: Okay. I'm Penny Kris Etherton. I'm a distinguished professor of nutrition at Penn State University and I've been on the faculty there since 1979.

I have a long-standing interest and expertise in understanding how diet affects risk of cardiovascular disease. I was a member of the second Adult Treatment Panel of the National Cholesterol Education Program. I chaired the diet subcommittee of the DELTA study, Dietary Effects on Lipoprotein Thrombogenic Activity, a multicentered, NIH-funded clinical study to look at the effects of diet on risk factors for cardiovascular disease.

Presently, I'm a member of the American Heart Association Nutrition Committee and the National Academy of Sciences DRI Committee for Macronutrients.

I'd like to disclose that I have been a consultant for Merck for their OTC lovastatin clinical

development program; however, the views that I share with you today are my own. Another organization, National Academy, paid for my plane ticket here, although Merck has paid for the taxi cab ride to this meeting here.

Since my area of expertise is nutrition, and cardiovascular nutrition in particular, I'd like to comment on what I see as a unique opportunity to achieve added benefits to the OTC statin program on cardiovascular disease with a nutrition program that will be a part of the OTC program. There is also an opportunity to prevent other diseases through good nutrition practices that will be promoted in the OTC program.

So my comments this morning point to the opportunity that is before us to have a significant impact on cardiovascular disease and other diseases with the OTC statin program because of the diet and lifestyle program that is a part of it.

While cardiovascular disease continues to be the leading cause of death for both men and women in the United States, and on my first overhead you see, between 1979 and 1991 there was a significant decline in cardiovascular disease mortality for men; however, since 1991 the incidence has remained

unchanged. Perhaps it's increased a little bit.

In contrast, cardiovascular disease mortality for women has increased over this time line. These trends are alarming, giving the marked increase in our understanding of risk factors as well as the development of effective intervention strategies for cardiovascular disease.

Collectively, the cardiovascular disease mortality data indicate that much more remains to be done on a population-wide basis to reduce both morbidity and mortality of cardiovascular disease. The CVD morbidity and mortality trends are a concern because they are a burden to society, they impact the healthcare system, and adversely affect the quality of life of individuals and families.

Diet and other lifestyle practices have been the cornerstone of intervention strategies for the prevention and treatment of coronary disease. A STEP I diet is recommended for the prevention of cardiovascular disease for the population at large and a STEP II diet is advised for coronary patients and persons at high risk of suffering a coronary event.

The obvious question that scientists have addressed then is how effective are these interventions? And based on a recent analysis of 37

dietary intervention studies that include weight loss and exercise, a STEP I diet decreases LDL cholesterol about 12 percent and a STEP II diet lowers LDL cholesterol about 16 percent.

While this LDL cholesterol lowering is important clinically, it's evident that additional strategies are required to have a more substantive impact on the incidence of cardiovascular disease.

Low-dose, over-the-counter statin therapy would be expected to decrease LDL cholesterol appropriate 15 to 20 percent and on this overhead here we see the results of drug studies that have been done showing a decrease of LDL cholesterol of about 25 to 26 percent and a greater than 30 percent reduction in the incidence of cardiovascular disease.

The combination of diet and low-dose over-the-counter statin therapy can provide a powerful and effective means to dramatically lower the incidence of cardiovascular disease on a population-wide basis.

Moreover, adoption of a healthy diet as part of a comprehensive consumer education and support program that includes low-dose, over-the-counter statin therapy could well have benefits far beyond those associated with cholesterol lowering and there are severe recent studies to support that.

One recent study, not shown on this overhead, found that women following a healthy diet were 30 percent less likely to die from all causes during their six-year study period compared to women who had the most unhealthy eating habits.

And on this slide, going beyond cholesterol lowering, we see two recent studies that show very dramatic effects of diet only on reducing incidence of cardiovascular disease. The Leon Diet Heart Study and the GISSI Prevention Trial.

Thus, approval of low-dose, over-the-counter statins may well facilitate implementation of a healthy diet and other lifestyle practices that could markedly reduce the incidence of CVD and other chronic diseases.

Over-the-counter availability of low-dose statins offers an exciting opportunity for population-wide health promotion efforts that both target CVD and extend beyond CVD when implemented and they will significantly improve the health of Americans.

Consequently, there is an urgent need to move forward in providing Americans with the opportunity to have access to these lifesaving products. Thank you.

CHAIRMAN BRASS: Thank you. Our next

speaker is Brett Kay.

MR. KAY: Good morning and I thank you for the opportunity to present here today. To give a quick disclosure, I am Brett Kay, I'm with the National Consumers League and the National Consumers League has received educational grants from pharmaceutical companies regulated by the FDA previously. These funds are less than 5 percent of our total budget and we have not been paid to speak here today.

The National Consumers League, which is America's oldest nonprofit consumer advocacy organization is pleased to testify today about possible switch of low-dose statin medications to nonprescription status. NCL has a long history of advocating for and educating consumers about safe and appropriate medication use, both prescription and nonprescription.

NCL is aware of the growing trend by consumers to take a more active role in their own healthcare and we are working to ensure that consumers are well informed in order to make the most beneficial choices about their own health.

According to consumer surveys that we have commissioned during the past several years, consumers

see their increased role in the healthcare system as a positive change. That an overwhelming majority, 86 percent, of consumers feel they have an increased role in their own healthcare is positive.

I'm going to cite a few samples from surveys that we've done over the past two or three years to give you some trends and then I'd like to present a couple of quick overheads on our latest survey that we did just about in the middle of June. So that is fresh data that just came back. We also presented some of that at the FDA OTC Part 15 hearing on June 28th as well.

NCL has also, as I said, focused more specifically in the area of coronary heart disease, which is America's leading cause of mortality.

In a survey that we did in 1998 to discern consumer knowledge about attitudes about coronary heart disease, 88 percent of respondents said that they would like to know as much as possible about lowering their risk of coronary heart disease and 52 percent did not know their cholesterol levels.

Further, 64 percent of Americans are confused about how to live a healthy lifestyle, but on a positive note, 85 percent did cite their doctor as the most reliable source for information about

lowering their risk of coronary heart disease.

NCL feels it is important to understand consumer's attitudes toward possible OTC cholesterol-lowering medications and more importantly, we want to see how a new OTC product would be perceived and how consumers say they would use such a product and that is some of the data I'll show you in a moment.

We are concerned that consumers would not consult their doctors before or during the use of an OTC statin. However, our survey results overwhelmingly demonstrate that consumer willingness to consult with their doctors and follow their advice.

Another concern has to do with the use of dietary supplements. Many consumers are currently using these products, which are untested and unproven to safely or effectively treat high cholesterol as well as many other serious health conditions. Further, many consumers do not tell their doctors about them which possibly may lead to dangerous interations or other side effects.

In our most recent survey, 28 percent of the population use these products regularly or often and another 65 percent are using vitamins. If consumers are already using these products to treat their cholesterol, they should at least be using ones

that are well tested and have a well-documented history of use. It is quite apparent that low-dose cholesterol-lowering drugs work when used appropriately to lower people's cholesterol levels.

If the FDA determines that the safety profile of a low-dose statin medication is sufficient and that consumers will be able to use them appropriately, we recommend that if such a product does switch to a nonprescription status, it is important that there first be a dual status of a prescription-nonprescription for such a medication.

Further, there must be clear labeling directions about warnings, precautions, side effects, and interactions. We also feel that there should be clear label directions urging people to check with their physicians before using such a product and to continue to have regular physician visits while taking the medication. And of course, we want to make sure that the labeling and package inserts are easy to read and to understand.

The methodology briefly, you saw up there already. We wanted to give you some of the survey topics, disease prevention and activities information, the attitudes, treatment in general, and then treatment specifically about cholesterol and OTC

treatment, whether or not it was a good idea or a bad idea which we'll move on to. I'm going to go through them quickly.

