DEPARTMENT OF HEALTH AND HUMAN SERVICES

FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE IN JOINT SESSION WITH THE ENDOCRINE AND METABOLIC DRUGS ADVISORY COMMITTEE

Volume I

Thursday, January 13, 2005

8:00 a.m.

Versailles Ballroom
Holiday Inn
8120 Wisconsin Avenue
Bethesda, Maryland

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LCDR. Hilda Scharen, M.S.,Executive Secretary

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C O N T E N T S

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. WOOD: If everyone would take their seats, we are almost ready to begin. Well, let me begin by welcoming you all to this committee to discuss over-the-counter use of Mevacor. I am going to begin by asking the committee to introduce themselves, and I guess we will start on this side, over here.

DR. RYDER: Steven Ryder, from Pfizer Research, and I am the industry representative on the Endocrine and Metabolic Advisory Committee.

DR. WOOLF: Paul Woolf, Crozer Chester Medical Center.

DR. BENOWITZ: I am Neal Benowitz, University of California, San Francisco, internal medicine, clinical pharmacology and medical toxicology, and Nonprescription Drugs Advisory Committee.

DR. CAPRIO: I am Sonia Caprio, from Yale University, pediatric endocrinologist.

DR. BLASCHKE: Terry Blaschke, clinical

pharmacology, Stanford University, on the NDAC.

DR. CARPENTER: Thomas Carpenter, pediatric endocrinology at Yale, and a member of the Endocrine and Metabolic Advisory Committee.

DR. FOLLMAN: Dean Follman, head of the statistics group at NIAID, and a member of the Endocrine and Metabolic Advisory Committee.

DR. DAVIDOFF: I am Frank Davidoff. I am an internist and Editor Emeritus of Annals of Internal Medicine. I am on NDAC.

DR. PATTEN: I am Sonia Patten. I am an anthropoligist on faculty at McAllister College in St. Paul Minnesota, and I am a consumer representative on NDAC.

DR. MCCLUNG: I am Mike McClung. I am an endocrinologist from Portland, Oregon, on the Endocrine and Metabolic Advisory Committee.

DR. CLYBURN: I am Ben Clyburn. I am an internist at Medical University of South Carolina, and I am on the Nonprescription Drugs advisory Committee.

DR. MAKRIS: Susan Makris. I am a

toxicologist with the Environmental Protection Agency, Office of Research and Development.

DR. CLAPP: Leslie Clapp, pediatrician from Buffalo, New York, a member of NDAC.

DR. SHADE: David Schade, University of Mexico Endocrine Division, and member of the Endocrine and Metabolic Advisory Committee.

DR. TAYLOR: I am Robert Taylor. I am a clinical pharmacologist and internist at Howard University, Washington, and I am a member of the Nonprescription Committee.

DR. SCHAMBELAN: I am Morris Schambelan, from the University of California in San Francisco. I am an endocrinologist and a member of the Endocrine and Metabolic Drug Committee.

DR. WOOD: Alastair Wood, I am a clinical pharmacologist from Vanderbilt.

LCDR SCHAREN: I am Hilda Scharen and I am the Executive Secretary for the Nonprescription Drugs Advisory Committee, with FDA.

DR. TINETTI: I am Mary Tinetti, from Yale University, Internal Medicine and Geriatrics, and I

am a Nonprescription Drugs Advisory Committee member.

DR. WATTS: Nelson Watts, endocrinologist at the University of Cincinnati, and member of the Endocrine and Metabolic Drugs Advisory Committee.

DR. NEILL: I am Richard Neill. I am a family physician on faculty at the University of Pennsylvania.

DR. WIERMAN: I am Maggie Wierman, endocrinologist, University of Colorado, and I am on the Endocrine and Metabolic Drug Advisory Committee.

MR. SCHULTZ: I am Jim Schultz and I am just a patient representative.

DR. SNODGRASS: I am Wayne Snodgrass, clinical pharmacology and medical toxicology and pediatrics at the University of Texas Medical Branch, on the NDAC committee.

DR. PARKS: I am Mary Parks. I am Deputy Director, Division of Metabolic and Endocrinologic Drug Products, with the FDA.

DR. MEYER: I am Bob Meyer. I am Director

of the Office of Drug Evaluation II, at the FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Deputy Director, Division of Over-the-Counter Drug Products.

DR. GANLEY: Charlie Ganley, I am the Director of Over-the-Counter Drug Products, FDA.

DR. BULL: Good morning. Jonca Bull, Director of the Office of Drug Evaluation V in the Office of New Drugs.

Conflict of Interest Statement

LCDR SCHAREN: I am going to read the conflict of interest statement. The following announcement addresses the issue of conflict of interest and is made a part of the record to preclude even the appearance of such at this meeting.

Based on the submitted agenda and all financial interests reported by the committee participants, it has been determined that all interests in firms regulated by the Center for Drug Evaluation and Research present no potential for an appearance of a conflict of interest with the

following exceptions:

In accordance with 18 USC 208(b)(3), full waivers have been granted to the following participants. Please note that the following consulting and speaking activities waived are unrelated to Mevacor and its competing products: Dr. Michael McClung for consulting for the sponsor and a competitor for which he receives less than $10,001 per year per firm; Dr. Morris Schambelan for consulting with a competitor for which he receives less than $10,001 per year; Dr. Paul Woolf for consulting with a competitor for which he receives less than $10,001 per year; Dr. Margaret Wierman for being a member of the sponsor's and a competitor's speaker's bureau for which she receives between $10,001 and $50,000 per year from the sponsor and less than $10,001 per year from the competitor; Dr. Nelson Watts for being an advisory board member for two competitors for which he receives less than $10,001 per year per firm; Dr. Neal Benowitz for consulting with a competitor for which he receives less than $10,001 per year and

his spouse's stock in the sponsor which is sponsor which is between $5,001 and $25,000 per year.

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 the Dr. Steven Ryder is participating in this meeting as a non-voting industry representative acting on behalf of regulated industry. His function at this meeting is to represent industry interest in general and not any one particular company. Dr. Ryder is employed by Pfizer.

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. Thank you.

DR. WOOD: In case any of you missed it, this is obviously an unusual meeting and I wanted to begin with summarizing some of the issues here.

We are usually asked on NDAC to consider the approval of over-the-counter products for the treatment of symptoms or diseases in patients where individual patients can identify their symptomatic problem and self-medicate to treat that problem. Now, in such a setting the patient can expect that they will derive benefit, usually symptomatic relief, from the product that should be obvious to the patient. Thus, the benefit to an individual patient should be clear, and the individual risk-benefit can be assessed both by this advisory committee and, most importantly, by the patient. So, they can ask the question how bad is my runny nose, or how bad is my headache, and does it justify the risks that are outlined on the package? The patient can also usually answer the question did this medicine help, after they have taken it

for some time.

The use of statins OTC is different. Our justified faith in their efficacy and their favorable risk-benefit profile is based on population data showing that populations who received these drugs and lowered their LDL do better than similar patients who do not. But individual patients cannot fully assess their levels of cardiovascular risk because is not a symptom, it is a statistical probability. Additionally, they cannot fully answer the question did this medicine help that we talked about earlier since they are practicing preventive medicine.

Thus, in contrast to our usual model, neither we nor the patient will ever know the individual patient who benefits from a statin, be that statin administered to them OTC or by prescription. But, of course, we always know the individual patient who suffers an adverse event. In other words, this represents a new model for OTC drug use, namely, seeking group benefit while trying to assess and, of course, minimize

individual risk.

Now, I think understanding that dynamic should be the overriding issue in our deliberations. It should inform and direct our discussions on the decision about the OTC indications and it was used by the agency in developing the questions that we will attempt to answer later.

These questions are designed to force us to discussion and to force us to come to some conclusion on whether the benefits of OTC lovastatin to the group outweigh the risk to the individual; whether individuals can identify themselves as appropriate for therapy; and, very importantly, conversely, whether we think that individuals at particular risks can be identified and excluded from therapy; whether the method of use, including all the self-screening and other techniques that we will hear exhaustively, I am sure, about later are appropriate; and, finally, whether there are additional measures that we think are required to maximize the benefit and minimize

the risk to patients from this product.

So, these are unusual issues for us to debate on NDAC where we usually address symptomatic treatments, and that is why I wanted to try and set the stage before we start.

Let's get right to the presentations. Charlie, do you want to start?

Welcome and Comments

DR. GANLEY: Before starting, I just wanted to thank the members of both advisory committees and the invited consultants for taking time out of busy schedules to participate in this two-day meeting.

I would also like to acknowledge the efforts of the review staffs and project management staffs of both the Endocrine and OTC Division for reviewing the information in a relatively short time and helping to put together this advisory committee. As always, we greatly appreciate the efforts of the advisory and consultant staff who make all the arrangements to conduct these meetings. I would also like to acknowledge the

efforts of the sponsor to respond to our questions in the review process in a very timely manner.

[Slide]

I don't think I can be as eloquent as Alastair in sort of laying out the issue here, but this is, indeed, a new model for an OTC drug. It is designed to treat an asymptomatic disease, which is not typical for OTC drugs. It requires long-term compliance to obtain a benefit. It requires laboratory monitoring for the individual to assess whether they have had a treatment effect and then some benefit from therapy. But it also requires a highly motivated individual to decide to use the product in the first place according to the product label for a long period of time.

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Now, when I think what are the hurdles for a drug coming to the OTC market, I usually divide them into two things: what are the issues related to the drug and what are the issues related to the disease? Let me just touch on the drug-related hurdles for OTC marketing.

The first is really that we have to make some determination of the assessment of the relative safety of the drug. What we mean by that

usually is what are the events that we are concerned about. Almost all drugs in the OTC market can be associated with serious adverse outcomes and generally we make efforts to try to minimize those; how often is this likely to occur, and are there measures that can be taken to help decrease this occurrence.

For the drug under review for today, there have been serious adverse events associated with therapy, particularly the possibility of serious muscle injury. There are some questions regarding what the risk is for liver injury. There also are populations that may be at increased risk for this, and can those individuals identify that they may be at increased risk and make a decision whether they want to use the product? Included in that are questions regarding underlying liver disease or individuals who have asymptomatic, undiagnosed underlying liver disease. Pregnancy or use by

women of childbearing potential is an issue, and also potential for drug interactions which could lead to a possibility of increased risk for serious muscle injury.

[Slide]

Now, the disease-related hurdles for OTC marketing are that there are multiple steps for a consume to assess their eligibility for self-selection to use the product. It requires some monitoring and knowledge of their cholesterol levels. After initiating therapy, is there some change in risk, such as the addition of a new medication, that may necessitate the individual to make a decision that they should stop the drug or talk to a physician? Most importantly I think, individuals need to understand, if they are going to use this drug, that they really need to take it for long periods of time to derive some benefit.

[Slide]

You are going to hear a lot today about consumer behavior studies. Members of the nonprescription committee, or many of them--we have

some new members today--are quite familiar with some of the terminology. We are going to make every effort, and I think Merck will probably make similar efforts, to try to describe these studies and what we tried to obtain from them.

The first type of study is a labeling comprehension study, and these are simply studies where we attempt to understand whether an individual can comprehend the information on the labeling. We use the results to adjust the labeling prior to an actual use study or prior to marketing the product. The results from these studies are not always predictive about behavior in that the consumer understands the labeling but their behavior will be different in a real-life setting.

Within the last several years we had an example of this where we were reviewing a drug that was clearly associated with significant risk of drowsiness, and there was clear warning on the label suggesting that they not drive. In the labeling comprehension study the individuals

understood this with greater than 90 percent comprehension but in the actual use study a half to three-quarters of the individuals drove anyway. I think what we lose in there is that people still have their lives and they have to go to work, or they have to pick up their children, and you don't get around that by just labeling a product all the time.

The other type of study is an actual use study. I am not going to go into great detail. I think you will hear more about this in Merck's and FDA's presentations. There are two terms you should know, one is self-selection. Self-selection is an individual making a decision whether they are going to use the product. De-selection is when an individual has already made a decision to use the product and they have to decide whether they need to stop based on a lack of efficacy or the potential for an adverse event.

[Slide]

The results of consumer behavior studies--based on literacy and education we really

cannot expect 100 percent success for all the objectives, and we do develop some hierarchy of priority in determining what are the most important things that we are trying to get across. All of us here will have different thresholds for tolerating behavior errors. Laura Shay, in this afternoon's talk, will go into that a little bit. It is really dependent on the health consequence of the error. For example, in the case of Mevacor or any other statin, if an individual develops muscle tenderness or pain in the muscles we would like them to stop. If they don't stop they risk potential for serious injury. In those situations, we would expect consumers to really understand that concept.

The other question with these types of studies is that they are not perfect studies. They are done in settings that are not totally consistent with how the OTC market works. So, sometimes it is difficult to extrapolate these data to an OTC population.

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The other thing I want to point out is

that you are going to hear a lot of different analyses today. The FDA discussion is going to focus on the "according to label criteria" and Merck will cover that in addition to multiple other analyses which I have listed here today. During the presentations I think it is very important for the committee to understand what analysis is being discussed and what the definition of that analysis is. As far as the committee is concerned, we don't expect you to remember all these acronyms but we are going to give you a quiz first thing tomorrow morning to see if you do remember them!

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Who is this product directed to? When you think about this going into the OTC market the obvious answer is it is the people with the criteria on the proposed Mevacor label, but who may actually use this? It could be any person who fits the NCEP guidelines for treatment. It could be simply people who have an interest in their health and in lowering cholesterol, folks who may eat cereal because of the potential to decrease your

cholesterol for example, or it could be the United States population.

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Other relevant information--OTC drug advertising is regulated by the FTC, not by FDA. This is important because advertising will lead consumers to look into using this product. During the course of the actual use study, when the study was advertised, there was some direction given to consumers that they could call an 800 number and they should know their cholesterol. But you can imagine, through advertising without some specific details as to what you need to know or what the risk may be, that you could include a much larger population.

The other issue is the economic implications of a switch. When considering a drug for switch, FDA does not take economic considerations into account during the decision process. This doesn't just apply to OTC drugs; it is also applicable to prescription drugs. So, the cost of the drug is not an issue and insurance

coverage is not an issue.

So, with those remarks, I think I will send it over to Dr. Parks who is going to give another introduction and give some past history and additional comments. Thanks.

Introduction, Regulatory History and Overview of Current Proposed OTC Program

DR. PARKS: Good morning, Dr. Wood, members of the advisory committee.

[Slide]

I will be presenting the regulatory history of Rx to OTC switch for lipid-lowering drugs. My presentation will also provide you an overview of previously submitted applications for nonprescription lipid-lowering drugs, including the initial Mevacor over-the-counter proposal and its deficiencies. I will provide an overview of the current Mevacor application and, finally, I will present to you areas for consideration on this current program.

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The first lipid-lowering drug proposed for

nonprescription use was a bile acid sequestrant. It was thought to be an ideal candidate for nonprescription use, at least from a safety perspective. There were two advisory committee meetings held on this application and the advisory committee members concluded otherwise.

As a result of the second 1997 advisory committee meeting, the FDA issued a guidance to industry on the over-the-counter treatment of hypercholesterolemia. That document concluded the following: that hypercholesterolemia is a chronic, asymptomatic condition requiring accurate diagnosis and testing and, therefore, this condition should remain under the directed care of a healthcare professional. In short, a recommendation was made that drug treatments for such a condition not be sold over-the-counter.

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In 1999 FDA received two applications proposing the nonprescription use of a low dose of two statins. Those statins were lovastatin and pravastatin, and their applications were presented

at two separate advisory committee meetings in July, 2000.

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The medical OTC program back then proposed the lowest dose of Mevacor for non prescription use. This dose was 10 mg. The patient population targeted included men over the age of 40 and postmenopausal women. Patients could not have a history of cardiovascular disease, diabetes or significant hypertension, and they should not be on prescription lipid-lowering thera[y. The total cholesterol targeted was 200-240 and LDL cholesterol of 130 or greater.

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The advisory committee members raised several issues in this application. For efficacy, it was noted that the sponsor did not incorporate current treatment guidelines. In particular, no treatment goals were defined for the consumer. In addition, clinical benefit could not be extrapolated from clinical outcomes data for the proposed dose of 10 mg and for the target

population. Finally, consumer comprehension was poor in this program, underscoring the complexities of treating hypercholesterolemia in the nonprescription setting.

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The safety concerns raised at that advisory committee meeting were not necessarily unique to lovastatin but are actually found for other drugs in this class. For muscle, all statins have been associated with rare cases of rhabdomyolysis. Lovastatin is metabolized by cytochrome P450 3A4 isoenzyme. This is the enzyme involved in metabolism of multiple drugs. Consequently, they were concerned that co-administration with potent 3A4 inhibitors might increase the risk of myopathy.

For hepatic concerns, all statins have been associated with increases in hepatic enzyme levels although these laboratory abnormalities rarely result in serious clinical sequelae. However, all statin labels recommend baseline liver testing and for some testing is recommended

periodically after initiation of therapy. The sponsor had to address how an over-the-counter product could be marketed when the prescription label for that product had recommendations for routine biochemical safety monitoring.

Another issue raised was that clinical studies for statins excluded patients with underlying liver abnormalities, either clinically diagnosed or chemically diagnosed. Consequently, the safety of statins in patients with undiagnosed liver disease had not been addressed.

Finally, all statins are labeled as pregnancy category X drugs. This means that the drug is contraindicated for use during pregnancy.

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Since the July, 2000 advisory committee meeting, several important events relevant to a statin over-the-counter program merit discussion. The first is that the 1997 guidance to industry was withdrawn in the year 2001 as it was apparent during the 2000 advisory committee meeting that there was potential public interest in making

available safe and effective therapies for the management of hypercholesterolemia in a nonprescription setting.

Second, and very much an integral part of the Mevacor over-the-counter program, was the 2001 publication of the National Cholesterol Education Program ATP III treatment guidelines. Recommendations made by the NCEP have established the clinical practice guidelines for managing dyslipidemia over the past two decades. These recent guidelines establish new risk categories, new goals of therapy, and were subsequently updated in July, 2004 to recommend even lower LDL treatment goals in patients with very high risk for a cardiovascular event.

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A detailed discussion of the ATP III guidelines is beyond the scope of today's presentation, but the publication of these guidelines has been provided to all members of the advisory committee in the background packages.

Relevant to this meeting is that the ATP

III guidelines establish new risk categories for the treatment of dyslipidemia. These risk categories identify the LDL cholesterol for which drug therapy should be initiated. It identifies the LDL cholesterol goal for which drug therapy should be targeting. There are essentially three categories.

The first includes patients who have established coronary heart disease or CHD risk equivalents. These are patients who have diabetes, peripheral arterial disease or clinical manifestation of atherosclerosis. These patients are at high risk for cardiovascular events. Their 10-year risk of having a cardiovascular event exceeds 20 percent.

The second category includes patients who have two or more risk factors for heart disease. The NCEP definition for risk factors includes an HDL that is less than 40, tobacco smoking, hypertension, a family history of early coronary disease and age according to gender. This category of two or more risk factors is considered

intermediate risk for heart disease.

The third category are the low risk category patients. These are patients who have no or only one risk factor for heart disease.

While the next two days we will emphasize drug therapy for hypercholesterolemia, it should be noted that the ATP III guidelines are recommendations on a background of lifestyle changes. The importance of diet, exercise and lifestyle modification cannot be emphasized enough in the management of coronary heart disease.

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In the current program to be discussed today the sponsor has proposed Mevacor nonprescription therapy to the following patient population, a primary prevention population with less than or equal to 20 percent 10-year risk of coronary-heart disease without underlying chronic conditions that would complicate consumer self-management. The product label proposes a consumer select a product according to the following: Males 45 years or older; females 55

years or older. The age cutoff for women is intended to exclude all women of childbearing potential in order to avoid inadvertent exposure in pregnancy. The LDL cholesterol should be between 130 and 170, and consumers should have at least one of the following, smoking, HDL of less than 40, family history of early coronary disease and hypertension.

The intent of this particular product label is that if a consumer can actually self-select appropriately on the first criterion, that is, age according to gender, they automatically have one risk factor for coronary-artery disease. If they then can self-select appropriately on the third criterion, that is, having at least one of the following, they will automatically have two or more risk factors for coronary heart disease. So, the summary here is that the target population is actually the two or more risk category that I described in an earlier slide based on the NCEP guidelines.

The proposed dose for a nonprescription

prescription lovastatin is a fixed daily dose of 20 mg. There is no recommendation to titrate up or down to meet treatment goals.