Some of the sample demographics for people that we pulled out total, about half were female, 41 percent age 55 and over, which is a population that probably would be most concerned with this area.

The education, some college or greater, 59 percent, so you have a fairly educated population. And the income of $35,000 and over was half of the population in this survey that we did.

And this was a nationally representative random dial of one thousand people, plus or minus three. Some of the same description, 49 percent, which is consistent with some of the other data we had previously, know their cholesterol levels, 41 percent believe their cholesterol level is high, and 29 percent believe they have a high risk because of that. Eighty-one percent have visited a doctor and of the people that we surveyed, 91 percent have health insurance and 89 percent have a prescription drug coverage.

We asked if it's a good idea or a bad idea. Sixty-five percent thought it was a good idea and the reasons they cited were that of expense, it

would be more readily available, it would help to lower their cholesterol, and only 13 percent said they wouldn't have to see their doctor. The bad idea, the 29 percent, as you see, said that there is a need to consult a doctor, 20 percent would be worried that they're not sure how to take it.

The recommendations, again, it's important we feel to have cholesterol tests and know the numbers, know the warnings, precautions, side effects. There should be an emphasis on interactions and ongoing consumer education campaign to keep people informed and aware about this issue. Thank you very much.

CHAIRMAN BRASS: Thank you. Our next speaker is Dr. Kasten.

DR. KASTEN: Good morning. I'm Dr. Bernie Kasten, Vice President and Chief Medical Officer of Quest Diagnostics Ventures. I'm a pathologist.

I'm here today to represent Quest Diagnostics Incorporated, the nation's largest laboratory provider. Quest Diagnostics has not received any monetary or nonmonetary incentives from any pharmaceutical company to present information to the FDA. Quest Diagnostics has business relationships with several pharmaceutical houses, but none has

sponsored our presentation.

Quest Diagnostics is the nation's largest and most experienced provider in diagnostic testing, information, and healthcare services, with locations throughout the United States, Mexico, and United Kingdom. We have 30 major regional laboratories, 300 rapid response laboratories, and 1,400 patient service centers conveniently located throughout the country making it easy for patients and people to have their samples collected. This is the nation's largest network of walk-in patient sites.

Why is a laboratory company testifying before an FDA panel that is considering the approval of prescription-only statin drugs for over-the-counter use? Simply, doctors rarely make a diagnosis or prescribe medications without first ordering laboratory tests to support their decisions. But our role doesn't stop there. Our testing and information are critical to the monitoring and treatment of patients once the doctor has prescribed medication.

There is perhaps no better example of this than with the statin therapies and other cholesterol-lowering therapies. In 1999, Quest Diagnostics performed more than 250 million tests. Over 30 million of these involved a cholesterol determination

ordered by a physician to diagnose, treat, or monitor patients at risk for cardiovascular disease.

As the leader in clinical testing, Quest Diagnostics offers patients and their physicians access to the nation's broadest network of laboratory services. Today the vast majority of testing we perform is as the result of a doctor's order; however, we are seeing patients taking increased responsibility for managing their own health.

We recognize that consumers are far more knowledgeable about health conditions and diseases than in the past. As a result, we are focusing our attention on specific diseases or disease groups and introducing new tests and information that offers insights to physicians and consumers in areas such as women's health, cardiovascular disease, and diabetes to name but a few.

Consumers are recognizing the value of these new tests. A recent report entitled Laboratory Industry Strategic Outlook 2000 observed, and I quote, "More patients are either asking their physicians for specific tests and paying for such tests out of pocket, or seeking such tests directly from laboratories and they are paying out of their pocket as well."

In response to an escalating demand from patients, direct-to-consumer tests will be more readily available in the future. Today, there are 30 states in which a patient can order a limited number of laboratory tests for themselves directly without physician involvement.

Direct-to-consumer tests are provided by laboratories and are becoming more readily available. Home testing kits also are becoming more readily available. Consumers want to know their cholesterol level. The National Cholesterol Education Program has contributed to this and many of our efforts have as well.

In the laboratory business, we are responding to clear demand from the consumers for greater access to their own personalized healthcare information.

A recent study published by the VHA and Deloitte & Touche indicated that 43 percent of the 40 million adults in the U.S. who use the internet were seeking health-related information. The study also showed that senior citizens were the largest consumers of healthcare information accessed over the net, that they were interested in services such as their test results and prescription information.

With the emergence of the internet as a major source of health information, Quest Diagnostics recently launched an web-enabled service for our patients, allowing them to gain secure online access to their own confidential results over the internet. We make patient's laboratory results available online in the 26 states where patient's right to access their own test results is not limited by local law.

If the FDA chooses to make statin drugs available as nonprescription drugs, Quest Diagnostics recognizes the continuing need to perform laboratory tests to assess a patient's treatment success, compliance, and potential side effects. We stand ready to provide all consumers and their physicians with lab services to support appropriate consumer lab testing nationwide for prescription as well as nonprescription drugs. Thank you.

CHAIRMAN BRASS: Thank you. Our next speaker will be Warren Pinckert.

MR. PINCKERT: Good morning. I'm Warren Pinckert, CEO of Cholestech Corporation. We are here on our own nickel, although all of the major pharmaceutical companies who have cholesterol-lowering drugs are our customers.

Cholestech is a company that manufactures

a point-of-care clinical instrument and also has a national testing service and recently launched a website called WellCheck.com that is focused on lowering cholesterol through interactive tools, goal setting, and measurement and motivation.

You've heard a lot of facts today about cardiovascular disease. Heart disease. We can be doing a much better job on it obviously. The cost of coronary heart disease estimated by the CDC in 1999 was $287 billion and 96 million Americans have high cholesterol and you just heard that only 50 percent of them even know their cholesterol levels.

I'm here today to try to make the Committees aware that technology now exists for consumers to know their numbers and to actively and personally manage their own healthcare. Cholestech makes the LDX which I brought up here. It is a CLIA-waived instrument. On a single drop of blood in less than five minutes, this instrument gives a complete lipid profile. Total cholesterol, HDL cholesterol, triglycerides, calculates LDL cholesterol, and if you want, it even throws in glucose.

We have ALT that has been approved by the FDA, 510(K) approval, and we have that in for submission for CLIA waiver. Our instrument is waived

under CLIA and that's very important because being waived under CLIA, we've learned, is a heck of a lot more than just being 510(K) approved.

We had to prove with this instrument through clinical studies that it is accurate and precise at the medical decision points that physicians need to make a decision and so we went through a lot of rigorous studies with the CDC and now we're involved with the FDA on the waiver thing to make sure that this gives accurate and precise results and can be used by an untrained user.

You put a single drop of blood into a disposable cassette, you put it into the machine, push run, that's all the operator has to do, and then less five minutes later you get your results.

That's important as we move on to trying to determine who should be on cholesterol-lowering drugs. If you're going to have to determine if your cholesterol level is 200 or 240, this instrument does it and you can tell right in a convenient site to you. You don't have to get up at 7 o'clock in the morning and go down to your hospital lab and have a venous draw.

We have a national testing service that we're developing that will provide testing in consumer

convenient locations. Locations that have pharmacies so that you're tested when you want to be tested and it is consistent high quality. We test under NIH guidelines.

We are trying to make it as low cost or free to consumers by using contributions from sponsors such as food companies and obviously pharmaceutical companies to offset the cost of the testing.

We also have an internet site, WellCheck.com that was just launched. That site was developed in conjunction with Stanford's Center for Disease Prevention.

We also used the NCEP diet one and two information that they have developed and we provide a fitness, a diet and nutrition, a pharmacy section, all virtual experts with contents from people who are not businessmen like us, but are trained professionals.

It's been reviewed by our medical advisory board and we have developed it so that that website will be able to be accessed by the patient's physician so that they are kept informed about what cholesterol levels currently the person has, how they're improving, and how they are doing on their fitness regimen, whether they have stopped smoking, their smoking cessation, all kinds of lifestyle tools.

I just wanted to be sure that the Committee was aware of this technology and other technology beyond the LDX. This just happens to be the one that I'm most interested in and obviously I know the most about. But there is other technology that is available at the point of care, so people can be tested. They can be tested at a low cost. They can know their numbers. And through technology like the internet, they can personally manage their cholesterol levels.

CHAIRMAN BRASS: Thank you. Our next speaker will be Dr. Pearson.

DR. PEARSON: Good morning. My name is Tom Pearson. I'm Chair of the Department of Community and Preventative Medicine at the University of Rochester.

By way of disclosure, I have had a number of speaker's bureaus and research grants from numerous pharmaceutical companies. I have been a paid consultant from both Johnson & Johnson-Merck, and Bristol-Myers Squibb advising them on the over-the-counter issues. However, for this meeting, I have received no remuneration or reimbursement whatsoever to come here and speak today.

My background is as a preventive

cardiologist interested both in the prevention of heart disease on the individual, but also on the population bases and my comments I have distributed on a two-page handout. I hope the Committee has available about the rationale for new approaches in population-based cholesterol lowering.

What I'd like to do is examine here this morning, very briefly, the public health need, perhaps the urgent need for new strategies to shift downward the population distribution of serum total and LDL cholesterol.

I had the opportunity to chair for the National Heart, Lung, and Blood Institute last September, a conference called the National Conference on Cardiovascular Disease Prevention, where we reviewed the trends in cardiovascular disease in the last decade in the United States.

In terms of morbidity and mortality, and the panel may not be aware of this, is that the morbidity and mortality for cardiovascular disease in general has declined at a slower rate in the 1990s than in the 20 years before that. Particularly with women and minority groups having even slower rates or even a stopping of decline in their cardiovascular disease rates.

In fact, stroke mortality from multiple sources of information has been flat since 1990 and possibly even going up in some subgroups.

Looking within this then, you can actually, with a couple of studies, much harder to come by data, suggest that the incidence of coronary disease, the new cases of coronary disease since 1990, actually has been flat. There hasn't been any decline. The declines in mortality have been from good, probably secondary care, but the new cases of coronary disease coming into our community are no longer going down.

This led us in that conference to examine risk factor trends in the 1990s and there is very good evidence that we've had stagnation of any progress in this area. You probably already know that smoking, blood pressure control, and physical activity have not changed much. Those are data from the Centers for Disease Control. We also know that obesity and diabetes, making the cholesterol issue a more important one, are now an epidemic scale.

In other data presented by Dr. Russell Luepker from University of Minnesota, show the cholesterol levels, which have reduced from 1980 to 1990, have not changed thereafter, suggesting that our

dietary and our high-risk pharmacologic interventions are basically burned out in terms of further progress in reducing population cholesterol.

So our conclusion from this, is that new strategies are needed to restart the declines in risk factors and their subsequent cardiovascular morbidity and mortality. Any such strategy will need to reduce moderate levels of serum cholesterol. That is between 200 and 240 for which the OTC statins are targeted.

This includes a high proportion of adults in this middle of the cholesterol distribution. About 30 percent of Americans have cholesterol between 200 and 240. And this moderate-risk group contributes, according to the Framingham Risk Predictions, approximately one-third of the myocardial infarctions and coronary events, and this group then are that not currently targeted for treatment, certainly under the prescription rules unless, ironically, they become high-risk by having a cardiac event.

One of the problems with that kind of a strategy is that the first presentation of coronary heart disease may be the last presentation of coronary disease because it's fatal in 20 to 40 percent of such individuals. These also of course bear high societal and healthcare costs for coronary heart disease

prevention.

The use of pharmacological agents in healthy adults has been shown to be safe and efficacious in the moderate-risk group. The very risk group that we're talking about as shown by the AFCAPS and TexCAPS study. Efficacy is demonstrated that we can reduce by 25 to 40 percent coronary outcomes including not only myocardial infarction, but the need for bypass surgery, etc., and the safety in that study has been demonstrated.

Therefore, our conclusion, or my conclusion, is that over-the-counter statins, in addition to other nutritional and lifestyle interventions, offer a safe and effective opportunity to reduce total and LDL cholesterol levels in that large population of Americans at moderate risk and which contribute a substantial portion of coronary heart disease cases in our society.

For this group we currently have no pharmacotherapy available which has had the testing and safety demonstrated that we've had for the over-the-counter statins.

Thank you for the opportunity to talk to the panel.

CHAIRMAN BRASS: Thank you. Our next

speaker will be Dr. Wolfe.

DR. WOLFE: Thank you. Our organization has a policy of not taking any funding from the pharmaceutical, diagnostic, or any other industry.

I'm going to talk about several things. One, risk assessment and the effectiveness of the drug. Secondly, compliance, monitoring of doses, and of adverse drug reactions. Third, safety issues, particularly focusing on interactions. And then finally the benefit-risk ration which is really what this should be all about.

Before even evaluating the risk implications of different cholesterol levels, a reliable test must be done, as you've just heard before. The FDA has recently approved several home diagnostic kits for cholesterol and there are serious questions about the accuracy of these tests, particularly because of the inexperience of the user. At the end of the testimony, I've got a verbatim, very complicated algorithm that someone who uses one of these tests needs to go through.

Other related steps in terms of arriving at risk assessment include the validity of patient's own self-assessment in terms of cholesterol level and other cardiovascular risk studies.

In the Merck study submitted to the FDA, significant proportions, almost a third and over half of people thought that they had cholesterol levels that were in range for eligibility for the over-the-counter drugs, but they weren't.

The serious problems in self-selection which would not likely be caught in the real world as opposed to the experimental world where people screen themselves, often without a cholesterol test, and decide to use the drug, are only the beginning of a cascade of other serious problems.

Even if patient self-selection worked, which it doesn't, and arrived at a group of patients who met the defined eligibility criteria, total 200 to 240, LDL over 130, a huge proportion of these people will not have any clinical benefit from using these drugs.

There is no evidence of a clinical benefit for a large proportion of these people. In the well-known AFCAPS/TexCAPS study published two years ago in the Journal of the American Medical Association, whereas those taking 20 to 40 milligrams of a statin did have an overall reduction in cardiovascular endpoints.

This was not true in the group that had an

HDL, a topic not discussed this morning at all, over 40. There was no clinical benefit in people with an HDL over 40 and it turns out that using the kind of population that seems to be targeted by Bristol-Myers Squibb and Merck, that a huge proportion of these people, estimated by the FDA to be 78 percent, have HDLs of 40 or over. And this is with a 10-milligram dose.

A repeat, there is no evidence at all of reduction in any group with a 10-milligram dose, but certainly, even with a 20- to 40-milligram dose, there is no clinical benefit if your HDL is over 40.

As you all know, HDL is an extremely important risk factor and tends to overwhelm some other risk factors, particularly with people with total cholesterols of between 200 and 240.

Compliance and monitoring. Prevention of cardiovascular disease must be part of a multi-pronged strategy to reduce risk. The use of heavily advertised statins out of the context of medical consultation may impair the development of an integrated long-term strategy for preventing strokes or heart attacks.

Diet and exercise, critically important components, may be thought to be less important if the

primary strategy seems to be a statin drug. And in that one survey done by the National Consumers League, a certain percentage of people thought you could just sort of go out and binge eat and you didn't have to pay any attention to diet, which sort of confirms that.