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The treatment goal defined in this population is an LDL less of 130, and this is in accordance with the NCEP guidelines. The NCEP does define secondary goals for therapy, for example, if a patient has hypertriglyceceridemia then non-HDL might be a second goal of therapy. This was not incorporated into the program, however, it was recognized that patients would need to actually have fasting lipid profiles to follow this, and it is also very complicated for consumers to understand secondary goals of therapy.

In order for consumers to actually follow current treatment guidelines, this proposal requires that they know the following things: Consumers need to know their baseline cholesterol values, and they need to know their cholesterol values while they remain on therapy. Consumers also need to know their baseline risk and changes

in health status that might alter the risk-benefit ratio of continuing lovastatin 20 mg.

[Slide]

You will hear from the sponsor momentarily how their clinical program addresses the deficiencies noted in the July, 2000 advisory committee meeting. For efficacy, the sponsor has summarized the LDL-lowering results of two previously submitted clinical studies, EXCEL and AFCAPS. They also summarized LDL-lowering results from the actual use study submitted specifically for this NDA. Based on these results, one can expect on average a 24 percent reduction in LDL cholesterol with the lovastatin 20 mg dose.

The clinical benefits of lovastatin 20 mg were extrapolated from the AFCAPS study. This was a 5-year placebo-controlled outcome study evaluating lovastatin 20-40 mg daily, and the primary endpoint was a composite of unstable angina, nonfatal MI and coronary-heart disease death.

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For safety, the sponsor approached these issues by re-evaluating the EXCEL and AFCAPS database. These two studies provided lovastatin

exposure data from close to 10,000 patients. The sponsor also evaluated their global post-marketing safety database from marketing until present. This is approximately 17 years worth of marketing, providing approximately 27 million patient-years of exposure. Although not on this slide, the sponsor has also reviewed clinical trial safety data for a similar statin, simvastatin.

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The conclusions from these databases, at least for muscle and liver safety concerns, are the following: The risk of myopathy and rhabdomyolysis is extremely low; that the 20 mg dose, if labeled adequately and understood by the consumer, is an acceptable dose for over-the-counter use. There is little to no hepatic risk in patients with normal hepatic function.

The safety of lovastatin in patients with asymptomatic liver disease, including viral

hepatitis, was not addressed in well-designed prospective studies. However, the sponsor has submitted an abstract of a study in approximately 40 patients and a retrospective study using lovastatin and other statins in patients with baseline elevations in liver enzymes. The results of these studies and the rationale from the sponsor as to why these data are sufficient to remove any recommendation for liver monitoring in a nonprescription setting will be presented by the sponsor.

Given the small number of patients evaluated in one study, the retrospective nature of the other and the exclusion of patients with certain liver diseases in that study, the FDA finds these data problematic and difficult to conclude that patients with any form of asymptomatic liver disease can initiate lovastatin without periodic monitoring, at least based on these data submitted.

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With respect to pregnancy safety issues, preclinical studies were conducted and reviewed

under the prescription NDA. You will hear from Dr. Karen Davis-Bruno the FDA's conclusion on preclinical studies submitted to that NDA. This product will retain its category X labeling based on the following: First, the FDA's interpretation of these data and, second, based on agreement or an understanding between the FDA and the sponsor that the risk of continuing therapy with lovastatin during pregnancy outweighs any benefit and the drug should, therefore, remain contraindicated for use during pregnancy.

A greater concern is the use of lovastatin in women of childbearing potential who may subsequently become pregnant while on therapy. Dr. Davis-Bruno's presentation is to provide the advisory committee members with background information to assess whether the risk of inadvertent exposure during the first trimester of pregnancy has been adequately addressed. This is particularly relevant as you hear the results of the actual use study presented by Dr. Daiva Shetty and the ability of women of childbearing potential

to make appropriate decisions on the purchase and use of this product.

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Over the course of the day and a half, we ask that you give consideration to the following: A critical outcome study of nonprescription lovastatin use is not practical, and an analysis of AFCAPS/TexCAPS does represent the best available data to date for some estimate of clinical benefit associated with over-the-counter lovastatin 20 mg.

However, several caveats of extrapolating from this database must be kept in mind. The first is that this was a post hoc analysis and that some of the comparisons no longer maintain the comparison of randomized treatment groups. None of the subgroups elected by the sponsor fully reflect the over-the-counter population as AFCAPS included patients who were titrated to 40 mg and were also treated to a lower LDL cholesterol goal. Finally, long-term benefit observed with AFCAPS assumes adherence to therapy in the over-the-counter setting.

We must also remember that over time changes in individuals' health status may occur. These changes may result in a change in the risk

classification for a patient such that more aggressive therapy is needed than what lovastatin 20 mg might achieve.

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Many of the safety issues will be addressed primarily through labeling, and the effectiveness of this approach is evaluated in one six-month actual use study. Similar to the efficacy concerns, the impact of changes in health status and the use of interacting drugs on the safety of lovastatin over-the-counter must be considered, particularly in the long term. This concludes my presentation. Thank you.

DR. WOOD: Thank you very much. Let's move straight on to Dr. Hemwall's presentation from the sponsor.

Sponsor Presentation

Introduction

DR. HEMWALL: Advisory committee members,

guests, FDA staff, I am Ed Hemwall, representing Merck Research Labs and Johnson & Johnson-Merck Consumer Pharmaceuticals.

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Today we will be discussing our new drug application for nonprescription lovastatin at a dose of 20 mg a day, with the proposed trade name of Mevacor Daily, however, throughout today's discussions and in your written background it is referred to as Mevacor OTC. The indication we are proposing for the OTC label is to help lower LDL "bad" cholesterol, which may prevent a first heart attack.

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As Drs. Ganley and Wood have noted, the concept of an OTC lipid-lowering drug and the accompanying self-management system that we propose represents an unparalleled challenge to the consumer in the OTC world. But it also represents an unparalleled opportunity to have an impact on an important public health problem in the United States.

Your predecessors on these committees reviewed an earlier version of this proposal, as described by Dr. Parks, for the 10 mg dose, in

2000, and they concluded that the benefit of the 10 mg dose was not sufficiently established with regard to cardiovascular risk reduction and, although the safety in an OTC setting was generally accepted, there remained many questions, which Dr. Parks has noted and which we are prepared to address today.

Finally, the ability of the consumer to appropriately self-diagnose and use the product required further investigation and that is the cornerstone of our submission to be discussed today, the CUSTOM study.

So, as noted, a few weeks after the last meeting in 2000, in part motivated by those discussions, FDA did lift the negative guidance which discouraged development of cholesterol-lowering drugs for over-the-counter use and this opened the door for a series of constructive interactions between FDA and J&J-Merck

for approving the OTC labeling approach and the designs and the objectives of additional consumer research studies, which we have done, and we are very appreciative of the guidance we have received.

[Slide]

Since that time, our development team has conducted extensive research to establish and test an improved approach to OTC cholesterol management. We have had input from the Food and Drug Administration and outside academic experts in the field of lipid management and primary prevention of cardiovascular disease. We have increased the proposed dose to 20 mg and instituted a treatment to the LDL cholesterol goal approach for our primary prevention target population that is consistent with the most current clinical guidelines established by the National Cholesterol Education Program.

We conducted a sophisticated actual use study, called CUSTOM, in which over 3000 consumers evaluated this OTC option in a naturalistic OTC setting, and over 1000 consumers elected to

purchase and use the product for up to 6 months. All this was part of a comprehensive consumer education and support program which we will review with you today.

[Slide]

The overriding question which you have been asked to contemplate today is can an OTC option enable consumers to have a greater role in the prevention of cardiovascular disease? In order to address the question we will examine the OTC target population and the labeling eligibility criteria which allow approximation of that population. We will look at the role of the Mevacor self-management system and, importantly, the role of the healthcare professional in directing and encouraging achievement of cholesterol goals and heart-healthy behaviors through a collaborative care approach. Also, the ability of consumers to act in general accordance with the label. The criteria that are on the label are intended to maximize both benefit and safety in the OTC environment. And, we will look at the

overall benefit-risk relationship for the individual and, more importantly, for the population at large.

[Slide]

Our presentation today will be that following my brief remarks Dr. Richard Pasternak will discuss the rationale for OTC availability of a statin drug in this target population and he will include an overview of efficacy and safety of lovastatin. Then, Jerry Hansen will provide some insights generated from our extensive consumer research and the development of the OTC self-management system, which is on display over there and I invite members of the committee, during the breaks, to take a look at it and also some of these exact same materials are in your briefing documents. After Jerry, we will have Bob Tipping who will review the results of our actual use studies, with principal focus on the CUSTOM study which tested the key elements of the self-management system. Finally, Dr. Jerry Cohen will complete our presentation with the perspective

of a preventive cardiologist, and the potential public health impact of increased access to a statin in a consumer-friendly lipid management system.

[Slide]

The following slides outline our consultants whom we have here with us, with expertise in several topics, who are here today to provide additional perspective on some of the questions which may arise during your deliberations over the next two days. Rather than read through the entire list of names, we have provided a complete list of these experts, in handouts printed on yellow paper, at your seats.

So, that concludes my introduction. I would now like to introduce Dr. Richard Pasternak. Dr. Pasternak is a former member of the National Cholesterol Education Program guidelines panel and co-author of several associated publications, and we are really proud to have him now as part of our Merck clinical research team. He will review the rationale behind over-the-counter Mevacor.

Rationale for OTC Lovastatin

DR. PASTERNAK: Thanks, Ed.

[Slide]

Good morning, ladies and gentlemen, members of both panels, the FDA and guests. I am Richard Pasternak. Prior to joining Merck this past September, I spent 22 years at Harvard Medical School in cardiology and preventive cardiology and that provided me with the kind of opportunities and privileges to participate in some of the activities that Ed Hemwall just mentioned.

[Slide]

Given my own strong and long-term interest in preventing heart disease, I am delighted to be here today to share with you the rationale for consumer access to an over-the-counter statin option. I believe that Mevacor OTC can further our current efforts in cardiovascular treatment through improved collaboration between healthcare professionals and the consumer, resulting in a potentially significant expansion of prevention of heart disease in America. I recognize that this

is, as Dr. Wood pointed out in his opening remarks, a very novel pathway that is being proposed and that there a number of important and very tricky issues to consider in the next two days. But, by the end, I hope that when you look at the strength and weight of the evidence you will agree that the benefit and risk arithmetic strongly favors an option for consumers to have access to OTC Mevacor.

The rationale I plan to review today is compelling and straightforward. It begins with the problem, the enormity of the current cardiovascular public health burden in the United States today in which huge treatment gaps continue to exist. Next, I will outline the proposed Mevacor OTC target population and the well-known product efficacy and safety information of lovastatin 20 mg. Finally, I will conclude by discussing the potential for Mevacor OTC to actually improve public cardiovascular health, both directly and indirectly, through increased consumer awareness action.

[Slide]

The problem is clear and known to everyone in this room. Cardiovascular disease is the number one cause of death and disability in the United

States today. If something is not done it will continue to be our greatest health problem. The annual number of coronary heart disease events is over a million per year, with an accompanying enormous economic impact.

As shown in the graph at the bottom of this slide, with our aging population our situation is only going to continue to worsen. In fact, with our current system it is projected that over the next 50 years the incidence of coronary heart disease will double to nearly 30 million.

[Slide]

It is well-known that reducing cholesterol is one of the most important actions that we can undertake to reduce the risk of heart disease, and I could have chosen a number of different figures to illustrate this but I have taken this figure from our ATP III update which depicts a log linear relationship between LDL cholesterol and the

relative risk of coronary heart disease. There is a well-known and well-accepted relationship between lowering LDL and risk reduction, such that for each one milligram/deciliter change in LDL cholesterol there is roughly a one percent change in risk. New information now also tells that the lower the LDL cholesterol, the lower the relative risk even down to levels below 70 mg/dL.

[Slide]

So, are we making progress in battling this disease? Well, despite our knowledge of the importance of cholesterol reduction, we have not been very successful at the population level. In fact, over 15 years of advances in treatment strategies and guidelines we have produced really minimal, if any, movement in the average total cholesterol in the United States population. Our national public health goals, as outlined in Healthy People 2000, have not even met a relatively modest goal. And, current data suggests that the relatively unambitious goal for Healthy People 2010 is also in jeopardy.

[Slide]

Why? Well, there are many reasons for this problem. One of the major reasons is that

there are minimum number of individuals actually being treated with cholesterol-lowering therapy. In 2000, the NHANES data showed us that while we were doing a pretty good job of getting individuals tested for their cholesterol, in fact less than a third to a fifth of people with elevated cholesterol levels were actually treated, and here I don't mean treatment with drug therapy only; this is treatment with either diet or drug therapy. This isn't due to lack of available therapy or insufficiently aggressive guidelines.

[Slide]

In fact, our guidelines recommend that a great number of individuals should, in fact, be treated. This figure shows estimates of the number of Americans recommended for treatment by the ATP III guidelines. Roughly 25 million people are at high risk or already have heart disease and are in need of secondary prevention therapy. There are

also roughly 11-18 million individuals at moderate risk in need of primary prevention.

[Slide]

Today, less than half the people who adverse event in the high risk group are actually being treated, representing a major gap. More importantly however for our discussions here, an even smaller number of people who are at moderate risk are actually being treated, with an estimated 60-70 percent treatment gap.

[Slide]

Most of the focus of prescription therapy has been, and this is appropriate, for the secondary prevention group. We certainly propose that that continues. So, what we do propose today is for you to consider the addition of an OTC statin option to help increase appropriate treatment in the moderate risk primary prevention group, a group, according to the ATP III guidelines, in need of more and specific attention.

[Slide]

Now that we understand the problem and

have identified a group in which an OTC option might play a positive role, it is important to clearly define a target population that is, one, consistent with the NCEP guidelines and that, two, can benefit from over-the-counter statin use.

[Slide]

You have already heard a brief outline of this from Dr. Parks and time doesn't permit me to go through ATP III guidelines in detail. You do have this in your background package. But for those of you not familiar with the format of the ATP guideline, let me take a moment to walk through the layout.

The horizontal rows here are organized around four designated risk groups. In fact, the moderate risk group that Dr. Parks referred to is really divided into two. Each column then lists the specific LDL goal; the level of LDL at which therapeutic lifestyle change is recommended for initiation; and the level at which drug therapy should be considered for initiation in each of the four risk groups.

In keeping with the guidelines, we are proposing the primary target of OTC should be those at moderately high risk, with two risk factors and

a 10-20 percent 1-year Framingham risk with LDL levels greater than 130, thus, qualifying for drug therapy.

In addition, however, we believe it is appropriate to consider OTC treatment for the group listed as moderate here. In fact, when we on the NCEP panel recognized the benefit of this group, the cutoff level for consideration for drug therapy was driven, in large part, by pharmacoeconomic considerations. Throughout our presentations today we will refer to the proposed OTC target collectively as the moderate risk population.

[Slide]

It is important to understand how this is actually approached in an OTC label. In consultation with the FDA, we considered and found it impractical to have consumers actually calculate their Framingham 10-year coronary heart disease risk score, something, unfortunately, most doctors

don't even do. Therefore, our OTC label approach utilizes a surrogate for the Framingham calculation. The OTC label includes people with elevated LDL cholesterol above 130 who have two risk factors, such as age or family history, and also includes the NCEP treatment goal of LDL less than 130.

It is important to point out that the proposed OTC label directs treatment within the context of a comprehensive cholesterol management approach, not just drug therapy. Consumers are encouraged to include lifestyle changes such as diet and exercise before and during use of the product. The Mevacor OTC program also includes a comprehensive self-management system to reinforce these lifestyle changes. Most importantly, the OTC system was designed not to be solely reliant on self-care. At the center of the OTC system, as you will see, there is a collaborative care approach taken that encourages healthcare professional interaction throughout.

[Slide]

The most critical element of OTC consideration is the proven efficacy and safety of lovastatin 20 mg. Statins as a class have a

long-standing and, as you have heard, well-documented history of efficacy and safety. Literally hundreds of thousands of patients have been studied in controlled clinical trials, and hundreds of millions of patient treatment years have been accumulated in the more than 17 years since these products have been on the market.

[Slide]

The accepted efficacy and safety of this class was summarized in a joint statement issued on behalf of the American College of Cardiology, American Heart Association and National Heart, Lung and Blood Institute, in which I was privileged to participate. I won't read the statement in its entirety but the key point is that statins, as a class, have clearly proven benefit and are extremely safe, with a low frequency of adverse events in comparison to the very large number of patients receiving these drugs.

[Slide]

This slide illustrates the depth and breadth of clinical trial experience with statins across all risk groups from the very high secondary prevention at the top of this pyramid where individuals in the trial had an over 50 percent

10-year risk of heart attack or cardiac death, down to the bottom of the pyramid, the large primary prevention base that was studied in the landmark AFCAPS/TexCAPS trial, a trial which showed benefit of lovastatin in a patient population all the way down to roughly a 6 percent 10-year risk of MI or cardiac death.

[Slide]

Importantly, these studies showed that regardless of the population studied in concomitant risk, there was a significant and similar magnitude of relative risk reduction from 25 to 50 percent in all these studies.

[Slide]

Similarly, other endpoint studies have also shown that significant relative risk reduction

is also achieved across different levels of baseline LDL, and I have applied some of the trial data to the earlier slide that I used. In fact, with the addition of data from the Heart Protection Study, which was analyzed after ATP III in 2001, we see that relative risk reduction and, therefore, treatment benefit occurs at LDL levels below the 2001 ATP III cutoffs for considering drug therapy. HPS was, in fact, one of the trials that led to the 2004 update.

[Slide]

Turning to lovastatin specifically, there is a well documented benefit. There are two major mega-trials that include over 15,000 patients, as you have heard. The EXCEL study was a 48-week efficacy and safety study with up to 80 mg daily of lovastatin. The AFCAPS was a 5-year outcomes trial studying lovastatin 20-40 mg in a primary prevention OTC-like population. At 20 mg LDL reduction is in the range of 20-25 percent; HDL increases of 6 percent and concomitant total cholesterol decreases were seen. Importantly in

the AFCAPS trial, a 37 percent reduction in a first coronary event was seen in this moderate risk population study.

[Slide]

Here the AFCAPS data is displayed with respect to its primary endpoint in a relative risk plot. The first line here represents the total AFCAPS cohort demonstrating the 37 percent risk reduction that I just mentioned. Although, as was pointed out by Dr. Parks, direct measurement of a benefit in an OTC target population is not possible, we are able to at least look at subsets of AFCAPS that allow an estimation or approximation of how risk reduction in an OTC population might look.

[Slide]

This next group is such a subgroup. It is a subset of the total cohort which achieved the OTC goal of less than 130 mg/dL and, again, a similar degree of risk reduction is seen.

[Slide]

Seen here is the subset within AFCAPS in

this post hoc analysis that strictly meets the proposed OTC label eligibility criteria and received only 20 mg of lovastatin throughout the five years. Of course, the confidence intervals are broader because the population is smaller. But it seems clear that there is a similar risk reduction that is achieved with 20 mg of lovastatin in the OTC eligible population as in the entire cohort. There are homogeneous results across these different subgroups.

[Slide]

Given the proven efficacy of lovastatin, let's turn our attention to the critical discussion of the safety of lovastatin. As the first approved statin in 1987, lovastatin does have extensive in-market safety experience with, as has been mentioned, 17 years of data for a total of more than 27 million patient treatment years.

The clinical data to support safety again includes AFCAPS and EXCEL with daily doses from 20-80 mg. You will see that there is a wide safety margin for lovastatin 20 mg with safety data up to

40 mg comparable to placebo.

[Slide]

Let's examine the potential concerns, first looking at the liver. Lovastatin is generally safe regarding the liver. We do recognize that currently all statin labels suggest baseline and most suggest periodic LFT monitoring. Our current knowledge regarding liver safety, however, has evolved. We know that asymptomatic moderate elevations of liver enzymes are seen with all statins and, in fact, are seen with virtually every lipid-lowering agent. The elevations are dose and potency dependent. They are often transient and resolve with continuing therapy. Importantly, there has been no demonstrated association or causality with permanent liver disease with statins.

As you have seen in the background package, we believe that liver enzyme testing is not necessary and is, therefore, not being proposed for the 20 mg dose in the OTC label-defined population. We are clearly prepared to address any

questions from the committee and have experts available to respond to this important issue.

[Slide]

Looking at the lovastatin clinical data, this table examines cases of consecutive ALT elevations exceeding three times the upper limit of normal. As you can see, LFT abnormalities by this definition with lovastatin 20 mg are exceedingly rare in both the EXCEL and the AFCAPS trial, and at 20 mg not statistically significantly different from what was seen in the placebo groups.