The evidence of poor compliance in these various trials that have been submitted by Merck, even in the short term, six months or less, with 25 to 31 percent of people dropping out by that time, bodes very poorly for the long-term compliance necessary for the drug to work in those people for whom it may actually be appropriate. Which is again I believe, a very small fraction of those who are targeted to get it.

Safety issues. According to FDA's analysis, which you'll hear much more of, of Merck's label comprehension study, only 66 percent of low literacy label readers, only 82 percent of high literacy readers, knew about the contraindicated lovastatin-erythromycin interaction, whereby erythromycin inhibits the metabolism of lovastatin and leads to accumulation of dangerously high levels of lovastatin.

In just two years alone of FDA's data,

there were eight reported cases of rhabdomyolysis, a very severe life-threatening disease with acute destruction of muscle, liberation of myoglobin, and acute kidney failure in some cases. Eight cases in patients who were simultaneously taking lovastatin and erythromycin.

This is a drop in the bucket because only a small fraction of these cases get reported and it's only two years worth of cases, it's only one statin drug, and this is with it not available over the counter.

The odds of interactions which are worrisome enough when drugs are available only by prescription, rocket up, and I would expect that if these drugs go over the counter we will see an enormously increased number of serious life-threatening reactions such as this.

Particularly when someone picks up something over the counter in a supermarket or a Seven-Eleven store, there is not likely to be any record in the pharmacy about this, unlike prescription drugs, and so the pharmacist doesn't even have a chance to intervene and say, "Whoops, you're already taking something else."

Finally, the benefit-risk ratio. The

benefit-risk ratio for the approval of a drug must clearly be greater than one to merit approval. If the benefit is zero, and I would argue that there is no significant evidence of clinical benefit in a large proportion of the people for whom these drugs are targeted, if the benefit is zero, then no amount of risk, however small, and I think it will grow with the interaction and other problems, is acceptable.

Finally, I'd just like to quote a now-deceased neighbor to the north, from Baltimore, H.L. Mencken, one of whose most famous statements was, "For every complicated problem there is a simple solution, and it's usually wrong."

The switch of statins from prescription to OTC status is really recklessly simplistic and it is not the right kind of solution to a complex problem. No one denies that we are not doing as good a job as we should in educating people about primary prevention, but to do it this way I think is a serious mistake and we strongly oppose the switch. Thank you.

CHAIRMAN BRASS: Thank you. Dr. Orloff.

DR. ORLOFF: Good morning. My name is David Orloff and I'm the Deputy Director of the Division of Metabolic and Endocrine Drug Products. Welcome.

Let me begin by recognizing the hard work of the FDA team, not all of whom you will hear from today, in their review of this drug application and their preparation for today's meeting.

What I'd like to do is to frame for you, the Committee that is, some of the broad issues that bear generally on the question of over the counter for chronic asymptomatic disease, and then to highlight for you some of the specific points on which we would like you to focus as you listen to the data presentations.

First, let me review for you the regulatory standard that guides us in our decisions regarding the over-the-counter marketing of drugs. A drug should be over the counter, according to regulation, if prescription dispensing requirements are not necessary for the protection of the public health, by reason of the drug's toxicity or other potentiality for harmful affect, or the method of its use or the collateral measures necessary to its use, and the drug is safe and effective for use in self-medication as directed in proposed labeling.

In other words, safe and effective, when used according to the label, without the necessary involvement of the physician or other healthcare

professional.

It is in this context that traditional over-the-counter drugs have been nontoxic generally, low abuse potential treatments, targeted to low-risk acute or chronic intermittent conditions characterized by mild, but present symptoms, and amenable to self-diagnosis.

These drugs have been generally intended for short-term use as monotherapy with the duration of use limited by response or nonresponse of symptoms. More specifically, recurrence, persistence, or worsening of symptoms logically and practically prompts the patient to search for more definitive diagnosis and treatment and presumably to cease use of the over-the-counter drug.

What is at issue here, however, is something markedly different. Dyslipidemia with atherosclerotic cardiovascular disease risk. This, in contrast, is an asymptomatic condition where diagnosis and follow-up require blood testing and interpretation. Where the treatment is intended solely to reduce the risk of life-altering or life-threatening outcomes. Where optimum benefit requires long-term compliance not only with the drug regimen, but with diet and lifestyle.

And where particularly as time goes on, the rule rather than the exception in treatment is titration to optimal effect, combination therapy, not only to address the dyslipidemia, but also to address co-morbid conditions.

And finally, all important in the long-term follow-up of this disease is vigilance for an anticipation of clinical coronary disease or cardiovascular disease in order to effect the best or the most favorable long-term outcome.

Let's talk in a little bit more detail about this issue of method of use and collateral measures necessary to use with specific reference to hypercholesterolemia.

When we approve a drug for prescription use, we do so based upon a reasonable judgement supported by data that the drug will be safe and effective if used according to the label, and at that point the responsibility passes to the healthcare professional and to the patient in a collaborate effort in the treatment of the patient's condition.

While we all recognize that particularly in the instance of hypercholesterolemia and cardiovascular disease risk prevention, there are serious limitations or failings of our current system

that make it a far from perfect means by which to address this problem for individuals and for the public.

What are some of those limitations? Well, the condition may be unknown to the patient so he or she may not seek healthcare. Healthcare may not be accessible to the patient. If healthcare is sought, the physician may miss the diagnosis, either because he or she doesn't look or because of the lack of knowledge of the disease.

The treating physician may have discomfort with existing therapies and thereby not prescribe when indicated, or alternatively may have an ignorance of some of the risks of some of the therapies and therefore inappropriately prescribe.

And even if everything else goes fine and the patient is initiated on therapy, there are a whole host of influences that impact on the follow-up system which will affect the system of refills, monitoring for both positive and negative effects, and for the progression of the disease.

Well, let's consider the hypothetical situation of an over-the-counter cholesterol-lowering drug. Again, when we approve a drug for over-the-counter use, it's based upon a reasonable judgement

supported by data that it will be safe and effective if used according to labeling.

At that point, in the case of over the counter, the responsibility or burden for its safe and effective use falls squarely on the shoulders of the consumer and there can be no relying upon the learned intermediary healthcare professional.

Well, what are the limitations in this system with specific reference to the treatment of hypercholesterolemia? Well, I think it's fair to say at the very least what is a potential problem in the Rx example is likely to be a much more prevalent problem here in the OTC example.

That is, the lack of ancillary care, the lack of reinforcement for long-term adherence, the lack of follow-up of the disease.

Furthermore, there are theoretical problems related to encouragement simply by the over-the-counter availability of the drug for treatment where it's not warranted, or for the use of the low-dose over-the-counter product when more aggressive therapy is necessary. This leads to the whole issue of off-label use, particularly related to the use of higher-than-recommended doses.

Furthermore, there may be an inference on

the part of many consumers that this over-the-counter therapy is optimally effective as monotherapy for the condition targeted.

And lastly, a theoretical trap, which exists certainly in the prescription realm of patients using drug without lifestyle change, which I think we all have to agree will clearly limit any potential effectiveness of the drug.

Well, what's the regulatory history in this area? This is the third time in the last five years that the issue of over-the-counter cholesterol lowering has been brought before the Joint Advisory Committee.

In 1995 and in 1997, the Advisory Committee considered the over-the-counter switch for cholestyramine, a nonabsorbed cholesterol-lowering agent. It was largely on the basis of the discussions of the 1997 meeting that the center for drugs issued a guidance for industry on over-the-counter treatment of hypercholesterolemia that in essence concluded irrespective of the intrinsic safety and efficacy of the drugs targeting this disease, that hypercholesterolemia per se was not an over-the-counter disease.