[Slide]

To analyze the potential safety concerns outside of the clinical trials environment in the marketplace, we refer to Merck's worldwide adverse experience system. The WAES database is comprised of spontaneous reports of adverse events in a post-marketing experience. It is voluntary reporting system. Reports are often incomplete and dependent on the terminology of the reporter and are not by case definitions. It includes all reports independent of perceived causality. Of

course, because of the way the data is collected, it can't provide incidence rates.

[Slide]

From this data set we can see that, as expected, the number of WAES reports of acute liver failure associated with lovastatin is very low. During the more than 27 million patient treatment years there have been only 25 reported cases of acute liver failure and upon outside expert review none of these cases could be clearly attributed to lovastatin.

[Slide]

Turning to muscle safety, while muscle pain symptoms do occur occasionally, actual muscle toxicity is extremely rare with low-dose statins. It occurs with all statins and fibrates, and it occurs particularly when these two are combined. Since muscle pain symptoms usually occur prior to actual muscle toxicity, this potential side effect is often recognizable by the patients. Patients recover when the drug is stopped and progression to rhabdomyolysis is rarely seen at any dose.

[Slide]

Going back to EXCEL and AFCAPS data, this table displays the frequency of CPK elevations

greater than 10 times the upper limit of normal. Again, we do not see statistically significant differences between placebo and lovastatin in either the 20 mg or the 40 mg doses. Both EXCEL and AFCAPS show low numbers and a very low rate.

[Slide]

While the definition of myopathy and rhabdomyolysis is evolving and sometimes confusing because it is used differently in different settings, using the definition shown here in these studies, there is additional data that with low doses there is no evidence of an increased risk of rhabdomyolysis. Across both trials there was a total of three reported cases of rhabdomyolysis for both 20 mg and 40 mg of lovastatin, one in the lovastatin-treated group and two in the placebo group. The one case with lovastatin in AFCAPS occurred post surgically in a patient being treated for prostate cancer. The patient had been taken

off lovastatin before surgery.

[Slide]

Post-marketing experience also shows the rarity of rhabdomyolysis directly related to low-dose lovastatin. Again, out of 27 million patient treatment years with lovastatin, there have been a total of 336 spontaneous reports of rhabdomyolysis. This equates to a reporting rate of approximately 1/100,000 patient treatment years, and 158 of these reports occurred without the use of a potentially interacting drug, and while not all reports indicate dose, 41 of the events were reported to have occurred with lovastatin 20 mg.

[Slide]

As previously stated, the potential for muscle concerns does increase when lovastatin is used in combination with certain potentially interacting drugs. Therefore, the OTC label takes a conservative approach by instructing consumers to talk to a doctor or a pharmacist if they are taking any prescription medication, listing potentially interacting drugs on the package insert and in

corresponding educational materials. With regard to these potential drug interactions, strong CYP3A4 inhibitors can increase plasma levels of certain statins and their active metabolites. But a key question for you to consider is whether this increase translates into comparable increases in symptomatic myopathy at the proposed OTC dose.

[Slide]

The AFCAPS trial, interestingly, actually helps us address this concern since the study was conducted before we knew details of the potential concerns with 3A4 inhibitors and co-administration in AFCAPS was actually allowed. Even in this kind of worse-case example we see similar numbers between groups for musculoskeletal adverse events, defined either broadly or narrowly, when we compare lovastatin-treated patients and placebo patients. Thus, while co-administration of a CYP3A4 inhibitor may increase the relative risk of adverse events the absolute risk appears to remain extremely low.

[Slide]

From the spontaneous reports WAES database

we see that there have been 178 reports of rhabdomyolysis with interacting drugs. Since cases of co-administration with fibrates, in this case 96 of these 97 were gemfibrizole and cyclosporine, are likely to be patients for conditions already under the care of a physician this concern for OTC usage is primarily with niacin and strong CYP3A4 inhibitors. There are 34 reports of rhabdomyolysis with niacin and 28 reports with strong CYP3A4 inhibitors. Approximately two-thirds of these cases include dose information and only 29 of the total of 178 were reported with the 20 mg use. Therefore, the data supports the conclusion that the clinical consequences of drug interactions with lovastatin 20 mg are unlikely given the strong clinical trial evidence, given the extensive in-market use over the last 17 years, and given the OTC labeling instructions that, as you will see, are effective in guiding consumers away from concomitant usage of potentially interacting drugs.

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Also regarding safety, as detailed in your

background package, there is the regulatory pregnancy labeling category for prescription lovastatin. This has already been noted by Dr. Parks. Since their initial approval, all statins have been designated pregnancy category X. This original classification was due to the non-specific findings in animals observed at many multiples of the therapeutic dose. Against this background, since there is no benefit to treat women with elevated lipids during the relatively short period of pregnancy, all statins have been assigned the category X labeling to contraindicate use in pregnancy. Even though there has been no clear signal from animal or human data, the proposed Mevacor OTC label contains strict warnings of "do not use if you are pregnant or breast feeding." There is data supporting the safety of lovastatin in pregnancy and we are fully prepared to address any questions from the committee and have experts available to provide the proper perspective on this important topic.

[Slide]

Therefore with respect to both efficacy and safety, lovastatin has a very strong product profile in support of OTC use. There is

significant benefit that has been demonstrated for the proposed OTC population on drug, clearly, both in terms of cholesterol-lowering efficacy and in terms of CHD risk reduction. Lovastatin has a very large safety database demonstrating a wide margin of safety at the proposed OTC dose. Potential risks will be further minimized by effective consumer-friendly labeling and education.

[Slide]

So, even though there is an appropriate target population in need of treatment and a positive product profile, is there really a consumer need for an OTC statin option--a question you will need to consider carefully? Our research tells us that there is demand for an OTC option. In the survey carried out this past year by the National Lipid Association, the details of which are also in your background package, they found that compared to five years ago the majority of

consumers are now making more health decisions on their own and, importantly, 72 percent of cholesterol concerned consumers surveyed said they were interested in learning more about an OTC statin option.

In another survey from the National Consumer League, three out of four consumers at moderate risk and not taking prescription therapy said they prefer an OTC option for health prevention.

Further proof of this interest can be seen by the fact that consumers already purchase more than a billion dollars worth of heart health OTC products yearly. That includes everything from supplements like garlic and vitamin E to foods that claim heart-healthy effects, such as oatmeal and orange juice.

Finally, as many of you in this room know, earlier this year the U.K. approved nonprescription Zocor, simvastatin, 20 mg for over-the-counter consumer use.

[Slide]

Finally, let's consider how this OTC option can help address the public cardiovascular health problem that I outlined for you at the

beginning of my presentation.

[Slide]

Looking at the distribution of total cholesterol among the U.S. population aged 45 and greater, we see that, like many biologic functions, there is a bell-shaped curve. Unfortunately, the peak of this curve is hovering around an elevated level clearly greater than the desired cholesterol level delineated by ATP III.

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What we are suggesting is that the Mevacor OTC option provides us with a unique opportunity to have an increased focus and consumer involvement in a comprehensive cholesterol management program that is ideally capable of achieving a leftward shift of this curve, in fact, a targeted population approach to CHD prevention.

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To conclude, today we have seen that there

is an enormous and growing cardiovascular public health problem that has not been adequately addressed. A key concern is the large moderate risk population which deserves preventive treatment but is achieving relatively little focus from our current medical system. We believe that the weight of the evidence indicates that this problem can be improved with Mevacor OTC, a drug that has proven to be appropriate for OTC from both efficacy and safety standpoints. There is clearly strong consumer interest in this OTC option, giving us the potential to greatly improve public cardiovascular health.

[Slide]

The key question that remains is can a consumer appropriately use Mevacor OTC in an OTC setting? The remainder of the presentation today will focus on that important question and I would like to now turn the podium over to Mr. Jerry Hansen, Vice President of New Product Development and Consumer Research, to begin the discussion. Thanks very much for your attention.

Mevacor OTC Self-Management System

MR. HANSEN: Good morning.

[Slide]

Today I will be reviewing the Mevacor OTC label and self-management system. It is important to note that the exact label and system I will be discussing were fully tested in the CUSTOM use trial which is why it is important to review them prior to the presentation of the CUSTOM data.

[Slide]

As was stated, the key issue today is whether consumers can play a greater role in cholesterol management. To that end, we have studied over 34,000 consumers over a number of years in the following areas, consumer understanding, including attitude and behavior; label development and comprehension; development of the self-management system; and the actual use studies. I will discuss the first three areas and Bob Tipping will follow me with a review of the use studies focusing on the CUSTOM use trial.

[Slide]

Our first step in developing the label and system was to gain an in-depth understanding of consumers who are likely to take action as a result of the OTC availability. The demographics of those interested is fairly representative of the U.S. population. They are older, which is consistent

with the proposed label, but income, race and education levels are very similar to U.S. averages. What is most interesting is that while demographics are representative, their attitudes and behaviors regarding their health are very different.

[Slide]

These people are extremely active in their own health care and believe in the idea of preventing disease. They are more likely than the general population to be knowledgeable on health issues; to diet and exercise; to take aspirin for heart health; and to take vitamins and supplements.

[Slide]

Despite their high involvement in their own care, they also have strong relationships with their doctors. Over 80 percent see their doctor at

least once a year. Over 70 percent have had a cholesterol test in the past year, and about 80 percent have discussed cholesterol with their doctor. A good way to characterize those interested is that they are motivated, health conscious consumers.

[Slide]

So, with this high involvement in their health care and their doctor, why not prescription therapy versus OTC? Well, an important finding is that these people have a general reluctance to prescription therapy and prefer instead to make lifestyle changes or to use OTC medicines.

[Slide]

Good evidence of this as it directly relates to OTC statins comes from a recent study conducted by the National Consumer League. The sample included people at moderate risk for coronary heart disease but who were currently untreated with statin therapy. This chart shows that there is a strong preference and greater likelihood of action with OTC. This group is three

times more likely to consider taking an OTC, recommending it to a family member or friend, and seeking more information about it than a prescription.

[Slide]

This slide outlines the reasons why the same population prefers OTC. On this graph the OTC preference is in yellow and the preference for Rx is in blue. This preference is driven both by practical reasons, such as better convenience because it is easier to buy and easier to keep taking every day but, more important, provides further attitudinal insights. When asked to describe a cholesterol prescription user versus an OTC user, they generally feel that a prescription is for someone who is sick and that an OTC is for someone who is healthy like themselves.

[Slide]

So, incorporating this consumer learning, we designed the Mevacor OTC self-management system to be far more than just a pill in a box. So, the label and support program we have developed through

rigorous testing over several years offers support and education that is unprecedented for an OTC product. The process we employed included designing a program that is consistent with treatment guidelines but is also understandable by consumers. We incorporated iterative consumer feedback from those likely to use, and then developed language and multiple tools to ensure we effectively communicated key messages. Finally, the program offers a comprehensive approach to clinical management, including addressing lifestyle changes such as diet and exercise.

[Slide]

Healthcare professionals play an important role in consumers' OTC decision process. Data shows that for any OTC product, for no matter how long it has been on the market, consumers usually consult a healthcare professional before using it. Nearly 80 percent of consumers say that a doctor's recommendation is very important in their decision about whether or not to purchase an OTC for the first time, and 64 percent say a pharmacist's

recommendation is very important. It is not surprising then that most consumers interested in Mevacor OTC will do so in partnership with their healthcare professional. In fact, over 80 percent claim they will talk to their doctor before using. A key element of our program, therefore, is to facilitate and encourage this interaction.

[Slide]

Because the package label is at the core of Mevacor OTC, our first step was to create a label that effectively communicates. The label and support materials are in your background for your review and, as Ed stated, the entire system is over there, at the side of the room, that you can review during breaks.

The key label messages include an OTC target consistent with NCEP guidelines. This was approximated on the label by targeting those with an LDL between 130 and 170. It is also for men 45 years and older and women 55 years and older. And, the user should also have one additional risk factor. These include positive family history,

smoking, low HDL and high blood pressure.

[Slide]

People who have liver disease, are pregnant or breast feeding, or allergic to lovastatin should not use the product. There are also strong messages for those at higher CHD risk to not use and to see their doctor about possible prescription therapy. Finally, there are clear safety warnings about potential drug interactions and muscle pain.

[Slide]

Again, taking a comprehensive approach to cholesterol management, the label instructions include encouraging lifestyle changes and cholesterol testing. Before using you must have tried diet and exercise to reduce your cholesterol, and had a fasting cholesterol test within the past year. Users are also instructed to test their cholesterol at six weeks to see if they reach goal. If they do, they should keep taking Mevacor OTC daily, test at least once a year and continue to diet and exercise.

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As stated earlier, we believe Mevacor is not purely self-care but a collaborative

partnership with healthcare professionals. So, the label strongly encourages this interaction by telling users to consult with their doctor or their pharmacist if they have any questions. Examples include that if someone does not reach their LDL goal they should talk to their doctor because OTC may not be enough for them. They should also talk to their doctor if there is any change in their health, and talk to their doctor or pharmacist if they start any new prescription therapy.

[Slide]

Label comprehension testing was conducted to ensure clear communication. The methodology included testing in a representative sample and in low literacy and ethnic subgroups. Again, the label used was the identical label used in the CUSTOM trial. The study employed both correct and correct/acceptable scoring, with acceptable generally referring to checking with the doctor.

[Slide]

The full results of the label comprehension studies will be presented by FDA but, in summary, the label results were very strong, with over 80 percent or more correct/acceptable for most measures and 90 percent or more

correct/acceptable for key safety messages. The label, therefore, is very effective at communicating key messages across all groups and also effectively communicates that consumers should ask their healthcare professional if they have any questions.

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So, once we had a clear understanding of the potential users and had developed an effective label, we went on to develop the Mevacor self-management system. The goal of the system was to provide additional information and tools to reinforce key label messages and to emphasize lifestyle changes. In developing the system we incorporated feedback from external experts, including professional organizations, key opinion

leaders and consumer behavior specialists. We learned that consumers like to receive information in different ways so we offer multiple methods of delivering information to appeal to these different learning styles. Importantly, all elements of the system are part of our proposed NDA labeling and, therefore, will be required in the marketplace. Like the label, the system I will describe was also fully tested in the CUSTOM study.

[Slide]

In the CUSTOM study the self-management includes three major health components, pre-purchase, in-store and post-purchase. But importantly, the program strongly encourages healthcare interaction through first looking at pre-purchase assistance.

[Slide]

The most common way that the consumer will learn about Mevacor OTC is through advertising. In this advertising there will be extensive communication and education, including the importance of knowing your cholesterol numbers and

highlighting that OTC is not right for everybody. To help consumers determine if it is right for them the program will offer eligibility assistance by directing them to their doctor or pharmacist if they have any questions. It also offers access to trained product specialists who will be available, toll-free, to answer questions about Mevacor and related services such as cholesterol testing.

[Slide]

The next step a consumer is likely to take is to visit a store to learn a little more about the product. So, let's review the in-store assistance we will provide. In-store assistance includes extensive support in the pharmacy. Importantly, we are proposing that Mevacor be sold as a pharmacy care OTC. To support this, we will be providing extensive pharmacist and staff training. We will also provide enhanced retail communication including interactive tools that will support the label.

[Slide]

I will now talk about each of these in

more detail. Pharmacy care OTC is a new approach developed by the American Pharmacists Association and other key pharmacy groups. The goal here is to provide expanded support for more novel Rx to OTC switches by facilitating greater interaction between pharmacists and consumers.

The features include that manufacturers will voluntarily distribute the product only in stores with a pharmacy; that it be available on the open shelf with current OTC products and not behind the counter; that pharmacist intervention is not required but strongly encouraged; and there is an expansion of supportive services such as cholesterol testing and counseling.

[Slide]

As I stated, we will be providing unprecedented in-store education and support for Mevacor OTC. Here is an example of a novel store shelf device we have developed and tested. It highlights two decision processes including information for first-time buyers primarily, should you take it, and repeat buyers, with messages

regarding getting to goal. It also offers extra tools such as tear-pads and eligibility wheels. These directly support the label but allow people to answer questions in a more interactive way. Finally, the shelf communication strongly encourages dialogue with the pharmacist which further supports the concept of pharmacy care OTC.

[Slide]

Now we will review post-purchase assistance. This includes programs and tools to support the consumer after they purchase the product and take it to their home.

[Slide]

Post-purchase assistance includes materials in the package, including an educational brochure; package insert Q&A; a quick start guide; and incentives for cholesterol testing.

[Slide]

Regarding cholesterol testing, this is a very important component of the Mevacor OTC system. Our toll-free number and our website offer assistance on obtaining cholesterol numbers and

where to get tested. We will also be offering in each box a high value coupon toward the six-week cholesterol test.

We have learned that doctor-directed cholesterol testing continues to be where most consumers prefer to be tested. However, other testing options are becoming increasingly available including tests in the retail setting, walk-in clinics, and at home.

[Slide]

Another important part of post-purchase assistance is the ongoing adherence program. This includes a toll-free hotline and website, educational video and American Heart Association cookbook, ongoing newsletters, postcards, and e-mail reminders.

[Slide]

This is how the adherence program works. It is customized to correspond to the date the user started taking the product. This ensures that the message is relevant to them at that point in their therapy. For example, the first three months focus

on eligibility and treatment to goal, while later communication focuses on diet, exercise, long-term adherence and health professional interaction.

[Slide]

While not a requirement, most consumers interested in Mevacor OTC want to and will partner with their healthcare professional while using. Therefore, we have structured the system to encourage and facilitate this.

[Slide]

To support this interaction, the program encourages ongoing dialogue concerning any questions regarding Mevacor OTC including testing and monitoring. The program also includes a risk referral program for those who are identified at higher risk and then directs them to their doctor for possible prescription therapy.

[Slide]

Here is an example of one of the doctor/pharmacist tools. In each package will be two cards, a doctor card and a pharmacist card. Users can fill out the inside of these cards with

information such as when they started taking Mevacor and list any other medications they may be taking. The doctor can then add this information to the patient chart and the pharmacist to the medication record.

So, as I have shown, the Mevacor OTC self-management system is comprehensive and offers the tools for a consumer to self-manage their cholesterol. However, each element of the program also strongly encourages healthcare professional interaction as needed.

[Slide]

In summary, those likely to take action as a result of Mevacor OTC differ from the general population, with these people being highly motivated and health conscious. The self-management system offers multi-faceted and unprecedented support to reinforce key label messages and was designed to drive interaction with healthcare professionals. Both the label and the support system were submitted as proposed NDA labeling and, therefore, will be required in the

marketplace. We have further demonstrated the feasibility of executing this commitment in the marketplace with key partners including retail, pharmacy and testing companies.

[Slide]

Finally, if approved, we commit to extensive post-marketing surveillance to monitor actual use in the marketplace and we will use this data to modify our program as necessary. That concludes my presentation. I know we are scheduled for a break now.

DR. WOOD: Let's just go straight on to Robert Tipping's presentation.

MR. HANSEN: Dr. Wood, I do just want to warn you that this is about 30-40 minutes and gets more technical.

DR. WOOD: That is okay.

Actual Use Study Results

MR. TIPPING: Thank you, Jerry and good morning to members of the advisory committee and representatives of the FDA.

[Slide]

I am Bob Tipping, a director in the clinical biostatistics department of Merck Research Labs. Today I will share with you some of what we

have learned about how consumers use Mevacor OTC and the self-management system that you have just heard about.

The data I will present today addresses three key questions about consumer behavior: Will the Mevacor OTC self-management system allow consumers to make appropriate initial decisions about the use of the product? Will they be able to self-manage the potential safety issues over time? And, will they be able to self-manage their cholesterol over time and obtain benefit?

[Slide]

To address these questions I will be showing you data from the large behavioral trial called CUSTOM, the Consumer Use Study of OTC Mevacor. It is important to realize that CUSTOM is a large trial, over 3300 participants and 800,000 data items. Given the time constraints of this meeting, I will not be able to show you all of the

data. Instead, I will focus on those results that address the key questions about consumer behavior.

[Slide]

Let me briefly review the CUSTOM study design. Participants were recruited using TV, print and radio advertisements. Ads did not include specific eligibility criteria. The ad campaign included ads designed to communicate to an ethnically diverse population and included a toll-free number for interested individuals to call for an appointment.

[Slide]

Study sites were set up to simulate an OTC retail environment. This included a shelf display and drug package consistent with marketplace plans. CUSTOM was an all-comers study. All participants, regardless of their label eligibility, were able to make a purchase decision. Participants reviewed the label and the other in-store components of the system to assess if Mevacor OTC was right for them. They were allowed to leave and return later if they felt they needed more information. The option to

purchase a cholesterol test was available. Study site nurses were trained to act as pharmacists and could answer questions but did not volunteer assistance unless asked by the participants. Interested participants were required to purchase study drug.

[Slide]

After making the initial purchase decision, participants were followed for six months of self-guided behavior and product use with minimal intervention. Visits were not scheduled. Participants returned to the site at their own initiative to purchase additional drug or a cholesterol test. Behavior around obtaining a follow-up cholesterol test following treatment to the goal messages and new medical conditions and prescriptions was observed.

[Slide]

Baseline and end of study lipid values were collected from participants who purchased the study drug in a way to have minimal impact on participant decisions. These lipid values allowed

us to assess the lipid-lowering effect of lovastatin 20 mg a day in an OTC setting.

[Slide]

At the end of the study eligibility information was collected. Participants were asked about new prescriptions, new medical conditions and adverse experiences. Information about diet and exercise and the reasons for inappropriate decisions were also collected.

[Slide]

A post-study survey was conducted in a subset of users to obtain additional information about specific behaviors.

[Slide]

You have seen this slide a few minutes ago when Jerry Hansen presented the Mevacor OTC self-management system. All elements of the system were evaluated in our CUSTOM trial. The system emphasizes a collaborative care approach, designed to support self-management while encouraging interaction with healthcare professionals. In fact, we will present data demonstrating that

consumers will seek out these partnerships with doctors and pharmacists in the OTC setting.

[Slide]

The analysis of behavior evidenced decisions about the purchase and use of Mevacor OTC. The analysis carefully considered interactions with healthcare professionals. The label contains numerous messages about talking with your doctor or pharmacist. Information about these interactions was collected and was an important factor in determining the appropriateness of use decisions. We also wanted to document the positive impact that this system had in creating new and maintaining existing relationships with healthcare professionals. Finally, we collected information from participants about their diet and exercise habits while on Mevacor OTC.

[Slide]

Turning now from study design to the CUSTOM study results--

[Slide]

Before we get into actual behavioral

results, it is important to understand how participants flowed through our study and to introduce the various populations to be discussed further into the presentation. In response to study advertising, over 11,000 individuals called our toll-free number. Of that group, 3316 scheduled an appointment and traveled to one of the study sites. This group, called the evaluator population, reviewed the label and the other in-store components of the system and made a decision about the purchase of Mevacor OTC; 2111 people decided not to purchase the drug and a little over 1200 did choose to purchase. The purchasers split into two main groups, those who purchased but did not go on to actually use the drug and a group that actually began to use the medication. Finally, there was a subgroup of 398 uses who participated in our post-study survey.

[Slide]

This slide presents a brief overview of the demographics of the evaluator population, and 59 percent were men. They had a median age of 53

years. As mentioned earlier, the recruitment ads were designed to reach an ethnically diverse population and we were pleased to see positive results from this, as evidenced by a 28 percent minority participation rate at this stage of the study. Twelve percent of the evaluator population was classified as low literacy based on the results of a validated adult literacy questionnaire called the REALM test.

[Slide]

Before discussion of behavior, and specifically behavior that resulted in the potential for an increased safety risk, it is important to provide a summary of the actual safety results from the use of lovastatin 20 mg in an OTC setting. There was only one serious drug-related event, an allergic reaction to lovastatin. One death occurred in the study. A 50 year-old man died of a stroke that was judged probably not related to study drug. There were no serious drug-related muscle or liver events. No new safety issues were identified and lovastatin was generally

safe and well tolerated by this population in a simulated OTC environment.

[Slide]

To better understand consumer behavior regarding the Mevacor OTC label, it is helpful to think about the label elements as falling into one of four quadrants. The top and the bottom rows of this table contain label elements for the initial and the ongoing use decisions respectively. The left column consists of specific safety warnings and the right-hand column contains label benefit criteria.

[Slide]

Safety warnings, summarized here, guide appropriate behavior from consumers with these conditions or situations so as to minimize the potential for a safety concern.

[Slide]

Benefit criteria target an appropriate population based on their age, presence of additional risk factors and knowledge of their complete lipid profile including triglycerides and

HDL. As mentioned earlier, these criteria were written to be readily understood by the consumer while allowing an approximation of eligibility according to ATP III treatment guidelines.

[Slide]

It should come as no surprise that many users in CUSTOM were not 100 percent compliant with each and every element of this multi-factorial label. A strict interpretation of the CUSTOM results along these lines can be viewed as a less than positive outcome, but if one sees some distinction between these label elements; if one believes that a "do not use if you are pregnant" warning should be evaluated at a different level than a specific age or lipid value cutoff; if one believes that people should have the option to make their own personal benefit assessment, then the CUSTOM results will demonstrate that consumers can be capable partners in the management of cholesterol and heart health.

[Slide]

So, will consumers make appropriate

decisions about starting to use Mevacor OTC?

[Slide]

From the population of 3316 who evaluated the product, there were 2111 who chose not to purchase. An additional 64 purchased the product but made a decision not to begin taking it. There were 659 people who began to use the product in compliance with both the label safety warnings and benefit criteria.

[Slide]

Taken together, this totals 86 percent of the population who came to one of the sites and evaluated the product.

[Slide]

There were an additional 109 participants who began to use the product despite a label safety warning that was relevant to them. Let's look at each of these groups more carefully.

[Slide]

Coming back to the study population slide, I will next show you data from 2111 non-purchasers and the 94 purchaser non-users.

[Slide]

This group of evaluators who chose not to purchase the product provides strong evidence that

the label and the other in-store components of the system are discouraging inappropriate people from using the product. Seventy-nine percent of this group indicated that they were not interested in buying Mevacor OTC. Nearly two-thirds of this subgroup stated that they believed Mevacor OTC was not right for them.

[Slide]

The group of 94 who purchased but did not go on to actually use the drug includes 64 people who actually left the site with Mevacor OTC. The majority cited that "my doctor advised me against using it," or "I learned it was not right for me" as a reason for not using the drug. These results provide strong evidence that the post-purchase components of the system are further discouraging inappropriate use of the product.

[Slide]

Returning again to our population slide, I

will next show data from the 1059 people who actually began to use Mevacor OTC, and remind you that we are still addressing the first of our three key questions, will consumers make appropriate decisions about starting to use Mevacor OTC?

[Slide]

The target behavioral goals established for the CUSTOM study were based on information from label comprehension studies. Typically, a level of 80 percent is regarded as a reasonable benchmark for correct and acceptable answers for each of the individual label elements. Our pilot comprehension studies of the CUSTOM label showed that most of the individual label elements were understood by 80 percent or more of those tested and, most importantly, the key safety warnings were understood by more than 90 percent. We know that label comprehension results do not always predict behavior, but we decided to apply the same 80 percent benchmark in evaluation of our behavior data, an even more rigorous test because it required being correct on all label elements

collectively, not just individual criteria.

[Slide]

Indeed, for the safety criteria 90 percent of the CUSTOM users demonstrated correct behavior around all label safety warnings jointly, exceeding the 80 percent benchmark and consistent with the label comprehension results for the individual safety messages.

[Slide]

Correct behavior according to the multiple label benefit criteria was not as high. It was 66 percent of the users closely adhering to the benefit criteria. Taken together with the label comprehension results that exceeded 80 percent for these elements and the excellent behavior around the label safety warnings, this suggests that consumers are understanding the label and are applying more individual judgment on the benefit criteria before beginning to use Mevacor OTC.

[Slide]

Looking jointly at all safety and benefit criteria for the initial decision to use, which was

a prespecified hypothesis of CUSTOM, this translates to 55 percent of the users behaving in a fashion consistent with all label elements. This number is obviously driven by the low adherence to the label benefit criteria and is roughly the product of the 90 percent and the 66 percent. Let's now explore the behavior within each of these bars more fully.

First, let's look at the safety warnings directed at the initial use decision. Recall that 90 percent of all users exhibited behavior that completely met the label safety criteria and 10 percent who did not comply with the label safety warnings. This 10 percent corresponds to 109 of our users.

[Slide]

Recall, this was an all-comers study. There was good representation from all of the safety decision areas among our evaluator population, the orange bars.

[Slide]

There were very few people with these

conditions who went on to actually use Mevacor OTC without speaking to a physician. There was no use by pregnant women. Use by people in the other four categories was low and there were no serious drug-related muscle or liver events among them.

[Slide]

The difference between the number of the evaluators represented in the orange bars with these conditions and the number who chose to use Mevacor OTC, the yellow bars, provides strong evidence that the safety warnings directed at the initial use decision are effectively discouraging inappropriate purchase and use of Mevacor OTC.

[Slide]

Now let's look more fully at the benefit criteria directed at the initial use decision. These are label elements referring to age, lipids and CHD risk factors. Recall that 66 percent with behavior that met or closely met label benefit criteria and the 34 percent who did not comply with the benefit criteria--that 34 percent corresponds to 357 of the user population.

[Slide]

But 72 percent of this group, based on their risk factors and their 10-year risk for

coronary heart disease, should be considered for lipid-lowering therapy according to ATP III guidelines. Let's now look at the specific label benefit criteria that cause people to fall into this 34 percent group.

[Slide]

Eighteen percent of users did not know their complete lipid profile. However, results from the study-mandated baseline lipid exam indicated that 93 percent of them had elevated lipids, a measured LDL at or above 130 or a total cholesterol of 200 or more. Fifty-one percent of this group did not know their complete lipid profile but they did know their total cholesterol value. This group had a median LDL cholesterol of 165. So, while they did not meet the strict label criteria, they are still very likely to obtain benefit from lipid-lowering therapy.

[Slide]

Sixteen percent of the users had self-reported triglycerides of 200 or higher. The label advises consumers with triglycerides greater than or equal to 200 not to use the product unless directed by a physician. This is to minimize the potential for use among people with possible

metabolic syndrome since they may require more personalized medical care. However, results from the study-mandated baseline lipid exam showed that 92 percent of this subgroup also had elevated lipids, with a median total cholesterol or 253 and a median LDL of 146. Nearly three out of four had self-reported triglycerides less than 400. So, again, while they did not meet all of our conservative label criteria, they are still very likely to obtain benefit from lipid-lowering therapy.

[Slide]

Eleven individuals indicated they would substitute Mevacor OTC for their prescription cholesterol-lowering medication without consulting their physician. This represents just one percent

of our user population and a very small percentage of the 609 evaluators who reported on being on Rx lipid-lowering therapy.

[Slide]

Finally, there were 70 individuals, or 7 percent of our users, who were at higher CHD risk. They reported having coronary heart disease, having had a prior stroke or being diabetic and chose to use Mevacor OTC without speaking to a physician.

[Slide]

Among the evaluators, there were 570 who reported having coronary heart disease, a prior stroke or diabetes. More than 70 percent of this group chose not to purchase Mevacor OTC.

[Slide]

However, 167 of them did choose to use Mevacor OTC and 97 of this group did it after consulting with a physician. That leaves 70 higher risk users from the earlier slide who began to use Mevacor OTC without speaking to a doctor.

[Slide]

However, 26 of these 70 did have a

physician interaction at some point during the study. Combining these 26 with the the 97 who consulted a physician prior to using Mevacor OTC, this totals 74 percent of this group who had an interaction with their doctor prompted by the Mevacor OTC self-management system.

[Slide]

Finally, it is important to note that 80 percent of this 70 had elevated lipids, and two-thirds of them were not on lipid-lowering therapy at the time they chose to start taking Mevacor OTC.

[Slide]

Now let me summarize the results you have just seen and address the first of our three key questions, will consumers make appropriate decisions about starting to use Mevacor OTC? From our population of evaluators, there were 2111 who evaluated and chose not to purchase. An additional 64 purchased the product but made a subsequent decision not to begin taking it. Finally, there were 659 people who began to use the product in

compliance with both the label safety warnings and the benefit criteria. Taken together, this represents 86 percent of the population that came to one of the study sites and evaluated the product. There were an additional 109 participants, representing just 3 percent of all those who evaluated the product, who began to use Mevacor OTC despite a label safety warning that was relevant to them. The behavior of these 109 individuals created the potential for an increased safety risk, however, there were no serious drug-related muscle or liver events among them--good evidence that consumers can select to use Mevacor OTC appropriately.

[Slide]

Returning to the key questions, I will now address both the second and the third questions together for a moment since they are both directed at the ongoing use decisions. While decisions about initial use are important, even more important are decisions regarding ongoing use because only those who use the product long-term

are going to gain a clinical benefit or place themselves at a potential safety risk.

[Slide]

Will the system allow consumers to self-manage the potential safety risks over time? From our population of 1059 users, there were 366 who actually experienced a new medical condition or got a new prescription, thus providing an opportunity to evaluate behavior regarding the label safety warnings for ongoing use. Of these 366, 94 percent made a decision about ongoing use of Mevacor that was consistent with the label. Only 6 percent made a decision that was inconsistent with safety warnings directed at ongoing use decisions.

[Slide]

Will the system allow consumers to self-manage their cholesterol over time and obtain a benefit? Again, from our population of users, 74 percent obtained a follow-up cholesterol test or had discontinued Mevacor OTC prior to the six-week time point directed in the label. Of those users

who did get a follow-up test, three out of four followed the label directives regarding the LDL goal. Finally, there was an impressive 21 percent reduction in LDL.

[Slide]

Again, based on label comprehension study results, we evaluated decisions about ongoing use against the prespecified 75 percent benchmark.

[Slide]

CUSTOM demonstrated behavior around all label safety warnings for ongoing use jointly to be 94 percent. As with the safety warnings for the initial use decision, this exceeded the target benchmark and was consistent with label comprehension results for the individual label elements.

[Slide]

As with the initial use decision, fewer adhered to the label benefit criteria, with 53 percent of the user population closely adhering to benefit criteria for ongoing use decisions. Taken together with the comprehension results for the

label benefit elements and the excellent behavior around the label safety warnings, this again suggests that consumers are understanding the label and are making their own personal benefit assessment for the continued use of Mevacor OTC.

[Slide]

Combining all safety benefit elements for the ongoing use decision together which, again, was a prespecified hypothesis of CUSTOM, we see that 50 percent of the users behaved in a fashion consistent with each and every label element. Again, this is no surprise given the results from the label benefit criteria, and is the product of the 94 percent and the 53 percent.

[Slide]

Now let's explore behavior within each of these bars more fully. First, let's look specifically at the safety warnings directed at the ongoing use decision. Here is the 94 percent exhibiting behavior that completely met the label safety criteria, and the six percent who did not comply with the label safety warnings. That six

percent corresponds to 21 individuals from the user population.

[Slide]

There were 693 of the user population who did not experience a new medical condition or get a new prescription during the study. That leaves 366 who did experience a new medical condition or a new prescription and exhibited a behavior that could be evaluated against the label safety warnings for ongoing use. The three bars to the right represent the number of users with each of these events.

[Slide]

And 270 of the 366 reported a new prescription during the study. Only two were for a potentially interacting medication where the person did not inform their physician about taking Mevacor OTC as directed on the label; 161 reported a new medical condition while in the study and only three of these were of concern. As discussed earlier, there was the individual who had a stroke and died before he could reveal to his physician that he was taking Mevacor OTC. One individual was diagnosed

with coronary-artery disease and did not inform her physician about the use of Mevacor OTC, and one individual was diagnosed with diabetes and, again, failed to inform his physician about use of Mevacor OTC. Sixty-three reported an unexplained muscle pain during the course of the study. All but 16 discontinued Mevacor OTC or spoke with a physician about this.

[Slide]

Now let me summarize the results you have just seen that address the second of our three key questions, will consumers be able to self-manage the potential safety risks over time? From the population of 1059 users, there were 693 who did not experience a new medical condition or get a new prescription during the study. An additional 345 experienced and event and made a decision about ongoing use that was consistent with the label safety warnings. Taken together, this represents 98 percent of the user population. There were 21 participants, representing just two percent, of all those who used the product who continued to use

Mevacor OTC despite a label safety warning that was relevant to them. The behavior of these 21 individuals creates the potential for an increased safety risk, however again, there were no serious drug-related muscle or liver adverse events among them--good evidence that consumers can manage potential safety risks over time.

[Slide]

Turning now to the third and final of the key questions, will the system allow consumers to self-manage their cholesterol over time and obtain a benefit? This question addresses behavior around label benefit criteria directed at ongoing use decisions. These are label elements directing consumers to get a follow-up cholesterol test at six weeks and comply with the LDL goal message.

[Slide]

And, 666 of our 1059 users, representing 63 percent, obtained a cholesterol test during the study. An additional 11 percent discontinued the study, many for an appropriate reason, before the six-week time point directed in the label. This

totals 74 percent of our user population making an appropriate decision about getting a follow-up cholesterol test.

[Slide]

Looking specifically at the 666 individuals or the 63 percent of the users who got a follow-up cholesterol test, 75 percent of this group followed label directives regarding the LDL goal message. This was largely composed of individuals who achieved an LDL less than 130 and made the decision to continue using Mevacor OTC.

[Slide]

Addressing another component of the third question, how did the results of CUSTOM, an uncontrolled, open-label study, compare to what is known about the lipid-lowering effects of 20 mg of lovastatin in controlled clinical trials?

[Slide]

In the CUSTOM trial a 25 percent reduction in LDL was observed in a subset of individuals who indicated they were fasting both at the baseline and end of study measurements. Looking at the

entire study cohort, regardless of fasting status, a 21 percent reduction in LDL was observed. These results compare very favorably with the large controlled clinical trials, AFCAPS and EXCEL, both showing a 24 percent reduction in LDL with the 20 mg dose of lovastatin.

[Slide]

Turning now to data about consumer who persisted with medication, before I present the results let me remind you that CUSTOM was not designed to be a persistence study. In fact, one of the goals of CUSTOM and of the Mevacor OTC label is to correctly influence people who shouldn't be taking the product to stop taking it. With that in mind, let's look at the CUSTOM persistence data.

[Slide]

Sixty-two percent of the user population were persistent with therapy through six months of the study. An additional 17 percent discontinued Mevacor OTC for an appropriate reason, such as not reaching an LDL goal, being advised by their doctor, or learning that Mevacor OTC was not right

for them. Taking these together, 79 percent of our user population made an appropriate persistence decision regarding Mevacor OTC. This is consistent with results from an earlier use trial of lovastatin 10 mg. In that study 72 percent were continuing with medication at six months and 49 percent were still on therapy at 18 months. These numbers compare very favorably to what we know about persistence with prescription statins.

[Slide]

Finally, what do we know about the self-management system and its ability to direct consumers to make appropriate decisions about diet and exercise habits? A MEDFICTS dietary assessment questionnaire was given to the user population at baseline and at the end of the study. This validated instrument provides a score to determine if an individual is on an AHA step-one diet or the more restrictive AHA step-two diet. Not only did more individuals move to the stricter step-two diet by the end of our study, but the number of users who are not on either of the AHA diets decreased

from 17 percent to 11 percent.

[Slide]

Now let me summarize the results you have just seen that address the third of our three key questions, will the system allow consumers to self-manage their cholesterol over time and obtain a benefit?

[Slide]

From our population of 1059 users, 74 percent obtained a follow-up cholesterol test or discontinued taking Mevacor OTC prior to the time directed on the label. Of those users who did get a follow-up test, 75 percent of them followed the label directives regarding the LDL goal. Finally, there was an impressive 21 percent reduction in LDL cholesterol--again, good evidence that consumers can manage their cholesterol over time and obtain a benefit.

[Slide]

Moving now to an important question about the ability of the system to promote consumer interaction with healthcare professionals, CUSTOM

provides information from a variety of groups to address this question.

[Slide]

Of the people who evaluated the product at the site but chose not to purchase, 22 percent of them reported that they did, in fact, talk to their doctor before making this decision. Physician interactions were reported by 57 percent of our user population at some time during the study and, finally, as I mentioned earlier, nearly three out of every four of our higher CHD risk users had an interaction with a doctor as a result of this study.

[Slide]

In conclusion, the Mevacor OTC self-management system discourages inappropriate use of the product.

[Slide]

The majority of consumers who choose to use Mevacor OTC will be appropriate for self-management. They will gain a clinical benefit, as evidenced by substantial LDL

reductions, and most importantly, will be at minimal safety risk.

[Slide]

Lastly, beyond the direct pharmacologic effect of the medication, the Mevacor system will have important public health benefits that include an increased level of interaction with healthcare providers and a general improvement in heart health awareness and behavior. That concludes my presentation. Thank you for your attention. I think it might be time for a break now?

DR. WOOD: Right. It sounded like a plea, right! Why don't we take a break and be back, ready to start, at 10:15?