It went into more detail in stating that

healthcare practitioner supervision was necessary in diagnosis, individualization of treatment, and in follow-up, and that safe and effective use of drugs in this area and the overall treatment of the disease could be assured only within the context of prescription access.

Well what has changed in the interim? First, let me make it clear that the lovastatin over-the-counter develop program was undertaken independent of FDA input. This is consistent with our stated position on the issue and our 1997 guidance.

Furthermore, the landscape on which this whole debate takes place has changed over time. There has been the marketing of dietary supplements for lowering cholesterol, most notably Cholestin, significantly a product containing lovastatin in spite of the legal efforts of the FDA.

There are foods available for cholesterol lowering, notably Benecol, a margarine made from plant sterols that inhibit the intestinal absorption of cholesterol. And there has been a proliferation of foods labeled as "heart healthy," notably oat bran and psyllium.

Finally, over 13 years of marketing since the initial approval of lovastatin and with the

completion of five placebo-controlled hard cardiovascular endpoint megatrials, there is a vast clinical experience with statins.

With this as the backdrop, what is the essential rationale for the over-the-counter switch of lovastatin 10 mg as put forward by the sponsor?

It is that there is a well-known, graded, and continuous relationship between cholesterol level and coronary heart disease risk that on the basis of the accrued clinical experience, the benefits of LDL lowering with statins has been established.

That there is a contention that there is an unmet medical need in an at-risk, non-NCEP-eligible population. There is a changing landscape as I've described, therefore unrestricted access for this low-risk population is warranted.

Now the sponsor actually relies more specifically for their rationale on the results of the AFCAPS/TexCAPS trial. You've heard mention of it already, you'll clearly hear mention of it as we go along today.

That trial showed a substantial benefit of lovastatin 20 to 40 milligrams in a low-rise, relatively low-risk, primary prevention population.

There was a similar benefit to that seen

for the total cohort in the 58 percent of that AFCAPS population who were OTC eligible according to the sponsors proposed definition. There is a large segment of the United States population that is OTC eligible by that definition.

Therefore, the sponsor concludes that the over-the-counter target population stands to benefit and should have lovastatin 10 milligrams over the counter as a treatment option.

Sufficed to say that, and you'll hear more about this on subsequent presentations, the degree to which the results of AFCAPS can be extrapolated to an expectation of benefit in the targeted over-the-counter population is something that I think merits your attention as you listen to the presentations.

Let me point out for you, however, something further important. The sponsor is proposing what we consider to be a new indication for the use of lovastatin. Specifically, as I've mentioned before, the proposed over-the-counter population is not currently targeted for drug therapy and, as you'll hear in more detail, the over-the-counter population is not the AFCAPS population.

And parenthetically you should also understand that prescription lovastatin is currently

labeled for use in the AFCAPS population, so there is no denying that that trial has demonstrated a benefit in the target population.

We need to address the question of whether this indication is supported by data and if it is, we need to address the question of whether over-the-counter access to lovastatin 10 milligrams is the way to address this presumed unmet medical need in this at-risk population.

You will hear presented today, by both the sponsor and FDA, data on the efficacy of lovastatin from controlled clinical trials, looking at both lipid-altering or lipid endpoints and hard cardiovascular endpoints, and you'll also hear efficacy data presented from the actual use trials, studies intended to mimic real-world, over-the-counter use.

You'll hear presentations on the safety of lovastatin, in this instance from the database of controlled trials, from the spontaneous reporting system in open market use, and, as inferred, from pharmacokinetic studies that shed light on the potential for adverse drug-drug or drug-food interactions with lovastatin.

And you'll hear discussion of label

comprehension and consumer behavior studies, all important issues in an assessment of the expectation of safe and effective use for an over-the-counter drug.

Lastly, let me jump forward and introduce to you the essentials of the questions that you'll be asked later which touch on the issues that I discussed earlier.

The first question: Whether Rx or OTC, is therapy with lovastatin 10 milligrams in the target population proposed warranted based upon evidence of clinical benefit and clinical safety and considering the balance of risk and benefit?

Second, if treatment with lovastatin 10 milligrams of the proposed target population is justified, can benefit be reaped with an acceptable level of risk in an OTC setting? And here issues of method of use and collateral measures necessary to use have to be important considerations.

And finally, is the evidence presented sufficient to support the expectation of safe and effective use of lovastatin 10 milligrams in the target over-the-counter population, directed by the consumer without the necessary involvement of a healthcare professional?

I thank you for your attention and I'll yield to the first presenter from Merck.

CHAIRMAN BRASS: Thank you. I'll now turn over the floor to Dr. Slater from the sponsor and as the sponsor prepares, I just want to inform the Committee that because we have a very tight time schedule today, there will not be an opportunity to begin discussion with the sponsor or the FDA until the afternoon session.

Therefore, in terms of issues raised this morning, I would ask the Committee to limit themselves only to the most succinct question of specific clarification of information presented and save the dialog for this afternoon.

DR. SLATER: All right, we're ready to begin. Good morning Dr. Brass, members of the combined FDA advisory panels, members of FDA, colleagues, guests, ladies, and gentleman.

Approximately 25 years ago the American physicians Brown and Goldstein published their elegant data that the hepatic LDL receptor was responsible for internalization of the atherogenic particle LDL, and that its absence resulted in this syndrome familial homozygous hypercholesterolemia.

Soon thereafter, drugs called statins were

discovered which inhibited cholesterol biosynthesis which resulted in up regulation of LDL receptor and sustained cholesterol lowering.

Approximately 13 years ago, in February 1987, I stood before a panel very similar to yourselves to describe the biochemical actions and safety of lovastatin and on that day lovastatin was recommended for approval in the United States by unanimous vote.

Since then five additional statins have been approved for use and an estimated total 101 million patients have received prescription statin therapy over these years.

Five major controlled long-term endpoint studies have been conducted with statins in over 30,000 patients and easily that number continue under study to further research the benefits of these medications.

You are well familiar with the data. The evidence to date demonstrates that therapy with specific statins reduces cardiovascular morbidity and mortality by one-third. Whether preventing subsequent events in patients with established cardiovascular disease or new events in otherwise healthy persons with higher than average cardiovascular risk, many

lives have been saved and quality of life improved for many more.

Nevertheless, against this background of major public health achievement, the incidence of coronary disease remains unchanged. While there is now widespread and growing appreciation of the risks of high cholesterol and while cholesterol testing is becoming more easily accessible, in the United States at least, it is estimated that only 50 percent of patients for whom the NCEP guidelines recommend cholesterol reduction by medication, are actually receiving such medication, and of these, a further approximate half have discontinued their therapy after only short-term use.

A burdened healthcare system often has little time for education about prevention and most patients prescribed statins to prevent a first event must pay voluntarily for this intervention.

With this in mind and believing in the lifesaving potential of lovastatin and it is long-term safety, we at Merck embarked upon a program to determine whether healthy individuals, but those identified as being at higher-than-average-risk for a first coronary event, could appropriately select and use lovastatin in an over-the-counter setting.

Our OTC program began formally in 1996 and as submitted to FDA, this NDA contains ten studies including controlled use, pharmacokinetic, open-label use, and label comprehension trials.

To describe this program to you today, our speakers are listed as follows: I'm Eve Slater, a cardiologist who has directed regulatory affairs at Merck for the past ten years and also have responsibility for this program.

Dr. Polly Beere will describe the subset of individuals who Merck has targeted for OTC use and the several lines of evidence which includes the AFCAPS/TexCAPS trial which she directed which have been used to estimate the individual benefit of OTC use.

Dr. Scott Korn will describe the safety information accumulated in our OTC trials, and as Dr. Orloff said, in the prescription clinical trial database, in the two large-scale endpoint trials conducted with lovastatin, AFCAPS and EXCEL, in a dosage ranging from 20 to 80 milligrams, and of course of AFCAPS in a primary prevention population, and in the post-marketing database which draws from 24 million patient-years over 13 years exposure.

Finally, Dr. Edwin Hemwall will describe

the series of trials which have led, in our view, to unique education and support system which achieves both proper selection and safe use.

With us today are the following outside experts who would welcome the opportunity to address your questions and concerns and they are Doctors Jeff Anderson, John Farquhar, Keith Tolman, and James Willerson.

In addition, we at Merck Research Laboratories have developed substantial in-house expertise in statin therapy and I won't read you their names, but the following individuals are here to represent their specific areas of specialty and certainly can be called up on to resolve any issues that come in discussion.

In the words of FDA, and I quote, "This NDA raises precedent-setting issues." Indeed, you are being asked to judge whether a medicine with exposure and safety consistent with other widely used OTC medicines can be made available for a chronic asymptomatic and life-threatening condition.

We at Merck believe that the time has come to set a new precedent as there is an unmet need. We believe that you should require of such a product a higher standard of safety and an unprecedented patient

education and support program.

We are hoping to convince you today that we have met these demands and that it is possible to carve out a subset of the population who are appropriately motivated to use lovastatin safely and responsibly in order to improve their risk profile.

In the words of Dr. Craig Ventor of Celera, "Medicine today has become the business of the consumer." If we as physicians and healthcare professionals fail to respond to what many are asking of us, increasing numbers of citizens will resort to alternative measures.

To fail to respond responsibly would, in my opinion, be an abrogation of our duty as healthcare providers.

So in the tradition of Merck Research Laboratories and in the true tradition of lovastatin, I am proud to present my colleagues and request your consideration of Mevacor for over-the-counter use. Thank you very much. I would like to introduce Dr. Polly Beere.

DR. PEERE: Thank you Dr. Slater. Good morning ladies and gentleman. I will present an overview of our rationale and the evidence that we believe supports the benefit of approving lovastatin

10 milligrams for nonprescription use.

The rationale for nonprescription access to lovastatin is to provide an effective additional option to achieve and maintain a favorable lipid profile for the individual who chooses to supplement current nonpharmacologic interventions to promote cardiovascular health. My presentation will review the following:

First, I will present the relevant background and considerations which support our selection of the population for which this product is proposed. Next, I will describe the characteristics of our proposed OTC population and review the data indicating that the risk of coronary heart disease can be significantly reduced by effective lowering of total and LDL cholesterol for this type of population.

Then I will demonstrate that the efficacy of treatment with lovastatin 10 milligrams daily produces significant and beneficial modification of the lipid profile. And finally, I will describe how we estimated the potential impact given the observed efficacy of lovastatin 10 milligrams, of having this additional option for effective lipid modification to promote cardiovascular health.

We based our rationale for identification

of the population for which this product is proposed upon three major considerations.

First, the relationship between cholesterol and the risk of coronary heart disease. Second, the evidence that risk reduction by chronic treatment to modify lipids is beneficial for persons at risk. And third, the recommendations of current clinical guidelines for risk assessment and treatment.

The importance of the cholesterol hypothesis as originally described by the Framingham Study demonstrates the positive and continuous relationship between serum cholesterol and the risk of coronary heart disease beginning at levels less than 180 milligrams per deciliter, indicated here by a risk ratio greater than one.

For persons in the range of total cholesterol between 200 and 240, which represents approximately 30 percent of the population, prescription treatment to lower cholesterol would not generally be recommended. It is from within this subset of the adult U.S. primary prevention population that we will consider the potential benefit of nonprescription use of lovastatin 10 milligrams.

As seen on this slide, the relationship between total cholesterol and the risk of coronary

heart disease is continuous and graded such that for each 1 percent increase in total cholesterol, there is an increased risk of approximately 2 percent.

In addition, there have been many prospective intervention studies with treatments of varium efficacy ranging from diets to drug that also demonstrate that for each 1 percent decrease in total cholesterol there is a reduction in risk of 2 percent.

With the availability of HMG-CoA reductase inhibitors, or statins, it has been possible to study the benefit of more aggressive lipid modification in controlled clinical trials.

Now I will briefly review the evidence from these studies. Shown on this slide are the four statin studies that have been referred to previously of cohorts with relatively high risk. These were designed to test the general hypothesis that treatment to lower total and LDL cholesterol would reduce the risk of coronary heart disease.

Three were designed as secondary prevention interventions pertaining to persons with preexisting coronary disease. And one, WOSCOPS, was designed as a primary prevention intervention pertaining to persons without a history of coronary disease; however, this study cohort had relatively

high risk due to male gender and high total cholesterol.

These studies demonstrated that chronic statin treatment using prescription doses of simvastatin or pravastatin for an average duration of at least five years significantly reduced the relative risk of coronary heart disease by at least 24 percent compared to placebo. Shown here for the composite endpoint of nonfatal myocardial infarction or coronary heart disease death.

The efficacy that was produced by these treatments in terms of LDL reduction, ranged between an average of 25 to 36 percent. This benefit was evident across the range of risk for cohorts with and without preexisting disease. The benefit was also evident across a broad range of LDL cholesterol and HDL cholesterol.

Of note, the majority of persons enrolled in these four studies would be recommended under current guidelines for prescription treatment to lower cholesterol.

Now I would like to briefly describe the results of a recently completed clinical trial that provides evidence of benefit for this type of treatment for persons who would not generally be

recommended for prescription treatment.

This study, the Air Force-Texas Coronary Atherosclerosis Prevention Study that has been referred to several times, was designed in 1989 to test the hypothesis that treatment with lovastatin in addition to recommendations for healthy diet and lifestyle will reduce the risk of coronary heart disease defined as a composite of the first fatal or nonfatal myocardial infarction event of unstable angina or sudden cardiac death.

The cohort of over 6,000 generally healthy men and women had on the average what would be considered moderate risk due to the presence of at least coronary heart disease risk factor, namely age. For men at least 45 years and for women at least 55 years of age. Unlike earlier primary prevention studies, inclusion of persons with ages greater than 65 years was also allowed.

The cohort had what would be considered generally average total and LDL cholesterol and below average HDL cholesterol based up on the U.S. adult primary prevention population within this age range. Of note, only 83 percent of the cohort would not be recommended for prescription treatment under current guidelines, 17 percent would be. At the time the

study was designed, none would have been recommended for treatment.

The treatment was lovastatin 20 to 40 milligrams daily compared to placebo. This resulted in an average LDL reduction of 25 percent. The results of this study, shown here as the cumulative incidence by group for the primary end-point analysis, demonstrated that treatment with lovastatin for an average duration of 5.2 years significantly reduced the risk of the first acute major coronary event by 37 percent.

Note that the difference between the groups in terms of the cumulative incidence appears to begin within the first year of treatment and continues to grow over time. This magnitude of benefit was consistent for all risk subgroups compared to the cohort overall.

For example, for both smokers and nonsmokers, those with and without hypertension, and all lipid subgroups as well as the other risk categories. Similar benefit was demonstrated for the secondary endpoints such as revascularizations and fatal or nonfatal MI.

The findings of AFCAPS/TexCAPS shown here in comparison to the four studies that I presented

earlier for the secondary endpoint nonfatal MI or death from coronary heart disease, demonstrates that the magnitude of risk reduction is consistent with the studies of much higher risk cohorts. The results of AFCAPS/TexCAPS demonstrate that treatment with lovastatin reduced the risk of a first myocardial event by 40 percent.

Unlike the other study cohorts, these results pertain to persons who would not generally be recommended for treatment according to treatment for prescription under current guidelines.