[Brief break]

DR. WOOD: We will just wait one more minute so people can take their seats.

Medical Perspective and Conclusions

DR. COHEN: Mr. Chairman, members of the committee, representatives of the FDA, my name is Jerry Cohen, and I am a full-time academician and cardiologist at St. Louis University. I spent

nearly my entire career in preventive cardiology.

[Slide]

I want to start off by telling you that a number of years ago, when I first heard about the possibility of OTC statins, I was skeptical about the notion and I had many questions. I am sure my initial skepticism and the questions I had then are similar to ones that you may have today. Your key questions probably include something like the ones that are shown on this slide.

[Slide]

First, is there really a need for an OTC option? Can't we just do a better job of what we are already doing, using the current treatment model? Secondly, is Mevacor 20 mg really safe enough for OTC use? Third, can consumers manage cholesterol effectively with an OTC product? Fourth, will OTC therapy divert consumers from a physician's care and from heart-healthy lifestyle practices? Finally, why should we do this? What is the overall benefit-risk ratio of Mevacor OTC?

These are all important questions and you

have just seen compelling data that addressed each of these questions individually. But in the end, for me, it was the totality of the evidence taken together which clearly convinced me that OTC lovastatin therapy poses not only a minimal and acceptable risk, but also, as we will see, has the potential to provide an enormous public health benefit. In other words, there is a highly favorable benefit-risk ratio. So, let's review the evidence.

[Slide]

The first question is shown here again on this slide. Is there really a need for an OTC statin option? Well, conversely, we might ask why not solve our problem by putting more effort into the current system of physician and patient education and build an even greater awareness of the cholesterol problem and the benefits of Rx therapy? And, why not just continue to get more aggressive with our national guidelines?

[Slide]

This is a slide you have already seen and,

as you have heard, despite our best efforts and the creation of the National Cholesterol Education Program 20 years ago, we have not made much progress, particularly in the moderate risk primary prevention group. As Dick Pasternak has shown us, cardiovascular disease is still by far our nation's number one killer and a huge treatment gap exists, somewhere between 6-15 million Americans. With the aging of our population, this will only get larger in the near future.

While there are a lot of reasons for the treatment gap, the major relevant factor to our discussion today is that many untreated people are reluctant to take prescription therapy. As you saw earlier, with the availability of OTC statins many of these same people are more likely to take positive action with an OTC product.

[Slide]

The next question is of utmost importance, is Mevacor 20 mg truly safe enough for OTC use?

[Slide]

I believe the answer is clearly yes.

Mevacor has an excellent and proven safety profile, especially at this low dose. We are not talking about a newly developed or newly released compound. We are not awaiting the results of another study. Lovastatin, as the first FDA-approved statin, has a proven track record of safety with more than 17 years in market experience. This equates to more than 27 million patient-years of treatment. As we have seen, Mevacor has a safety profile reasonably similar to placebo at up to twice the proposed OTC dose.

If the product is safe at this dose, is cholesterol too complex for consumers to accomplish on their own? After all, high cholesterol is a chronic, asymptomatic condition and it has been said that this is somehow different from the way OTC products are presently used by consumers.

First, let me say that the treatment of chronic asymptomatic conditions is not a new concept for OTC products. Consumers have been taking OTC products for such conditions for many years. In fact, over 35 million Americans are

currently using calcium supplements every day to prevent osteoporosis. Approximately 26 million people use low-dose aspirin for heart health, with a quarter of those doing so on their own. This is an interesting observation given the fact that both aspirin and Mevacor have proven cardiac benefits, and both are among the standards of care. Yet, the risk of having a serious adverse event with low-dose aspirin is actually greater than it is with lovastatin 20 mg.

Perhaps the most relevant example to the discussion today is that over 14 million Americans are currently using heart health supplements, many of which are of questionable safety and benefit--questionable safety and benefit. So, if the concept of OTC therapy for chronic asymptomatic conditions isn't new, how strong is the evidence that consumers can self-manage their cholesterol?

[Slide]

This slide reminds us of the key data that we just saw from the CUSTOM study, as well as the data from two previous actual use studies with OTC

lovastatin. There is a strong consistency in the findings here. A vast majority, about 90 percent, had pretreatment total cholesterol values of greater than 200 mg/dL. Only a small minority were already taking a statin at the time of the OTC purchase. Most importantly, consumers did very well with regard to our concerns about safety. With safety labeling in mind, between 90-97 percent appropriately selected the product. In addition, about two-thirds appropriately selected, in accordance with the labeling, for benefits.

Now, not everyone behaves strictly in accordance with the label, but these data represent what is likely to happen in the real world, and that is what this OTC study, the CUSTOM study, was all about, getting a real-world experience. What is remarkable here is the consistency of the data which, I might add, supports prior observations showing that the large majority of consumers do appropriately self-select for management of their cholesterol.

[Slide]

But how does this compare to the current state of prescription care when looking at the results of statin therapy? When considering the

benefits of an OTC statin, all of the parameters shown on this slide--obtaining cholesterol goal, appropriate persistence with therapy, and an average LDL cholesterol reduction--are, at the very least, comparable to, if not better than what was seen in the Rx population.

This may be surprising, or perhaps not so, when considering the fact that self-selected OTC users are different from and may be more health conscious and motivated than many prescription users. Whatever the reason, we can clearly see the most important bottom-line outcomes which are the key determinants of coronary heart disease prevention. Persistence of therapy and the magnitude of the LDL cholesterol reduction compare very favorably to the prescription experience.

[Slide]

But no matter how appropriately consumers manage this condition, it is not intended to be a

substitute for or to take the place of traditional health care. So, we must ask will OTC divert consumers from physician care and from heart-healthy lifestyle practices? It is an important question. And, it is important for us to remember that the Mevacor OTC program was designed to do just the opposite. It was designed to encourage consumer interaction with their healthcare providers in order to receive appropriate therapy, whether that therapy be OTC for those at moderate risk or prescription medication for those at higher risk.

[Slide]

This slide shows the system worked. Not only did the majority of users, as shown in the middle bar graph, consult healthcare professionals about their OTC use, 22 percent of the people who didn't even purchase the product consulted a physician or doctor or a healthcare provider as a result of the OTC program. Also of considerable importance, three out of four higher risk consumers interacted with their healthcare providers as a

result of the OTC experience. These data clearly demonstrate that Mevacor OTC is not an isolated self-care product but is complementary care which encourages interaction with healthcare professionals.

[Slide]

As shown in this slide, consumers do not get complacent about their heart-healthy behaviors as a result of taking Mevacor OTC. More than 90 percent maintained or improved their heart-healthy lifestyles of diet and exercise, confirming that Mevacor OTC did not distract consumers from these important interventions. Any of you who saw the headline story today in "USA Today" about the new diet guidelines can see that diet and exercise are being emphasized more than ever.

[Slide]

So, I think we can say that there is a clear need for OTC statins. There is an acceptable safety profile and there is demonstrated appropriate and effective consumer behavior without diversion from other heart-healthy practices. But

in the final analysis what is most important, considering all OTC users--all--is the overall benefit-risk ratio.

[Slide]

In answering this question let us first see how Mevacor OTC can narrow treatment gaps. OTC can directly increase the number of moderate risk individuals treated. Although these are rough estimates, our analysis shows that an approximate 4-5 million moderate risk individuals will likely seek OTC treatment. Thus, by focusing on this moderate risk group, the treatment gap substantially narrows.

In addition, not estimated here, we also know that there will be some moderate risk individuals who will be seen by their physicians and put on prescription therapy as a result of heightened awareness of their cholesterol problem stemming from the OTC program.

[Slide]

Likewise, in the high risk group there will be an estimated 1-2 million people who will

communicate with their doctors and possibly be put on prescription therapy as a result of the OTC program. Finally, in terms of this bar graph, we also know from the CUSTOM data that, while not ideal, there will be some usage of the OTC product in this higher risk group. What are the consequences of such use? Compared to otherwise taking no action, which surveys suggest is the usual outcome, I would submit to you that this is a favorable result--a very important recognition.

The overall effect of OTC statin availability is narrowing of the treatment gaps for both the moderate and higher risk groups. Now, OTC statin therapy is not a panacea for the entire treatment gap and it will not fix all the problems. But it is also very compatible with our current efforts which may be increased in terms of the effectiveness of Rx and any subsequent change in the guidelines. These are not mutually exclusive types of intervention. However, as shown, it will substantially reduce the size of the gap by reaching a portion of the at-risk population which

is not currently being reached.

[Slide]

Now I would like to consider the population shift in the distribution of LDL cholesterol which will occur as a result of OTC Mevacor. This slide displays the distribution of baseline LDL values, shown here in blue, among the CUSTOM users.

[Slide]

The overlay, now shown in yellow, shows the end of study, and this is the CUSTOM actual use data, with LDL levels achieved. Together, they clearly demonstrate the classic leftward shift in the LDL distribution. This is a direct effect of Mevacor OTC. Given the strong positive graded and continuous relationship between LDL cholesterol and risk, as was shown by Dick Pasternak in an earlier slide, this means that nearly all users will potentially benefit by a reduction in coronary heart disease risk. Think of that!

[Slide]

It is of interest to note that this goal

of shifting the population curve is not a new concept. In fact, over ten years ago the expert panel of the National Cholesterol Education Program, Dick Carleton's panel, published these curves that show the potential complementary and additive benefits of an increased focus on primary prevention to our current treatment efforts.

The blue line here is the cholesterol distribution at that time which has not changed much since 1991. The yellow dotted line projects the effects of treatment per the then existing ATP guidelines if they were widely applied. And, the orange dashed line shows how the complementary effect of a 10 percent decrease in cholesterol further shifts the curve, and this is similar to what we have just observed with OTC Mevacor in the CUSTOM data set that I showed you with the blue and yellow bar graphs.

[Slide]

Finally, and most important, is the projected overall benefit of Mevacor OTC. Utilizing the CUSTOM risk distribution and assuming

a conservative coronary risk reduction of 25 percent--AFCAPS/TexCAPS actually showed a 37 percent overall reduction--for every one million consumers taking the product, we can expect to prevent between 25,000 and 35,000 coronary events over the next ten years. Given the strong safety profile, the overall benefit-risk ratio is clearly highly favorable.

It was in recognition of this fact that our colleagues in the U.K. approved the use of an OTC statin last year. They got it; they saw the benefit in terms of the benefit-risk ratio being highly favorable. The time is ripe for this important OTC option to be available to consumers in the United States. Many consumers are concerned, informed and motivated and are already active in terms of their own health care. We should provide them with better and safer options than what is currently available to them OTC. With aging of our population, now is the most opportune time to make possible an OTC stain option.

In closing, we have asked ourselves many

questions that at first glance seem new and potentially challenging. But when we look at the strength and totality of the evidence we also see that we have a great opportunity for reducing the burden of cardiovascular disease.

Mr. Chairman, members of the committee, my hope is that today we can look at the totality of the evidence and recommend approval of Mevacor OTC to reduce the huge burden of cardiovascular disease in the United States. The challenge is before us, but so too is the opportunity. Thank you for your thoughtful consideration.

Questions from the Committee

DR. WOOD: Thank you, and thanks to the sponsor for sticking so well to the time. Let's take about 30 minutes of questions from the committee, or less if we run out, and then we will move on to the first of the FDA presentations after that and before lunch. Questions from the committee? Neal?

DR. BENOWITZ: I actually have a lot of questions but I will just start with one to let

other people have a chance. One of the issues that is really important for over-the-counter medications is the patient's capacity to understand benefits versus risks. This is something that we deal with in practicing medicine as well, and one of the things that is always an issue is when you talk about relative risk changes in primary prevention.

You may be talking about a 35 percent reduction of risk, but looking at the data that are presented, it really is looking at a 2 percent or 2.5 percent change in absolute risk over six years. Nowhere do you really talk about absolute changes in risk, and I think that is an important question for a patient. They have to know that 25 people have to take this medicine for six years, at a minimum, to prevent one event. It is true that there is great population benefit, but when we are talking about individuals there needs to be some consideration to give an individual the information to make a benefit-risk appraisal. You did talk about absolute risk for safety issues, but you

didn't talk about absolute benefits.

So, I would just like to hear someone address the question of how do we really give the patient the proper information to make an intelligent risk-benefit analysis.

DR. WOOD: Who wants to take that?

DR. HEMWALL: I will at least start. I guess what you are asking is to somehow also include in our education and support materials more explanations of what really is meant by a reduction in risk for heart disease. In this case we are talking in the realm of 25-50 percent, depending on which study you look at and the patient population. That is certainly possible. In fact, that would be something we would be more than willing to put in the right perspective for patients so they would understand that, and make that as part of their decision.

DR. WOOD: I think what he is asking is if you have a similar percent reduction in relative risk across different populations, the absolute risk will be reduced differently in the lower risk

group. Is that what you are getting at, Neal?

DR. BENOWITZ: Exactly. In secondary prevention it is easier because the absolute benefit is great. But the debates in primary prevention have always been the small absolute risk benefit.

DR. WOOD: I think that is the question.

DR. PASTERNAK: Just to amplify it--thanks for the question and it is an important question. There are a couple of responses to that. First of all, people make those choices--low risk or moderate risk people make those choices every day when they decide to go running, when they go on a diet, when they take an aspirin. So, people are capable at some level of making that kind of decision.

Second of all, as Dr. Cohen showed at the very end, we think there really is a substantial benefit to this population, and the number needed to treat--and we can discuss whether the right number is 28, 38 or 48--is actually a fairly favorable number in terms of preventing an event.

It is comparable to the number that is needed to treat that is seen in some of the secondary prevention trials.

Finally, you are correct that I focused on relative risk, but my principal aim in discussing that was not to obscure the low absolute risk but to make it clear to everyone that the relative risk reduction is consistent across a wide variety of populations, a wide level of risks. It has been said by some that there is no benefit to this and I think understanding and comparing relative risks is a way to get at understanding that.

DR. WOOD: Dr. Woolf?

DR. WOOLF: I have a question for Mr. Hansen. You have a very elaborate display that will be in the pharmacy for the patient to decide to go on Mevacor OTC or not. Are there other models that have been previously used in the pharmaceutical industry that have helped to guide the patient to the appropriate or inappropriate use of a drug? If so, what are they?

MR. HANSEN: To be honest, this is

unprecedented, and this program that we have put together has gone to more lengths to help the consumer out, both with the healthcare professional and to do it on their own, than anybody has done in the past.

I think the example of the one that got the closest was smoking cessation products. It was mandated in their NDA that they did have support materials. There were audio tapes available and there was a support program that they could enroll in, and enrollment in that was fairly high.

I think the other precedent with smoking cessation is that there was a commitment that smoking cessation products not be sold in convenience stores, and that commitment--even though it was ten years ago--is still being upheld today. So, in essence, those two are the closest but obviously we are breaking some new ground.

DR. WOOD: Dr. McClung?

DR. MCCLUNG: I want to come back to the issue about the absolute risk and benefit. The absolute risk numbers have a time element, or at

least the number needed to treat has a time element in it. We have been told about the two percent reduction in absolute risk and the retrospective population that would have met the criteria for OTC, but that was over a five-year interval of time. And, the absolute risk for the side effects was described in the CUSTOM study over a six-month interval of time.

If I have done my math correctly, if there is a 2 percent reduction in absolute risk over 5 years, that is 0.2 percent over half a year. And, we are told that the incidence of muscle symptoms in the CUSTOM study was 60/1000 patients or 0.6 percent, and that 16 of those patients had muscle symptoms and continued therapy, which is an incidence of 0.16 percent, not very different from the absolute benefit that would be derived.

So, I concur strongly that we ought to make sure that we communicate what the absolute risk and the absolute benefit is, and to put it in the context that not only physicians can understand, which is often not the case, but

certainly to put it in a perspective that patients can understand.

DR. WOOD: Dr. Watts?

DR. WATTS: I would like a little more information about the patient interactions in the CUSTOM trial, or the subject interactions. In the reading material I think there was mention about the time involved, but I would like a better explanation of how much time each individual spent trying to master the material in the package insert, and also a little more information about the circumstances at the testing center. We were told that there was a display set up, but we are not told whether that really matches the surroundings that a patient or prospective buyer would be in with competing products, other people passing through, distractors that might interfere with their attention span to the material they are expected to master.

DR. WOOD: Does somebody want to respond to that?

DR. HEMWALL: Well, I understand your

question to be along the lines of how realistic was the pharmacy setup in the CUSTOM study at the study sites. There were, in fact, store front settings in strip malls. They were set up to appear as if they were operating pharmacies but, of course, when one walked in, it was clear that they were not an operating pharmacy but they had simulated shelf setups and the consumer was asked to actually go and evaluate the material as if it were on the shelf with mock other products next to it. But it was not a fully functioning pharmacy.

Although we have done other studies in pharmacies, some of the questions that we tried to answer in these various studies caused us to do different things in design and this was clearly a self-selection and then an ongoing use study. Therefore, we elected not to do this particular study in working pharmacies. But we did try to mimic that experience. But in all of these studies--and I think FDA recognizes tha--you can only get so close to creating the true, natural environment when you are also doing a study that is

conducted under IND with all the appropriate regulations that go along with that.

DR. WATTS: The other part of the question was the amount of time the average subject spent reading or trying to comprehend the package insert material.

DR. HEMWALL: We did not record that amount of time. Again, they had as much time as they wanted. They not only had the package to look at on the shelf with the shelf display--the same one that is shown here--and interact with those materials but there are tear-pads that they could remove, go home and get further information. So, in fact, a lot of people, as Bob Tipping explained, actually went home and came back later, either after having consulted with a physician or gotten their number somehow and returned. So, in some cases the amount of time they had to consider the product was several days. In other cases they made the decision within several minutes and probably, you know, an entire range within that.

DR. WOOD: Dr Tinetti?

DR. TINETTI: My question relates to discussions that have taken place concerning the safety and benefit in an elderly population, which

I will define as greater than 75, given the little data that exists in your studies. As I looked at it, in the AFCAPS/TexCAPS, the exclusion criteria was age over 73. The average age was upper 50s to lower 60s. It looked like in the actual use study there were also very few very elderly people. So, without evidence of either benefit or safety in this age group, how comfortable do you feel? Particularly, these people have multiple co-existing conditions. It is clear they are a target audience for you because it was mentioned several times this morning that the aging population is one of the important reasons to push forward with this.

And a related question, I haven't heard much discussion, or in the materials, about the softer, if you will, more subjective adverse outcomes related to statins that always anecdotally have been discussed--depressive symptoms, mild

cognitive changes. I was just wondering what discussions and concerns have been raised in those areas.

DR. PASTERNAK: Well, both those questions are important. You are correct, in the AFCAPS/TexCAPS trial most elderly were not included. I think our answer to that is that if one looks across all of the clinical trials at subgroups such as they exist, the elderly group has a result that is consistent in terms of relative risk, often greater in terms of absolute risk reduction than younger groups.

The two trials that addressed the most elderly include PROSPER, a study of pravastatin, and the Heart Protection Study, a study of simvastatin. They were specifically designed to look at that question and in those, including the age groups you just mentioned, there was a highly statistically significant benefit that was homogeneous with the results in other groups.

So, I think that the weight of the evidence for statins in the elderly is that

relative risk is consistent and the absolute risk is often even greater because the absolute risk in that population is very high.

I am not quite sure of the answer to the other question. Others on the panel might wish to respond but, you know, statins have been looked at for a long, long time now. One of the points of our ACA/AHA/NHLBI statement in 2002 was to try and review all of these other notions that statins might somehow be doing something else that people need to worry about, whether it is something important like cancer or other less important issues. As you probably know, there are also those who are arguing on the other side, that they are useful. I think most of those observational kinds of looks have not borne out in either direction and we have to stay focused on what we know these things do.

DR. WOOD: Frank?

DR. DAVIDOFF: Yes, I am having considerable difficulty interpreting the CUSTOM study, as interesting as it is, because it seems to

make the assumption about user eligibility based on several criteria that are on the product label and that are widely accepted, but it does not take into account other primary prevention strategies that are easily available to people and are widely used, in particular low-dose aspirin.

So, I will limit my question to that, which is were data collected on how many people were taking low-dose aspirin in the CUSTOM study? Because from what we have seen of the data with low-dose aspirin, it reduces risk over the longer term by just about the same amount that statins would in a primary prevention setting. Albeit, aspirin does have certainly its own risk profile, which is another issue, I just have difficulty knowing what the actual risk and, therefore, what the actual benefit would be for people who enter this trial or who took OTC statins in the marketplace because we really don't have an idea of what their risk status is if we don't know if they were taking low-dose aspirin.

As a related sub-question, are there data

on potential marginal benefit for taking statins in addition to low-dose aspirin? Because there may be, in which case that would be encouraging, but there may not be.

DR. HEMWALL: There are a lot of questions within that one question. Yes, we do have the information on who took low-dose aspirin in CUSTOM and we can get to that in a minute. But I think the larger question revolves around the concomitant use or the additional benefit with regard to taking low-dose aspirin and a statin. I would like to introduce Dr. Tony Gotto, who is willing and able to comment on that particular topic.

DR. GOTTO: I am Tony Gotto, from Weill Medical College. We recorded the participants in AFCAPS/TexCAPS who were taking aspirin. We didn't differentiate between whether it was low dose or regular aspirin, but just aspirin use. In virtually all of the secondary prevention trials with statins there has been a high use of aspirin, in the CARE study about 80 percent, and that is about typical for the secondary prevention studies.

There was significant aspirin use in AFCAPS/TexCAPS as well. This group was very active physically and there was a major emphasis on lifestyle changes for all of the participants in this study with group sessions, and we hammered away at diet and exercise, and these were very health conscious individuals. I think they certainly qualitatively reminded me of the description of the typical OTC patient. But all of the statin trials have shown a benefit on top of aspirin use, on top of beta blocker use, ACE inhibitor and various other things that are controlled for. And, low-dose aspirin has not been approved by FDA yet, has it, for primary prevention?

DR. PEARSON: I would like to comment. I am Tom Pearson, from the University of Rochester. I had the opportunity to chair the American Heart Association primary prevention writing group which endorsed the use of low-dose aspirin for the primary prevention of heart disease.

Part of the issue directly related to the question is that, in fact, in January was presented

an analysis looking at randomized, controlled trials of a statin, pravastatin, with the observational arm of aspirin use. This was presented as part of a presentation to the FDA advisory group on metabolics. The suggestion is that there is at least an additive effect and very possibly a synergistic effect which you could, in fact, bring into a variety of mechanisms to explain that. But it is at least additive, and some of our statistical friends would suggest it is even synergistic.

DR. WOOD: Thanks.

DR. SCHAMBELAN: My question gets back to the self-management system and the specific issue of the pharmacy interaction. Is the plan not to market this OTC product in convenience stores and supermarkets in which there is not a pharmacy? Is that going to be specifically interdicted? It seems like a lot of educational materials would not be available in that kind of a setting, and that is certainly where a lot of OTC products are sold.

MR. HANSEN: Yes, we are clearly

recommending that this be sold in stores with a pharmacy only and no other outlets.

DR. WOOD: Dr. Snodgrass?

DR. SNODGRASS: I will just ask one question. It relates to the risk-benefit ratio considerations and that is, what is the risk of not being evaluated by a physician? That is basically my question. I realize they attempt to involve healthcare professionals in this but it seems to me that there are a number of causes of so-called secondary dyslipidemias, besides diabetes and thyroid, obstructive liver disease and renal failure. I don't know that patients who will have some of these conditions or some degrees of them will be aware of this. I think there is also the issue that those persons in your study who knew enough to know about their cholesterol may, of course, have had some interaction with their physicians so you may have selected away from those who would less likely have this knowledge.

DR. WOOD: Someone want to take that?

DR. COHEN: Yes, thank you for the

question. I can understand the first part of it but help me if I am not answering quite the question that you asked afterwards.

If we look at the benefits of this program overall, it really necessitates, in terms of proper use, that the person knows something about himself or herself with regard to the label. Indeed, the CUSTOM study showed exactly that. So, someone who has never seen a physician, who doesn't know their blood pressure--they know whether they smoke, they know their age and they could qualify just on that, and the family history, and not have any other medical knowledge except that they don't know their lipids which, of course, is part of the labeling there.

So, I think in this situation if someone took it without knowing what their cholesterol is, again, you would have to come back to a high enough risk patient who would benefit regardless of what that was. And, we can pick a number, whether it is higher or lower or exactly what we would expect as an average, and this might happen over a period of

time with other people being involved and not knowing their cholesterol.

If you shift their curve to the left, then I think we will see, as Dick Pasternak showed on his slide, a reduction in risk estimates based on the LDL reduction that will be achieved using the Mevacor OTC product. The issue is, is the safety there for that person who is unknown, and I think from the data that we have seen here this morning that the safety is there. So, that benefit-risk ratio for that person who has not seen a physician, who has not been evaluated is still favorable I think. Certainly, hopefully, he or she will see a physician more likely because of the result of reading the label, being in the program, recognizing the importance of knowing these data and getting follow-up than they would have perhaps otherwise. Does that address your question?

DR. WOOD: Can I just follow-up on that question? It seems to me that there is an underlying assumption that is somewhat untested and probably wrong. That is, the comparison for OTC

lovastatin that should be made is one against physician care which is 100 percent perfect--

[Laughter]

--and that is what I mean by probably wrong. How do we know it is probably wrong? Well, the first way we know it is wrong is that almost the only way that someone can get a cholesterol measured in this country is by going to a physician. So, almost by definition and going back to Dr. Snodgrass' question, the population that you have studied has to be a population of patients who have failed to receive adequate cholesterol control in spite of being seen by a physician.

Then, the second part of the question relates to toxicity and following the warnings. Again there is an unspoken assumption, which is also I think probably wrong, and that is that if patients, indeed, saw a physician the warnings would be clearly followed explicitly and absolutely. And, we know from lots of data--you know, just think of three drugs that have been withdrawn, Bacyol, Resulin and cisapride--in each

of these cases there were explicit warnings on the drug label and in each of these cases, and in the case of Resulin particularly, we know that only a tiny percentage of patients were following the specific monitoring warnings that were out there. So, I was a bit surprised that you all didn't address that in the presentation.

DR. COHEN: Well, let me just come back to your first point, and that is that these are patients who may have seen a physician and the physician didn't act appropriately. We don't know that. In fact, the physician may have acted quite appropriately in the sense that they assessed the risk, they recognized high cholesterol, and perhaps wanted to recommend an Rx therapy. What is unique about this population is that it is an OTC-driven type of population where they say, you know, Rx is for a sick guy. I am a healthy person. I am concerned that my cholesterol is too high. I will continue doing whatever, including buying other heart-healthy supplements.

So, I think these people may be in the

system. They may be seeing their physician and we have data to show that. But, in fact, I think they are, for whatever reason, not following through in terms of an Rx or not getting an Rx in the first place, perhaps related outcome the healthcare system.

DR. WOOD: There is another response.

DR. HEMWALL: I do want to acknowledge your comments, Dr. Wood. In fact, we are not trying to compare to the healthcare system here. I think in one of the earlier slides that Dr. Cohen showed, we did pretty well according to what is currently in the literature about management of statin therapy, certainly not worse.

DR. WOOD: I just wanted to be polite! Dr. Follman?

DR. FOLLMAN: Yes, I would like to discuss the issue of potential under-dosing with the over-the-counter strategy for Mevacor. First, Dr. Cohen had a slide, I think it was 181, which showed the distribution of baseline LDL levels. I have a copy of that here, and I was counting up the

percentages greater than 170 and it looks like about a third of the patients in the CUSTOM study, with all the scrutiny, etc. that was involved in that study, had LDL levels which are not in accordance with the label and they would probably be better off being seen by a doctor and getting optimal statin dosing and therapy. So, there is this concern about potential under-dosing at the point of purchase.

Another thing has to do with the potential under-dosing over time. So, if you look at the label at the back of the box or some of these brochures, etc. that you have, there isn't really mention made, as far as I could tell, of the importance of getting LDL tests, say, every year. So, the way this is being marketed or proposed is chronic treatment. So, you just keep using it presumably forever. So, for a person like that who is going to continue to use it and not recognize that his LDL is creeping up past 170-200, or something, seems to me an error of omission in the label.

So, two issues about under-dosing, one at the time of purchase and then concern about upward drift which won't be recognized by the label, or

encouraged to be discovered by the label.

DR. PASTERNAK: Dr. Hemwall is going to have a comment about the last part of that with respect to the label, but we obviously would have loved it if everybody who had an LDL over 170 had more potent LDL-lowering than was available from 20 mg of lovastatin. But, remember, these are people who didn't get any other therapy.

I have heard a lot, not only in the context of thinking about this but kind of on the street, about the potential under-dosing with 20 mg of lovastatin. Remember a couple of things. First of all, there is this 1:1 relationship that for every milligram/deciliter LDL lowering there is one percent change in risk. So, while it is not the optimal risk lowering that a very large dose of a very potent statin in a very high risk population will achieve, remember, we saw on the average 20-25 percent LDL lowering and that is associated with a

substantial relative risk reduction of roughly 25 percent. So, it is true that greater degrees of risk reduction are possible, but this is still a very impressive degree of risk reduction and certainly comparable with the kinds of things people try to do every day to improve their risk.

In terms of the LDL test, I think it is the same sort of comment. We would have been delighted if everybody had behaved appropriately--a comment that is kind of consistent with Dr. Wood's a moment ago. When in other settings we have tested how physicians do with respect to LDL monitoring, there is that same problem. So, it is not optimal. It is not optimal in this population and it is not optimal in the standard of care these days.

DR. HEMWALL: I just wanted to make sure we gave a complete response to the question with regard to the messages that are in our materials for ongoing monitoring not only of your cholesterol--and the label specifically says if you have reached goal get your cholesterol tested once

a year--but it also says that one should be on the lookout for any change in their health condition and that they should see their doctor for any change in those conditions. We actually measured that in CUSTOM. We had people, as Bob Tipping pointed out, develop diabetes that didn't go to their doctor during the course of the CUSTOM study.

Another feature of the support and management system is the ongoing communication that goes on well beyond, into the future, where they will be receiving communications and regular messages within the materials. I urge you all to look at the materials that are in the box that we provided for you. Also the newsletters that come on a periodic basis when one opts into the program all encourage that retesting and the continual need to reevaluate your health status and the need to see a doctor.

DR. WOOD: Dr. Watts?

DR. WATTS: The success of the program is in large part dependent on the patient's accurate knowledge of their cholesterol level to know

whether they are appropriate to initiate their therapy, and their follow-up cholesterol level to know whether they are reaching goals. What I haven't gotten a clear picture of, though it may have been woven into all this, is information about the validity of patient self-reports of their lipid results, both for the initial assessment of whether they are appropriate candidates for OTC Mevacor and for subsequent studies to know whether they are meeting goal.

MR. HANSEN: This is going to be a tag team because I am going to first start with the general population knowledge of cholesterol numbers and the ranges because that is important if this product is approved in the general market. Then Bob Tipping will come up and show you exactly the people in CUSTOM who did know their numbers and how accurate were they in those self-reported numbers because we did test at the end of the study. So, if I could have slide 1938?

[Slide]

This is in the general population. We did

the study this year, and it shows a couple of things. First of all, awareness of total cholesterol numbers was virtually 100 percent and that is why it is not on the chart. Then, what you will see is the subfractions of LDL, HDL and triglycerides.

There are a couple of things on the chart, first of all, the knowledge of these terms--and this is just knowledge of the terms--has increased over time but it is certainly higher for total cholesterol than the subfractions but we are making progress.

Now I would like to go to slide 1943 because this is getting closer to home. This is actually do people know their own values?

[Slide]

This, again, is on an ongoing basis and we will show you trends. So, this is total cholesterol and can people describe their own cholesterol? For the most part, their total cholesterol--over 90 percent can describe it. Only 28 percent can give you a specific number but 91

percent can describe it as either being high, borderline high or normal.

[Slide]

If you go to the next slide, you will see that there is a drop-off on LDL but still pretty good numbers. Less know their specific number but, again, they have heard from their doctor or know for themselves and they can describe it as either being high, borderline high or normal.

Now, the real key question is how did people in CUSTOM who said they knew their range do compared to their actual values, and Bob Tipping will show that.

DR. WOOD: Well, the other question, going back to my point, is presuming they heard from their doctor that that is normal, that may not fit with the criteria from the panels. Do we know that? Do we actually know that when a patient says their cholesterol and their LDL is normal that that means that they don't fit the treatment criteria as dictated by the various recommendations?

MR. HANSEN: If we don't answer your

question we will come back, but I think what Bob is going to show is that people were able to describe either their exact number or whether it was in a range of either normal, high or low. Then we went back and looked at those numbers and he will tell you how well they were able to match those up. I think that will get to your question but, if not, I will clarify.

MR. TIPPING: Thanks, Jerry. Before I describe some numbers for you, let me just remind you a little bit of the design where behavioral decisions were based on an individual self-reported value but we did obtain the baseline actual measured values so we were able to address the question of what is the accuracy or the validity of that.

With our user population, we had 660 individuals who reported that they knew their value and then we were actually able to obtain the baseline value, and for 76 percent of them those two values agreed with regard to the ranges described.

DR. WOOD: Dr. Schade?

DR. SCHADE: Yes, I have a question. I am having trouble finding the information, and it may

be me, but my question is about diabetes. I understand this may not be the direct population being targeted but they actually represent a huge risk for atherosclerosis, but as I understood it from the presentation earlier this morning, the labeling or the package insert is going to state that if you have diabetes you should not take this drug. Is that right or am I confused about that? How are you actually handling a case when a patient knows they have diabetes?

DR. HEMWALL: Yes, that is one of the messages right in the main part of the label, that you are not to take the drug if you have diabetes, without first checking with your doctor. So, it is not a contraindication but it is a statement that says that you need to talk to your doctor if you have diabetes. In fact, we hope that if they find out that they do, they may need more comprehensive care than simply an OTC.

DR. SCHADE: Yes, that would be of concern to me only because I can see a rush of patients coming in, pointing to me, saying that they cannot take this statin and, by definition, other statins. It would be worrisome to the patient as well. I am concerned about that.

DR. HEMWALL: Well, that is a good concern, and I would want to take that into consideration with the team as far as perhaps even putting more of that information in the educational materials about the importance of having your lipids treated and to see your physician. It is not that it is a bad thing if you are a diabetic to take a statin, but more that you should be doing it in collaboration with your physician.

DR. SCHADE: Yes, I think some more explanation is needed because most of my patients who have diabetes read something and they immediately think it contains sugar, or something, because all these cold medicines and everything else contain that same statement and I get lots of calls when a patient gets a cold--can I take this,

this and this? And, inappropriately, they end up not taking something that would help them.

DR. HEMWALL: That is good advice. We would want to factor that into our materials.

DR. WOOD: That is a good point. Dr. Carpenter?

DR. CARPENTER: Going back to your earlier description of a lot of this process, challenging or raising new approaches to how we structure the paradigm of practicing preventive medicine, I consider that a great deal of obstacles and certain patients' access to various medications is cost. I just wondered if anyone has speculated whether insurance coverage for statins would change with an over-the-counter designation and if that would have any impact on getting this to the people of concern in contrast to using it as a prescription.

DR. WOOD: Well, it may well do but I think it is probably not the remit of the committee to address the financial issues, however controversial that might be, unless the FDA wants us to address that.

DR. MEYER: I would say it is to the degree that the issue of the overall benefit to the population has been raised, which also isn't

strictly our purview. I think it might be interesting to hear the answer to the question.

DR. WOOD: To rephrase the question, will it be covered under insurance? Is that the question?

DR. CARPENTER: Is there any information to indicate that with a change to over-the-counter status it would substantially affect availability because of lack of insurance coverage?

DR. WOOD: And I would extend the question, and would it result in other statins being taken off coverage for Rx?

MR. HANSEN: This was a key concern of ours because the goal of our program was to actually get people into the system and get on either OTC or prescription therapy if possible. So, we actually went out and did a study, an independent study with Towers Parent that was published in The Journal of Managed Care Pharmacy,

in November, and the results were pretty interesting. We had a good representation of most of the large managed care organizations and they have covered over 100 million lives, and the findings were that they view cholesterol as very different than they do allergy or heartburn, like with the recent switches of Claritin and Prilosec, that cholesterol is for more serious treatment. They also recognized, as we showed in the treatment gap, that most of the treatment today is with the high risk people with higher dose statins. So, they really don't feel like they would be capable of down-shifting or downstreaming those consumers because that would be bad medicine and, in fact, they may be liable for that. So, we do not see any evidence that there will be any major changes in formulary.

The only balanced statement I will give to that, however, is that if a person did come in and they were appropriate for the OTC label and were not on prescription lowering at the time, managed care said, hey, there is not a problem. As long as

they are appropriate for OTC, they can try that product and if they don't get to goal, certainly, we would put them on prescription therapy--so, a clear delineation between the person who is on an Rx today. No, we are not touching those people. In the future, if they fit the OTC profile, potentially.

DR. SCHWARTZ: Sandy Schwarts, University of Pennsylvania. I have been advisor to some of the PBMs and to some of the medical insurers regarding Medicare coverage decisions. You have to be careful. They make their own coverage decisions. But I think it is safe to say that an OTC preparation would not be covered by current plans, but also that it almost certainly would not affect the other current statins on therapy because of the dosing differential for treatment targets. For example, even PPIs, people who require higher doses of PPIs can still get coverage under almost every insurance plan in the country while you can get low-dose PPIs over-the-counter.

DR. WOOD: Dr. Neill?

DR. NEILL: I have a couple of questions. Several of the speakers have mentioned the treatment gap for these moderate risk patients, and

I am interested in data, if you have it, that looks at all 11,000 callers, of whom 3300 were evaluated, and in those groups how many were treatment eligible and how many were already on treatment pre and post CUSTOM? In other words, I am looking for evidence of efficacy that this self-management program does what you suggest that it would do when it is OTC in this CUSTOM study. Then I have a second question after that.

DR. HEMWALL: Well, the first answer is fairly simple. We did not collect that kind of information from the callers regarding their demographics or the type of information that you are looking for.

DR. NEILL: As a family doctor that takes these phone calls when advertisements end up on television, I am anxious to know for those 7000 or 6000 patients that did not present to be evaluated, what was the enticement for the 3000 that did, and

what was the dissuasion for those that did not?

DR. HEMWALL: Well, again, this may be in part an artifact of doing a study where you don't have a pharmacy in your local neighborhood which would carry the product in the real world. So, in the seven geographic areas in which we conducted the study, each had two sites. Here, in the Washington Beltway area, we had a site I believe in the Silver Spring area and one up--there is a northern side and a southern side and I can't remember the exact cities. We can get that.

But the point was that a lot of people realized, once they made the phone call, that they might have to either travel to a study site or they decided that there was something that was inconvenient for them and they didn't want to participate. They weren't given very much information, as per FDA working with us on the protocol--not to explain to them a lot about the study, other than that it was, indeed, a study; it was not something were you were actually purchasing a retail product. Although they were also told

that they would have to purchase the product and that may have dissuaded a lot of people who thought they were going to get free medicine.

DR. WOOD: You have a second question?

DR. NEILL: I will hold it till later. Thanks.

DR. WOOD: Dr. Clyburn?

DR. CLYBURN: We heard a lot about the OTC population and how they are interested in prevention and not necessarily wanting to acknowledge that they have any chronic illness like hyperlipidemia. Are we going to facilitate their denying that they have hypertension, obesity and hyperglycemia by putting medicines over the counter to treat hyperlipidemia?

DR. WOOD: It sounds like perfection is the enemy of the good, right?

DR. HEMWALL: I am not really sure I understand the question. Could you repeat it, please?

DR. CLYBURN: We spent a lot of time hearing about the OTC population being different

than the regular population, and that they are unwilling or don't want to acknowledge any chronic illness, are more interested in prevention. Are we going to make them feel good about themselves with over-the-counter medications and allow them to deny other illnesses?

DR. HEMWALL: No, I don't think that is the case but I think Jerry Hansen, who has done an awful lot of the consumer research and has a better understanding, may be able to address that question.

MR. HANSEN: This is a tough question because it has kind of emotional behavioral insights involved with it. So, I am not exactly accurate but I think I can say, after talking to 30,000 consumers over the past seven years, I can probably get pretty close. Hypertension and diabetes are viewed very differently by a consumer than is high cholesterol. I think you have probably all seen that in your practices.

The burden that high cholesterol has that those other ones don't is that diet and exercise is

usually tried first and if you don't succeed, that is considered a failure by the patient and oftentimes by the doctor as well. So, this is a situation where the patient really doesn't want to admit they failed or admit that they are sick and would like to try an intermediate step in between, whereas we don't see that with hypertension or some of the more serious conditions like diabetes.

DR. WOOD: Dr. Clapp?