So in summary of the background considerations I have just reviewed, I demonstrated that the risk of coronary heart disease is positively associated with total cholesterol for the adult U.S. primary prevention population including the range that would be considered average.

I presented the evidence that the risk of coronary heart disease can be significantly reduced by lowering cholesterol for both higher and lower risk cohorts and that this benefit is evident even for persons who would not be treated according to current clinical guidelines.

With these considerations in mind, I will now describe how we identified our proposed OTC

eligible population.

It was the intention of this OTC development program to complement and support current clinical guidelines. Therefore, demographic and lipid characteristics were selected on the basis of their association with relatively increased risk of coronary disease within the primary prevention population.

Our population is defined for men having at least the age of 40 and women at least one year postmenopause, who further have a total cholesterol in the range of 200 to 240 milligrams per deciliter, and an LDL of at least 130 milligrams per deciliter.

We chose this cholesterol range for which coronary heart disease risk management other than prescription drugs is currently advised and selected the LDL criteria to include persons who would have an LDL above the current desirable goal for this risk group.

We did not want to include persons who might warrant more individualized risk management and prescription treatment. They are directed to their physician if they are considering use of this product.

Having defined our OTC-eligible population, we estimated the risk of coronary heart disease in this segment of the adult primary

prevention population. We did this by looking at subgroups of the Framingham Heart Study and the placebo group of AFCAPS/TexCAPS that would be OTC eligible according to the criteria I just presented.

Based upon the five-year incidence, we estimated that the risk of myocardial infarction would be in the range of 2.8 to 3.6 percent and that the risk as a border composite would be in the range of 5.3 to 5.9 percent.

Of note, observations from the Framingham Heart Study exist for beyond two decades demonstrating that the 20-year incidence of coronary heart disease in this population, the OTC-eligible subgroup, is 22 percent.

Therefore, we estimate that for our OTC-eligible population, the average annual risk of a major coronary heart disease event would be approximately 1 percent.

To put this risk in perspective, we estimated that based upon over 170 million U.S. adult primary prevention candidates, approximately 15.5 million, or 9 percent, would meet our criteria for OTC eligibility and use of nonprescription lovastatin.

We also estimate that this OTC-eligible subgroup, given the approximate annual risk of

coronary heart disease of 1 percent, would contribute greater than 150,000 new cases of major coronary events annually, or in other words, 17 percent of the projected estimate of almost 1 million new cases.

Based upon these estimates, we believe that our OTC criteria appropriately define a segment of the U.S. adult primary prevention population at substantial risk of coronary heart disease for which additional risk management and risk reduction by more effective modification of the lipid profile would be beneficial.

Now I will present the data pertaining to the effectiveness of lovastatin 10 milligrams.

I will review the data that demonstrates consistent and clinically meaningful efficacy of lovastatin at the proposed nonprescription dose of 10 milligrams with the reference of two placebo-controlled studies and two large open-label OTC-use studies.

On this slide, the results of the two randomized placebo-controlled studies, number 61 and 75 are presented. They are shown as the percent change from baseline for the major lipid parameters. Both studies have a placebo run-in phase of diet, and they both have 12 weeks duration for double-blind

treatment. Baseline lipid profiles were similar for these two studies.

The standard intention to treat analysis was used to compare the two groups and establish efficacy. Changes in the total cholesterol, LDL cholesterol, and the ratio of total to HDL cholesterol compared to placebo were highly significant.

Furthermore, the magnitude of efficacy demonstrated by each protocol was similar. The results of these studies can now be compared to the efficacy that we observed in the OTC-use studies.

This slide shows, in addition to the two placebo-controlled studies, the efficacy demonstrated by the two open-label OTC-use studies. The observations are based upon paired comparisons for those persons who had data at both baseline and at eight weeks, those who used the product.

The magnitude of efficacy upon all of the lipid parameters was similar to the observations from the placebo-controlled studies, and the average data, therefore, are presented on the right in yellow. I will refer to these values later for estimates of benefit.

As Dr. Hemwall will present, the magnitude of this efficacy persists for persons who continue to

take drug for up to 18 months.

We addressed efficacy in another way, by assessing how many people within the study cohorts had an untreated LDL of less than 130 milligrams per deciliter. We chose this because it is the most aggressive treatment goal according to current clinical guidelines for either prescription or nonprescription treatment of primary prevention candidates at risk.

For the 10-milligram dose shown on the left for the three OTC studies, we found that between 68 and 75 percent of the cohort had an untreated LDL less than 130 with a 10-milligram dose. Shown on the right for comparison, for the AFCAPS lovastatin-treated patients only on 20 milligrams before titration, we can see that an additional 12 percent of the cohort are able to have an untreated LDL less than 130.

From the results of these two placebo-controlled studies, we conclude that lovastatin 10 milligrams significantly reduces total and LDL cholesterol as well as the ratio of total to HDL cholesterol in persons with a lipid profile meeting our criteria for OTC use. We also observed that this same magnitude of effect can be achieved in OTC-use

studies.

Therefore, we believe that these studies clearly establish the efficacy of the 10-milligram dose in the OTC setting.

Now I will present how we estimated the impact of long-term treatment with lovastatin, considering the evidence of primary prevention, the relationship between lipid changes and the risk of coronary heart disease, and the projected benefit given the observed efficacy of lovastatin 10 milligrams.

First, to consider the evidence of primary prevention, we addressed how the primary prevention study AFCAPS/TexCAPS is relevant to the proposed OTC-eligible population.

First, it is important to note that the overall results of the study with lovastatin extends the benefit of treatment to modify the lipid profile to a primary prevention population of generally healthy men and women with average total cholesterol and LDL and below average HDL. The majority of whom would not be treated with a prescription under current guidelines.

In addition, even with the consideration of the differences in dose regimen, the cohort, the

duration between AFCAPS and what our proposed OTC population and treatment would be. This study confirms and extends the applicability and the relevance of the relationship between beneficial modifications of the lipid profile and reduction and risk of coronary heart disease that has been established as I demonstrated earlier by many studies of relatively higher risk cohorts.

This relationship can be applied to persons with a total cholesterol in the range of OTC eligibility. Specifically, the findings are relevant and supportive because 58 percent of the study population would be OTC eligible.

Therefore, we explored the effect of treatment upon the risk of coronary heart disease for the large subgroup of AFCAPS/TexCAPS that would be OTC eligible and I'd like to illustrate how we carved out this subgroup. We defined it by the total cholesterol range of 200 up to 240 and an LDL of greater than 130.

As you can see, this represents 62 percent of the cohort overall, and we further restricted it by excluding persons with diabetes or with hypertension treated with more than one drug, and that is how we arrived at the 58 percent of this larger cohort that would be OTC eligible.

And we performed the same primary endpoint analysis that was done for the study overall, shown on this slide. A highly significant reduction of 44 percent in the risk of coronary heart disease was observed for this subgroup with a similar early separation between the two treatment groups within the first year of treatment.

The magnitude of benefit with treatment was similar to what was observed for the cohort overall. Using this data therefore, we are able to describe the relationship between risk reduction and changes in the lipid profile.

We found that for a 1 percent decrease in total cholesterol or LDL cholesterol, or the ratio of total to HDL cholesterol, the estimated risk reduction ranged between 2.3 and 2.8 percent. This relationship, based upon the results of the AFCAPS/TexCAPS for the OTC-eligible subgroup, is consistent with earlier studies of higher-risk cohorts.

Therefore, for this reason, we believe that it is appropriate to apply this relationship to estimate the impact of long-term treatment in our OTC-eligible population given the observed efficacy of lovastatin 10 milligrams.

We used the observed efficacy from the 10-milligram studies to project the relative risk reduction if this dose was used long term by applying the estimated decrease in risk as I just described. Shown on this slide is the actual observed efficacy based on the average that I presented previously.