DR. CLAPP: My interest is in the labeling of the product with regards to women who are under 55. Apparently, the reason that it has a pregnancy X categorization is because of the risk to the fetus to women of childbearing age. In this regard, the product is being marketed for women who are over 55. I am not sure if there is clarity on the package with regards to the reasons that women under 55 should not take the medication. Since that doesn't seem to be addressed, should that be listed in terms of "do not use if you are a woman of childbearing age," rather than a woman who is pregnant or lactating.

DR. HEMWALL: Yes, I think we can probably add additional language to the label in that regard, but it is important to recognize that the

reason that this drug is category X is because there is no benefit to treating a woman during the short term of pregnancy for lipid lowering, and there is an equation which goes into category X. And, if there is no benefit whatsoever, then even a small amount of risk renders it to be contraindicated and that is why the statins are category X, because there is no benefit to treating high lipids during pregnancy.

But the labeling question is a good one. In fact, other OTCs have already adopted that. As you well know or many of you may well know, the NSAID category of drugs, which encompasses quite a few of the OTC products, do have concerns about disruptions in the pregnancy or harm to the fetus with regard to inhibition of prostaglandin synthetase and all over-the-counter NSAIDs carry specific labeling warnings about not using the product in the third trimester with that exact type

of language which you suggest. So, certainly, there is room to strengthen the message in the Mevacor label beyond just do not use if you are pregnant or breast feeding.

DR. CLAPP: Then my question to you is additionally that if the reason for under 55 is because of concern of pregnancy--

DR. HEMWALL: No, the 55 is according to the NCEP guidelines as a risk factor. One of the risk factors is age for heart disease, 55 for women and 45 for men. The paradigm is know your lipids, between 130 and 170, and have two additional risk factors, and you automatically have one of those risk factors by having the age for men or women.

DR. CLAPP: So, then teasing out the risk to the unborn fetus, should there be something specifically noting that women of childbearing age should avoid this medicine because of the risk to the fetus, unless they are prescribed the medication by a physician?

DR. HEMWALL: I think the message would be more along the lines of if you are planning on

becoming pregnant you should not be taking this drug. The data that we have so far, and we would be happy to go into much more detail, is that the risk to the fetus, as seen in clinical outcomes, is very much similar to what would normally be a category C drug but, in fact, if a woman is inadvertently exposed in an unintended pregnancy the risk to the fetus is very small.

DR. WOOD: Could I make a suggestion--this is obviously a very important topic--but that we hold this until after the next presentation which is going to address this directly, and then we can come back to it in detail if we want? Dr. Parker?

DR. PARKER: My question is about the label comprehension study. My question is whether or not it is adequate. My understanding is that there were 696 patients and that over half of them were under the age of 45, and less than 10 percent of them were over 65. I guess I have a little trouble with that. If the purpose of the label comprehension study is to assess whether or not the label is adequately comprehended, the target

population for users is really small in that. So, I would like someone to address that.

I understand from the slide presented that looked pretty good, greater than or equal to 80 percent had acceptable responses on the measures. What about those that were incorrect, and was that data used in redeveloping the label so that it was more adequately understood? How was the data from the label comprehension used in CUSTOM?

DR. WOOD: Somebody want to address that?

MS. LEVY: My name is Stephanie Levy, and I run the label comprehension studies. If you could just ask me your questions one by one, I will be happy to try to answer them.

DR. PARKER: Could you address the adequacy of the study, number one--696 patients, less than half of them in the target age--excuse me, half of the participants in the label comprehension study were under the age of 45.

MS. LEVY: Yes, we designed this study in conjunction with advice from FDA. It was designed to be a representative sample. However, we did

feel it was important to supplement for low literacy groups, but it was felt to be important to include people who were not in the target group to confirm that they were not appropriate to use the product as well. In terms of women under 55, we did have 254 women in the study of that age group.

DR. PARKER: So, 255 [sic] women that would not be users of the drug were tested on their ability to comprehend the label. Is that correct?

MS. LEVY: That is right, because comprehension is supposed to test among the people who can use the product, do they recognize that, and among those who can't use the product, can they recognize that as well.

DR. PARKER: What was the performance on the label comprehension study of understanding your eligibility based on your age alone?

MS. LEVY: I can show you information that shows the self-selection among that group of women, but we don't have data that links that that is the reason but, certainly, we have self-selection among that group of women, if you would like to see it.

DR. WOOD: I think the question is, is there an age-related difference in the comprehension study. Is that the question?

DR. PARKER: Did these people understand the label well enough to be able to decide whether or not they are age eligible?

MS. LEVY: Could I have slide 1751, please?

[Slide]

These are the self-selection scores, both men and women in the different age groups. We looked at correct/acceptable scores and also correct and acceptable separately. You can see among the women under 55 years old, and there were 254 of them, 92 percent got a correct or acceptable score; 76 percent completely correct saying that they could not use the product.

DR. PARKER: Thank you.

DR. WOOD: I know we have more people who want to ask questions. I just want to be sure I have covered everybody at least once. Is there anyone who has not had a chance to ask a question

and wants to ask one that I missed?

[No response]

Then let's go to Dr. McClung.

DR. MCCLUNG: I want to come back to the differentiation--this is an easy question, by the way, that has a specific answer--in the jargon we have heard today, the OTC versus the Rx guys, one of the strong justifications for having Mevacor be over-the-counter is that patients would accept an OTC medication more than a prescription medication. Let me ask exactly how that question was asked where you got those answers. Was is asked "would you prefer to have a prescription or over-the-counter remedy for your heart health program?" Or, was the question asked "if lovastatin was available over-the-counter and by prescription, would it make a difference in your selection on the basis of lovastatin availability in those two ways?"

If you compare a prescription drug and an OTC drug, you have described that people who want OTC things don't want to see themselves as sick.

The other distinction is that patients see over-the-counter preparations as being natural and safer in some ways than chemical prescription type drugs. So, to compare prescription drugs with over-the-counter preparations like vitamin E isn't quite the same as comparing the acceptance of a specific product, in this case lovastatin, and a prescription versus in an over-the-counter circumstance. So, can you describe actually how you asked the question to derive the data that you presented to argue that over-the-counter availability would increase the interest among those who might choose to take it?

MR. HANSEN: Yes, let's look specifically at slide 58 if that answers the question. I believe it has the exact wording of the question.

[Slide]

So, what the National Consumer League did, because this was a concern of theirs as well and they wanted to understand what is the magic of OTC, they went out and asked people who were untreated, either at potential or known moderate risk to

themselves, which of the products you would more likely take action with.

The further description of this was that they are exactly the same product, exactly the same dose. The only thing that differs here is the distribution of the product. So, here are the results that you see, which one would you rather consider taking? Again, this was 20 mg Mevacor or the equivalent, whether it is OTC or Rx. You can see that 3:1 they would much more likely take action with an OTC than a prescription, which is the basis for our being resistant to Rx versus OTC. So, that is exactly how the question was worded and exactly how it was put into perspective, that this is exactly the same drug, the only thing that differs is how you get it.

DR. MCCLUNG: Does that assume that the cost is the same? Many people with prescription drugs are paying $15 for an Rx drug and they are paying whatever it is for an over-the-counter, so did that make any financial assumptions?

MR. HANSEN: I can't remember whether in

this exact survey they did put a price around it or not. We have had other surveys however where we put a price range, and we have certainly not finalized the price for Mevacor, but in the range of 75 cents to a dollar a day, just to put it into perspective. And the numbers you see there are very consistent across studies, that people, in that price range for an OTC, would prefer--at least the person we are targeting, would prefer to try OTC first versus Rx.

DR. WOOD: Dr. Woolf?

DR. WOOLF: To me, the CUSTOM study is a pivotal study so I would like to get some more information about exactly how it was conducted, sort of the nuts and bolts.

In the simulated pharmacy, what was the role of the nurse/pharmacist? Did this individual provide guidance if asked; provide guidance without being asked? What exactly did this person do?

Secondly, what was the cost to the participant for the drug, and how does the cost compare to what it is likely to cost in the

marketplace if it were approved for over-the-counter use?

MR. TIPPING: Your question was in the CUSTOM study design what was the role of the study site nurse that was acting as a pharmacist, and what was the cost of the medication. The study site nurse was there to answer questions but was specifically instructed not to volunteer any information. So, the participants could interact with them in a couple of fashions. They could ask a specific question about the label and they would get an answer to that specific question. Or, they could initiate, of their own accord, a full eligibility--is this product right for me? At that point the nurse would take them through all the eligibility criteria.

The second part of your question had to do with the cost of the product. It was $15 a box.

DR. WOOLF: And how does that likely compare to what it would be if it were marketed?

MR. HANSEN: Again, we haven't finalized the price. It is certainly within the range of

what we charge in the marketplace.

DR. WOOD: Dr. Watts?

DR. WATTS: We have heard a lot of information about the patients who self-selected to use Mevacor OTC, but I don't recall hearing much about the patients who decided not to use Mevacor OTC, and that information might be helpful in getting some idea of how effective this approach would be in making inroads to this treatment gap. So, I would like to know, if possible, what percentage of those who chose not to take the drug would have been candidates for the drug, that is, the proper age, the proper LDL cholesterol and other risk factors.

DR. HEMWALL: While we are getting that slide, I think Bob is going to have an answer for you, but we don't have as complete information on the people that were evaluators as we do on the people that were users. We have some information on some evaluators who went through an eligibility assessment but our information is less complete on them just because that was the way that we were

able to maintain hands-off on making sure they made the decisions on their own.

MR. TIPPING: Thank you for that question. It had to do with the people who didn't purchase the product. Right? If I could have the slide that we just talked about?

[Slide]

I am glad to get that question because we feel that this is a very important group too. If you recall from my presentation, there were over 2000 of these individuals who took the time to come to the site and do an evaluation of the product and then chose not to purchase.

They broke out in this fashion: 438 indicated that they needed more information and they left the site and didn't come back. There were 1673 of the 2111 who decided not to purchase. Of that group, applying all the label criteria--age and everything--98 percent of them were ineligible. In fact, if you come down a little bit more, there is 64 percent that is a subset of the 1673 and it is an important subset because they specifically

said they don't think Mevacor OTC is right for them. So, in this subset virtually each of them was found to be ineligible by some component of the label.

DR. WOOD: Dr. Taylor?

DR. TAYLOR: For your product to be effective over the long haul, a high degree of compliance is needed and you have shown in your CUSTOM that you did get some fair results. I am curious, did the individuals know that they were in a study? For example, did they sign a consent form?

The second question is were they provided any incentives for returning to improve their compliance?

MR. TIPPING: Yes, your question was did the participants in CUSTOM have to sign a consent form. That was the first part of your question. The answer to that is yes, but only after they had gone through the process and made a purchase decision.

Your second question I think had to do

with incentives--

DR. TAYLOR: To return; follow-up basically.

MR. TIPPING: No, there were no incentives--

DR. TAYLOR: For example, travel stipends, cash stipends?

MR. TIPPING: Only at the end of the study after all the decision processes had been made, there was reimbursement for travel. But during the whole course of the study as behaviors were being observed there were no incentives to return to the site. I would also remind you that they had to come back and actually purchase the drug, or if they needed a test or wanted a test, purchase the test. So, no real incentives to encourage--

DR. TAYLOR: But they received something at the end as a sort of end of study incentive?

MR. TIPPING: At the end of the study they were reimbursed for their expenses for traveling back and forth to the sites. There was no knowledge that that was coming during the course of

the trial.

DR. WOOD: That wasn't in the consent form? That is hard to believe. So, they just got a Christmas present at the end and that was astonishing to them?

[Laughter]

Presumably, just while we are thinking about that, the people who didn't show up and dropped out presumably didn't get the payments? Which is the question which I think is being addressed by Dr. Taylor, one of them.

MR. STRUBLE: My name is Bill Struble. I am part of the clinical team at Merck. To answer your question about compensation, the advertising for the study did indicate that they would be reimbursed for time and travel, as well as the consent form. It was designed not to be a sufficient amount to be an inducement or an incentive, and that was done in conjunction with the institutional review board. They didn't get that money until the end of the study, as Bob had said.

DR. TAYLOR: Did they know how much they were going to get at the end of the study?

MR. STRUBLE: We told them what the amount

would be when they returned at the end of the study, yes.

DR. TAYLOR: And on average, how much was that? Do you remember?

MR. STRUBLE: Pardon?

DR. TAYLOR: On average, how much was that?

MR. STRUBLE: They were to receive $35 per visit and $75 at the end of the study because we had an extensive list of questionnaires that they had to go through at the end of the study. What you have to keep in mind is that they were responsible for paying for their medication, as well as purchasing the cholesterol tests, and we considered that when we decided what the reimbursement should be because there is also time and travel expenses that were involved in that.

MR. TAYLOR: The other question I had was what percent of your participants that were users

had insurance?

DR. HEMWALL: We have that answer. It will take a minute to get it.

DR. WOOD: Why don't we move on to the next question and then you can come back to that?

DR. HEMWALL: The answer is 43 percent.

DR. WOOD: Let's go on to Dr. Neill.

DR. NEILL: Currently, the ATP III guidelines recommend that anybody that has an elevated LDL be evaluated for secondary causes of dyslipidemia before treatment, and if those causes exist they be treated, and if they are still not at target that treatment be initiated to get them to target. Am I hearing that the ATP IV guidelines will remove that requirement or recommendation? This is clearly only a guideline.

DR. PASTERNAK: Yes, it is clearly only a guideline, and as far as I know, there is no ATP IV planned yet, unless somebody in the room knows something I don't know. Remember, the label enjoins the user to seek the attention of their doctor at some point, and suggests that they have

to have their LDL cholesterol measured.

DR. NEILL: I am going to interrupt briefly because I actually looked at the box that was used in the study and there is nothing on the exterior of the box anywhere that suggests that you need to see a physician to be evaluated for secondary causes of dyslipidemia. Now, I am presuming, because they have another LDL, that at some point that has happened but that is a presumption that appears to have been made based on the fact that a consumer can walk into a pharmacy and know their LDL. I don't know whether that is a valid presumption to make, but the question is only peripherally related to that. It is more related to whether or not that is something that we believe is necessary and, if so, is there some way that that is included within this self-management package that exists that I haven't looked at yet?

DR. PASTERNAK: Someone else on our team may remember some of the details of it, but we certainly do recognize that there are secondary causes of hyperlipidemia and that a physician needs

to consider that for patients.

DR. HEMWALL: Again, I think it is all about the overall program that was intended to get consumers to their physicians, and these are primary prevention people that are otherwise in good health but they are warned in the label against having diabetes and also, as you probably noticed, if their triglycerides are above 200 they should not be taking the product if they don't talk to a physician.

So, there are a number of touch points which allow the consumer to recognize that they need to talk to a physician but it is not the same, obviously, as being worked up completely for high lipids, and may not be what actually happens in medical practice as well.

DR. NEILL: I may be missing this but I don't see any of those things on the exterior of the package, and I haven't heard with they are in the self-management materials that are available for consumers before they make the purchase. Now, I have new bifocals and that could be a big part of

the problem--

[Laughter]

DR. HEMWALL: I am looking at the label and it says do not use unless directed by your doctor, if you have very high LDL cholesterol, that is, above 171; if you have high triglycerides, above 200; or if you have a health HDL, good cholesterol, above 60. Also, do not use if you have had a stroke, diabetes--

DR. NEILL: I have found it.

DR. HEMWALL: Okay, and this is expanded upon within the materials, of course, to give more context to all that information. Referring to one of the earlier questions, we are not saying you shouldn't use a statin if you have these conditions but you should see a doctor first.

Also, I want to correct a statement we gave a little earlier about insurance coverage. That 43 percent number was for people who had prescription coverage, not just health insurance, and 82 percent had health insurance.

DR. WOOD: Frank?

DR. DAVIDOFF: Yes, I am interested in the apparent difference between the apparent requirements for approval of an over-the-counter

drug, that might be used by many millions of people on an over-the-counter basis, versus the information or evidence requirements for that same drug to be given to a much smaller number of people in a prescription setting. Because it appears that here, if a decision is made to go forward with OTC lovastatin, it would be on the basis of a single non-randomized, non-controlled, short-term study with no major clinical endpoints but, rather, a surrogate variable measured.

That prompted me to start thinking about the opportunity that industry had here to actually provide a landmark study. This is a historic opportunity. If an OTC drug for chronic use for primary prevention is to go forward, there would be the opportunity to demonstrate that it was, indeed, the statin that was having the benefit. Because I can envision a scenario in which there was a placebo arm in the CUSTOM study but, because there

is such a strong interaction with physicians, there might have been at least as much, or perhaps almost as much benefit from having been interactive with physicians and it may not have been the drug at all that really produced much of the primary preventive benefit. I would like to ask the question why a placebo arm was not included.

DR. HEMWALL: Well, first let me address one of your comments where you said this would be available to a much wider group of people. I don't think that the OTC population could ever come close to the Rx population that is currently receiving statins.

But having said that, the question that you are asking about the placebo control and the level of rigor that is required for an OTC switch is quite different from that required for the original approval of a drug as a new chemical entity, and I think our colleagues from the FDA would be willing to speak on that. This is the standard for OTC drugs to actually show consumer behavior in the hands of the consumers, and in

these observational studies typically placebos are not used because they are open-label and the consumer knows what they are getting.

Also, I might add that we have done three earlier studies of this same type of actual use in our first application so that we do have quite a range of data, using different studies designs, with very consistent results, as shown by Dr. Cohen in one of his later slides.

DR. DAVIDOFF: But if I may, the day a drug like this goes over-the-counter it is available to the entire U.S. population, much more than the limited and targeted population that is available by prescription. So, I think that that is a substantial difference.

The other point is that we really don't know the efficacy of an over-the-counter statin over six years or five years in an over-the-counter situation. Even if we did know that, we wouldn't know how much of that was attributable to the drug being available over-the-counter and how much of it was due to the interaction with physicians. The

CUSTOM study is actually a rather complex intervention study. The intervention consists of more than just the drug.

DR. HEMWALL: That is absolutely right. That is exactly what the program is intended to do, to be more than just a drug, but to create that level of education and awareness among the consumers that use it to get them to interact with the healthcare system as well, whether it be a pharmacist or doctor, and that is what we actually intended to show with CUSTOM.

Keep in mind that, despite the limitations of the open label, we did have a 21 percent reduction in cholesterol across the entire population of those that fasted at both baseline and at the end of the study, and an overall 24 percent which is very consistent with the placebo, controlled trials.

DR. DAVIDOFF: If I may, that is in the group in whom you did manage to measure both at the beginning and at the end. It doesn't take into account the larger denominator of people who would

be likely to take this in an open over-the-counter situation. Furthermore, we don't know how long that lasted because they weren't followed for five or six years. So, I would repeat that we do not know the efficacy. It is probably not zero but I don't think it is 20 percent.

DR. WOOD: Frank, just to follow-up on that, I am having some difficulty following that. Isn't that also true for every Rx study that we do? I mean, you know, we study ACE inhibitors in heart failure and we extrapolate that to the entire population with heart failure and make conclusions from that. I am struggling to understand what the difference is here, particularly when you have such a large database of efficacy, real efficacy not sort of symptomatic efficacy.

DR. DAVIDOFF: Yes, but that efficacy begins to melt away when you take into account long-term adherence; when you take into account the degree of risk to start with. This is a much lower risk population than the prescription drug risk group. And that is true for all primary prevention

studies. I repeat, I don't think it would be zero but I think to rely on efficacy data and to make direct extrapolation from efficacy data from the randomized trials to the over-the-counter situation, even including data from CUSTOM--I have some difficulty with it. That is really all I am saying.

DR. WOOD: Dr. Patten hasn't spoken.

DR. PATTEN: Yes, I would like to ask a question about the AFCAPS/TexCAPS cohort in the post hoc analysis. We are given figures for the size of the cohort and we are given the initial gender breakdown, with 5608 men and 997 women, but we are not given a gender breakdown after that. So, I would be interested to know if enough women made it into subpopulations 2 and 3, where event rates were examined, so that we know that gender is or is not a factor here in the event rate.

DR. HEMWALL: In the complete AFCAPS cohort there were about 900 women and the same magnitude of risk reduction was seen although it did not reach statistical significance. So, if you

were to slice that further into the OTC cohort, then you would also not see the same level of statistical significance but the magnitude of risk reduction was similar. We have an expert here on women's cardiovascular issues who can address more completely the role of risk reduction in women, which may in some cases be different, if you would like to hear some discussions along those lines if that is part of your overall question.

DR. PATTEN: It is.

DR. HEMWALL: I will introduce Dr. Sandra Lewis.