We used the relationship as described and the estimate of risk reduction in order to project the impact of long-term lipid modifications to estimate the relative additional benefit that could be expected upon public health by making this treatment option available.

With the following assumptions of approximate annual risk of 1 percent, defined as I did based upon the Framingham Heart Study and the AFCAPS placebo group, a treatment and observation period of at least five years, and an estimated risk reduction of 30 percent approximately, which is taken from the estimates shown on the previous slide from 27 to 35 percent, the impact of chronic treatment can be given with the following example:

For every 10,000 people at risk, 500 events would be expected without OTC treatment. With treatment, we would expect 350 events. Therefore, treatment would prevent 150 or one-third of the

expected first major coronary events.

Alternatively, to prevent one event, the number of persons needed to treat would be approximately 60 to 70 to prevent one of them. Such estimates are similar to calculations for stroke prevention in the elderly with antihypertensive medication for which the number need to treat is approximately 200.

Furthermore, we believe that this is an appropriate estimate as it is consistent with the actual rates observed in the OTC-eligible subset of AFCAPS/TexCAPS using the 20- to 40-milligram dose, based upon which we can calculate that for 10,000 people treated, 230 events would be prevented for more than 500 expected. In other words, this would translate to a number needed to treat of approximately 43 with a higher dose.

Therefore, we believe that this treatment would result in a substantial primary prevention benefit.

In summary, we have demonstrated that the proposed OTC-eligible population is at substantial risk of coronary heart disease. The OTC-use studies confirmed the efficacy of lovastatin 10 milligrams and demonstrated in the OTC-eligible population that

effective modification of the lipid profile can be achieved by treatment with lovastatin 10 milligrams.

Furthermore, we have demonstrated that the projected impact of chronic treatment with lovastatin 10 milligrams is to significantly reduce the risk of coronary heart disease for both the population and the individual.

Therefore, we believe that there is substantial evidence to conclude that the benefit of Mevacor OTC would be an effective new option to promote cardiovascular health by clinically meaningful modification of the lipid profile.

Thank you for your attention and consideration of this proposal. Dr. Korn.

DR. KORN: Good morning. I've had the opportunity to review the lovastatin safety data from the prescription trials, from the spontaneous reports during marketed use, and from the nonprescription studies. My talk will summarize the data from these three sources.

Merck believes that a nonprescription medication should have the following attributes:

It should have a very well-characterized safety profile. There should be a low incidence of medically significant adverse experiences. There

should be a large margin of safety. There should be no need for periodic laboratory tests to monitor safety. And the labeling should be able to clearly communicate how to safely use the product.

The data I will present this morning shows that lovastatin 10 milligrams meets these criteria.

My presentation will begin with a review of the data from two large post-approval trials of lovastatin. These studies evaluated prescription doses of 20 to 80 milligrams per day.

I will then discuss three issues that have been recognized for years and are addressed in the current prescription label. These issues related to the liver, the skeletal muscle, and the potential for drug-drug interactions.

At the end of the talk, I will give an overview of the safety from the nonprescription clinical studies with lovastatin 10 milligrams.

As Dr. Slater mentioned, we have extensive experience with lovastatin. It has been marketed since 1987 in the United States and there have been an estimated 24 million patient-treatment-years worldwide.

The vast majority of that exposure has been at doses of 20 milligrams per day or higher. There have

been, we estimate, 720,000 patient-years with the 10-milligram dose available by prescription.

The safety profile has been very well characterized in two large post-approval placebo-controlled trials. The Expanded Clinical Evaluation of Lovastatin, referred to EXCEL, randomized patients to receive placebo or 20, 40, or 80 milligrams per day of lovastatin for 48 weeks.

As Dr. Beere mentioned, in AFCAPS/TexCAPS participants were randomized to placebo or received lovastatin 20 or 40 milligrams per day for an average of five years. Approximately 15,000 people participated in these two studies.

Lovastatin was extremely well tolerated in both of these long-term trials. The adverse experience profile of lovastatin 20 milligrams was similar to that of placebo in both of these studies. EXCEL demonstrates the large margin of safety with this product. In that study, doses up to 80 milligrams per day were well tolerated.

In both trials, the age, gender, or race of the participant did not impact the safety of lovastatin.

This slide presents data from EXCEL and the data is included in the current prescription

labeling. An adverse experience is defined as any unfavorable change in the body, whether or not it is considered related to the use of the product.

There were ten clinical adverse experiences that were considered possibly, probably, or definitely drug related by the investigator and occurred in 1 percent or more of the patients receiving lovastatin 80 milligrams. That data is shown in this column, the 20 milligram and placebo data is shown for comparison.

As we see, the most common adverse experience the lovastatin was flatulence, followed by constipation, headache, or muscle soreness, referred to here as myalgia. None of these adverse experiences occurred in the statistically higher incidence with lovastatin than with placebo in this trial.

AFCAPS/TexCAPS confirmed the excellent tolerability of lovastatin that was seen in EXCEL. The lovastatin and placebo groups were similar with regard to the proportion who had a serious adverse experience, drug-related adverse experience, the proportion who discontinued due to an adverse experience, and a proportion who had a serious drug-related adverse experience.

In fact, there was only one participant

who received lovastatin and had an adverse experience that was serious and considered possibly drug related.

I would like to point out that the 34 percent number is not surprising given the five-year duration of treatment in the trial.

Review of the published literature and spontaneous report databases further provides additional reassurance as to the large margin of safety with lovastatin. We are unaware of any case where a patient died after an overdose of lovastatin alone.

The American Association of Poison Control Center database contains information on 2,634 exposures to lovastatin. There was no serious toxicity in any of those exposures to lovastatin alone.

It is also worth noting that there have been no reports of drug abuse with lovastatin. There is no pharmacologic reason to expect abuse with lovastatin given that its primary site of action is the liver and the drug has no recognized effect on the central nervous system.

I would now like to turn our attention to three safety issues that are discussed in the prescription labeling. These are the potential to

develop abnormalities related to liver function tests, the muscle syndromes that have been rarely observed with the statins, and the potential for drug-drug interactions.

On in-depth review, these three potential issues do not appear to be absolute barriers to OTC approval of lovastatin 10 milligrams.

There are two types of liver events that have been observed with lovastatin. There are asymptomatic aminotransferase elevations and there are very rare reports of bona fide, clinically-apparent liver disease.

In patients treated with lovastatin, these asymptomatic elevations in what are usually called liver enzymes, do not in fact indicate drug-induced hepatotoxicity and do not pre-stage the development of very rare reports of liver disease. Rather, these asymptomatic elevations appear to be related to the pharmacologic effect of the product.

This slide presents the mean ALT by treatment week from AFCAPS/TexCAPS. The liver responds to inhibition of HMG-CoA reductase by increasing the number of LDL receptors and the liver also has an undermined physiologic response that increases alanine aminotransferase, or ALT.

We see there is a small, clinically insignificant increase in ALT over the first six weeks of treatment with lovastatin that is maintained for the duration of treatment. This mean value remains well below the upper limit of normal in this population.

This clinically insignificant increase has been observed in other trials of lovastatin and with other statins, but the mechanism intracellularly responsible for this has not been determined.

The fact though, that this increase occurs during the same time frame as the maximum change in cholesterol metabolism indicates that the increase is probably related to the cellular decreases in cholesterol.

Now asymptomatic aminotransferase elevations have been considered to be potentially clinically significant if they are confirmed to be greater than three times the upper limit of normal.

These elevations have been observed with all the statins, with the fibrates and with niacin. With lovastatin, we have seen that these elevations generally resolve when treatment is discontinued or even if treatment is continued.

In many cases, the clinical trials show