DR. LEWIS: Sandra Lewis. You know, women are different and women have been included in many of our trials. I was the lead investigator of the subset looking at the CARE study which looked at a group of women who had had a heart attack but had total cholesterols less than 240. At that time we were not treating patients who had total cholesterols less than 240, independent of risk. So, this was a secondary prevention trial, and the women in the CARE trial actually had a more

significant reduction in myocardial infarctions, stroke, risk of cardiac death, bypass surgery, angioplasty. There are women included in many of our secondary prevention trials and also in some of the primary prevention trials. The risk reduction across the board is very similar to the men although, because of numbers, they may not reach statistical significance because of small numbers. And we need to get more women into these studies.

I think particularly the differences between a woman's perception about cardiovascular disease is really key to this OTC question. Women look at responsibility for having developed heart disease as having done something bad, and they are very anxious to be proactive about their health, patient centered responsibility. So, for a woman to have the option to take a product that is going to make her heart healthy, instead of being told that she has an illness, is a really positive thing. We have an epidemic of cardiovascular disease in this country. We have decreased our mortality rate for men. So I see this as a

tremendous opportunity for a very special group of women that would take the opportunity to benefit.

DR. WOOD: We have two more questions, Dr. McClung and then Dr. Follman, unless there is someone else.

DR. MCCLUNG: Let me ask you briefly about the muscle complication of statins. Is there a relationship between time of exposure and the probability of experiencing muscle problems? That is, is there a susceptible cohort that is more apt to develop the problem early in exposure or does the risk increase exponentially with long exposure, or is the risk simply linear with time?

DR. WOOD: Maybe I can answer that for you. From the Baycol database, many of the people there developed rhabdomyolysis very quickly when they were switched from one drug to another, and many of them virtually within a few days or weeks when they were switched. The reason that may be a relevant database is that the incidence there was much higher than has been with any other drugs. Now, for this one I don't know.

DR. MCCLUNG: But is that quite the same thing? Switching from one drug to another could be a difference in drug. But if a patient is on a

drug that is known to cause that, is the probability of experiencing the problem in the first six months of exposure different than in their third or fourth year of exposure?

DR. WORTMANN: My name is Robert Wortmann. I am from the University of Oklahoma. I didn't hear the last part of your question. The first I think had to do with when do people who develop muscle complications from statins do that? Is it linear with time or is it sudden? And, it is all over the map. There is no consistent pattern with statins that are still available. Some can get it right away; others after weeks; others after months; others after years. Cerivastatin was a different compound than those that are still available. It is metabolized differently and I think it had reasons why it developed more rapidly. There was a second part to the question?

DR. MCCLUNG: No, I just restated it in a

clearer way the second time.

DR. ORLOFF: Let me just make a comment from the FDA side, that it is the impression from everything we know about statins that there is no cumulative dose-related toxicity, and I think that is what Dr. McClung is asking. There are a lot of unknown factors that go into the development of myopathy but it does not appear to be related to duration of use per se.

DR. WOOD: Dr. Follman, you have the last question unless someone else has something.

DR. FOLLMAN: Thanks. I just wanted to expand on what Dr. Davidoff was talking about earlier. I am new to the over-the-counter world and I think things are different here than in the prescription world. So, if we are evaluating the evidence for a prescription drug we compare placebo to the treatment. That is because in the real world the drug isn't available to anyone so it is proper, I think, to compare, say, a statin to nothing, say, in 1988. This is a different world now when we are considering the over-the-counter

use of Mevacor. Statins are currently available so I think the question in my mind is not whether statins work compared to nothing, but how would statins in an over-the-counter world compare to the way statins work in the current prescription world.

So, the numbers of efficacy that we have heard quoted, say, the number needed to treat 25, 48 or whatever, is for the statin versus nothing comparison. I think the relevant comparison is how would they work in a prescription world compared to an over-the-counter world. We don't really have evidence of that directly here. But, in my mind, the ideal thought experiment would be to randomize, say, cities to the current prescription world or to an over-the-counter world and then see what the cardiovascular event rates would be comparing city to city. I realize that is not doable whatsoever, but I think that gets at the idea of, you know, you can't compare statins versus nothing; you have to compare statins to some partial use of statins.

If this is approved, there will be some people who take Mevacor over-the-counter who would

have used prescription statins if we didn't approve it and they might get better treatment. So, I think there is not really direct evidence on this comparison that I am interested in, prescription versus over-the-counter as opposed to statin versus nothing.

Interestingly, in the packets that you gave us there was what I would probably term sort of an approximation to this thought experiment I just mentioned, which is the lipid-lowering component of ALLHAT where they randomized about 10,000 patients to either a fixed dose of pravastatin 40 mg versus usual care. So, you can think of the fixed dose of pravastatin as sort of an over-the-counter world and then the usual care as a prescription world because in that trial people on the usual care arm got prescription statin as they felt it was necessary. During the course of that trial about 30 percent of the people in the usual care arm ended up on a statin, and overall there was no difference in CHD event rates between the usual care and the fixed dose of

pravastatin arms in this long trial with a lot of people.

So, to me that is somewhat relevant to this. It is a different drug, and so on. It is not a pure comparison with the prescription world to the over-the-counter world but it seems to be the closest approximation and the most evidence that we have available. I think it is not very promising for an over-the-counter statin if you take ALLHAT seriously as an approximation for this thought experiment.

DR. WOOD: Didn't ALLHAT show that there was no difference between the arms?

DR. FOLLMAN: Right.

DR. WOOD: So that would seem positive.

DR. PASTERNAK: I would like to respond just to the ALLHAT issue. I had the opportunity to write the editorial discussing the ALLHAT results, and the title of my editorial is consistent with the comment I am about to make, which is "Less is Less." The important part to understand about ALLHAT is that the delta LDL, the difference

between the treatment group and the control group at the end of the study was about 12 percent total cholesterol difference.

The other important point to consider for ALLHAT is that if one looks at the point estimate, yes, it is correct that it was not statistically significant, it was a negative study. But the point estimate of risk reduction fits exactly along this log linear line. That is, the group had about a 10 percent risk reduction because the sample size wasn't statistically significant.

So, our point and my point in that editorial was--and I think it is important to think of this in the context of the individual who is getting treatment--that there is risk reduction associated with LDL lowering. For those individuals who get a 20-25 percent LDL lowering, as we have shown will happen with 20 mg of lovastatin, their risk will be lowered by 25 percent. It gets very complicated comparing one study to another, and I think it is important to view ALLHAT as fitting in the context, not as a

study which proves that that particular statin or that particular way of administering a statin doesn't work.

DR. FOLLMAN: I guess I would just say--you know, you mentioned that in that trial there is a delta LDL of about 11 percent or so, and I am wondering would that be the delta LDL or something even smaller in a prescription versus over-the-counter world. The issue to me would be would we be improving the public health with over-the-counter Mevacor compared to the usual prescription world we have now?

DR. WOOD: That may need at some point some comment from the over-the-counter people to explain the criteria for approving an over-the-counter drug I guess. But that could wait until after lunch. Dr. Caprio had a question.

DR. CAPRIO: I have a question. Given the increasing prevalence of non-alcoholic fatty liver in our population, I haven't seen anything recommending testing for NFTs prior to starting this. This is quite concerning because we are

seeing patients with very high ALT.

DR. HEMWALL: That is an excellent question, and we actually have a fairly comprehensive answer to that question. It may not be that we want to start off on that discussion right now. I will ask Dr. Wood.

DR. WOOD: I think I agree.

DR. HEMWALL: But we do want to come back to it.

DR. WOOD: So, why don't you think about that over lunch and we can start with that when we get back from lunch? How about that? Is that okay with you?

DR. CAPRIO: Yes.

DR. WOOD: Neal?

DR. BENOWITZ: I have two very specific clinical pharmacology questions and I just want to follow up. I know we talked a lot about this on the compliance issue. One is that there was a statement in the brochure that we got about renal disease and changes in lovastatin metabolism, that that would be contraindicated. I didn't see that

in the package insert stuff.

The second thing is that these are health conscious people, taking dietary supplements and I didn't see anything about interaction with dietary supplements, like St. John's wort and things like that.

The compliance issue--just thinking back, I have had a lot of experience with smoking products over-the-counter and there are two important issues that I think we have to think about. One is that even for short term, even for three-month OTC instruction, compliance is terrible. Most people stop taking it after a few weeks. The more you comply, the better you do and I am very concerned that this six-month trial will not reflect the six years that it takes for a number needed to treat at 40.

The other thing is the cost issue. Cost is a big question. That has certainly been raised with the smoking products. If we did these calculations right, four boxes at $15 a box is 33 cents a pill versus the projected 75 cents to a

dollar pill which would also enhance compliance in a six-month trial. So, I think I need some reassurance that people are not going to be just throwing away their money by taking the pill intermittently or taking it in a way that is not going to benefit them. So, those three questions.

DR. HEMWALL: I heard a question on labeling warning or statement on renal disease. As of our understanding, there is no concern with renal disease with the 20 mg dose. We haven't put that in the label but that is something that is often seen in OTC drug labels and, certainly, if there were data to support it and FDA were in agreement we would consider putting that in.

I want to answer a couple of those questions about compliance over the long term. I think we do have some good data. It is certainly not five- or six-year data but this is data that is fairly unique for an OTC drug. Could I have the slide that shows the 076 results?

[Slide]

This is a study that we did with 10 mg in

our earlier program. Although the dose is different, I think it is important to see the compliance that goes over an 18-month period. The top line shows the number of pills being taken over the time frame, representing the percentage of people that were 75-100 percent compliant over this time frame. Then, the bottom line shows the actual number of people that stayed on drug during that time frame.

So, you can see that after about 18 months we have about 50 percent still taking OTC Mevacor under the simulated conditions of an actual use trial. These numbers actually compare very favorably to what is seen in the prescription environment, and the numbers are in fact, in some cases, dramatically worse than this. These numbers are perhaps most consistent with what is seen in patients that are taking a statin for secondary prevention after having had their first coronary. But the numbers for people in primary prevention are much lower than this, probably falling off to about 30, 35 percent, and those data are in our

background package in your materials.

The other thing to point out is that there is a strong precedent with over-the-counter aspirin which people take every day fairly easily and simply without any concern. We have very good data from the aspirin manufacturers on compliance over the long term. So, we think that that is also typical of users who might use a product like this, the heart-healthy, motivated consumer, which would again show that they would have higher compliance levels possibly than their prescription counterparts.

DR. WOOD: Was there someone else who wanted to comment?

[Slide]

DR. HEMWALL: This is just a review of all the studies that have looked at compliance with statins over different time periods. Of course, even these studies only go out to two years at most, where the persistence rates vary from 25 percent to 64 percent, and then looking at the three Mevacor studies that we have so far for six

months and one for 12, and it doesn't have the full 18 months on this slide for the 076 study. Those are the numbers that compare to what is published for prescription statins.

DR. WOOD: Any other comments?

[No response]

In that case, I have to do the usual bureaucratic stuff. In the spirit of the Federal Advisory Committee Act and its Sunshine Amendment, the committee should refrain from discussing this topic during lunch, any other breaks or this evening. Please save your discussion for the open forum of the meeting. I am told on good authority that it is all right to ask a waitress if this is a low cholesterol lunch and it is all right to look for an asterisk on the menu! Let's try and be back at 1:15 and we will start promptly at that point with the liver function test discussion.

[Whereupon, at 12:15 p.m., the proceedings were recessed for lunch until 1:15 p.m.]

A F T E R N O O N P R O C E E D I N G S

DR. WOOD: As I promised before we broke for lunch, we are going to give the first few minutes to the sponsor to present some of the liver data. So, if the sponsor is ready, let's get started.

DR. HEMWALL: Thank you, Dr. Wood. We had a question before the break about liver function monitoring and I want to see if I have the question right. It is looking at people that might have undiagnosed liver disease that would take the product without having a baseline test.

DR. WOOD: I think there were two questions. One was excluding people who might have liver disease and I guess unasked there, but relevant, is whether these people are truly at greater risk for developing liver disease after they take the product. Then the second question I think was related to whether there was a real risk of liver disease from this product at this dose, at least that was my understanding of the question. Is that right? Okay, the questioner acknowledges

that.

MR. HEMWALL: We will start by introducing Dr. Paul Watkins who will address this from the perspective that he has in the academic frame.

DR. WATKINS: Paul Watkins, University of North Carolina. I guess I will address the second question first. That would make sense to me. The question is can statins at this dose--lovastatin--cause significant liver injury? That is the question that I heard.

The sponsor has provided a lot of data in the packet about this. The original concern about statins as being potentially liver toxic came out of preclinical studies which showed that in certain animal species that drugs, and lovastatin in particular, caused hepatocellular necrosis. Then, when the drug proceeded into man, there were observed LFT elevations, alanine aminotransferase elevations. So, a reasonable assumption was that severe live toxicity was a problem.

However, in the last five years there has been a re-thinking of the issue. In the

preclinical models, you can actually reverse the toxicity by nutritional supplementation and mevalonate, suggesting that this is a pharmacologic action related to the cholesterol-lowering property. Furthermore, in man, in all the clinical trials that have been done, there really has not been a signal for clinically significant liver disease relative to placebo arms. And, in the post-marketing reports, although there have been reports of severe liver injury, including acute liver failure, the incidence has not been distinguishable from the anticipated background after 27 million patient-years. So, the true risk of severe liver disease is extremely low and indistinguishable from the anticipated background incidence of idiopathic liver injury.

I am sure there is data the company could show to back that up if there are any specific questions, but the consensus is that liver monitoring is not useful during treatment with the drug. As I say, I don't think that is in contention. The question is are there

subpopulations where there may be a higher true risk of significant liver injury, and preexisting liver disease is the question raised.

That has been addressed, and in the sponsor's book there are the study results of Chalasoni et al., at the University of Indiana, that looked in a large database at patients who had abnormal liver tests, abnormal serum ALT, and were started on statins, followed for six months and compared it to a larger population of people who have chronic liver disease, elevated ALT, and did not go on statins, and found no difference in the incidence of mild and severe ALT elevations between the two groups.

I understand there is a larger study being done at Kaiser right now by the company that has preliminary data that supports the same observation that the incidence of ALT elevations is not increased in patients who have preexisting liver disease.

But I think the fact is we know that patients who have preexisting liver disease do not

have a very significant risk certainly of having severe liver injury when going on lovastatin from the post-marketing experience. That is because about one-third of patients who have hyperlipidemia have fatty liver somewhere in that spectrum. And two percent or up to two percent of the American population has chronic viral hepatitis. And, what the Chalasoni paper showed us was that physicians who dutifully measure baseline ALT will still start some of those patients on statins in spite of an elevated ALT.

As Dr. Wood pointed out, physician compliance with monitoring for liver events is notoriously poor, and in the Chalasoni experience only about 50 percent of patients had a baseline check at all. So, given this enormous background of chronic liver disease in the population and the incomplete and poor nature of monitoring, I think it is reasonable to assume that in the 27 million patient-years there are many million that reflect people with underlying liver disease and, in spite of that, there is this remarkable track record of

safety where you really cannot distinguish a signal above the anticipated noise.

So, in summary, there will be people undoubtedly who don't read the label or don't know they have preexisting liver disease who would go on and take the drug. But it is my opinion, and I know Keith Tolman's as well, that the risk in terms of liver injury is very small for those individuals.

DR. WOOD: Dr. Caprio, does that help?

DR. HEMWALL: I wanted to follow-up with something that Dr. Watkins mentioned, and this is the Kaiser Permanente study. I also wanted to make sure that the committee is aware that there is an application in review by FDA to relax the liver function monitoring requirements in the lovastatin Rx label to be more consistent with the idea that an OTC might be available that does not require liver function monitoring.

One of the key questions at hand where the data are still fairly sparse, although the Chalasoni study was just mentioned, is the concern

about people that do have undiagnosed liver disease and what would happen to them if they took a statin without having a baseline liver function test. And, there is a study that is under way where the results have come in that we have only been able to share preliminarily with FDA, but they have been kind enough to allow us to share that with the committee today. But keep in mind that the FDA have not actually reviewed all of this data and given us their own input on it. Can I have the first slide?

[Slide]

This is in the Kaiser Permanente database where we looked at two different patient cohorts, those that were exposed to lovastatin with evidence of liver abnormalities; those who were unexposed, patients with the same level of evidence of liver abnormalities but who did not take lovastatin, and then examining lab inpatient and outpatient databases used in the exact same way for both cohorts. Next slide.

[Slide]

The disease inclusions covered virtually any type of etiology that would result in liver disease so that we are covering all the bases where

we have, in fact, been a little weak in that in the Chalasoni study, done in Indiana University. We do have patients with viral hepatitis. So, the retrospective chart review as done and we found the following--next slide.

[Slide]

There were approximately 7000 patients exposed to lovastatin with liver disease, and we used Hy's Rule as the endpoint which is multiple lab abnormalities in a well-defined and accepted outcome endpoint for liver disease. And, the total person-days of people exposed to lovastatin in this group was, as you can see, over two million, with an incidence rate of 2.6/10,000 proceeding to having more advanced liver disease as defined by Hy's Rule. In the control group there are about 37,000 individuals who did not receive lovastatin but had liver disease and were followed to reach an outcome defined by Hy's Rule, and there were 626

patients who had that outcome. That makes an incidence rate of 11/10,000 person-days. So, the incidence rate with those exposed to lovastatin is actually statistically lower than it is with those not taking lovastatin, and we won't draw any conclusions from that and we will let FDA review the entire study, and also the various cuts of the data that are still forthcoming. But I thought it would be important for the committee to know that this study has been done and at least the preliminary numbers are looking very strong in favor of the liver safety of lovastatin even in people that have preexisting liver disease.

DR. WOOD: Unless there are any burning questions, let's move on. Dr. Davis-Bruno?

FDA Presentation

Reproductive and Fetal Toxicity

DR. DAVIS-BRUNO: My name is Karen Davis-Bruno.

[Slide]

I am a supervisory pharmacologist in the Division of Metabolic and Endocrine Drugs. I have

been asked today to provide you with an overview of the lovastatin nonclinical or animal developmental data.

[Slide]

As a means of introduction, what I will first do is provide an overview of pregnancy category labeling in accordance with the Code of Federal Regulations, or the CFR. Then I will discuss CDER's interpretation of the lovastatin developmental data which supports the current pregnancy category labeling. Then I will move on to a discussion of CDER's interpretation of the developmental data.

I should add that Merck has submitted an extensive amount of developmental data, over roughly a 24-year period which represents roughly 40 such types of studies. So, in the interest of time constraints, I certainly can't go into details of every single one of those studies but, instead, what I will do is provide a broad overview of CDER's analysis of that submitted data. As I mentioned, the data is subject to interpretation

and I will try to point out areas where our interpretation differs from that of Merck's.

One of the differences in data analysis between the sponsor and CDER is in the definition of maternal toxicity. This has implications in determining the clinical relevance of these animal findings that were observed, and I will spend a good deal of time discussing that.

Lastly, I will briefly define CDER's interpretation of the drug-related fetal and neonatal findings, which include fetal and neonatal mortality; developmental delays and skeletal malformations.

[Slide]

The Code of Federal Regulations, or the CFR, specifies pregnancy category labeling for drug products. This slide summarizes the various categories in order of increasing human concern, from A down to X.

It is noteworthy that the determination of a specific category depends not only on the human data but also the animal data that is available,

and certainly the relative risk-benefit ratio that is perceived. So, for example, pregnancy categories A and B, which you see at the top of the slide, are reserved for cases where there is no perceived human risk.

Category C, which is shown in the middle of the slide, is reserved for cases where there is no human data although there may be animal data that demonstrates a fetal risk. However, the important point to make is that the risk-benefit ratio is acceptable for the indicated use.

Category D applies to cases where there is human fetal risk based on actual human studies or on post-marketing data, but in these cases the benefit outweighs the risk. Examples of these type products would be products that are used to treat a life-threatening type indication.

Last is pregnancy category X in which the product is contraindicated for use during pregnancy in pregnant women because there is a human and/or animal series of data that indicate a fetal risk. But in this case, it differs from the other

categories in that the risk-benefit ratio is unacceptable. That is, the risk outweighs the clinical benefit.

[Slide]

Since its approval for marketing in 1987, Mevacor has been labeled as a pregnancy category X, as are all the statins. The rationale for the current pregnancy labeling is summarized on this slide.

There are no well-controlled studies in pregnant women for Mevacor. There are, however, some post-marketing reports of fetal adverse effects on live births. In these cases exposure has been established and it appears to occur within the first trimester. However, the caveat is that it is limited data so the cause and effect cannot be demonstrated. However, there clearly are findings and this would certainly not allay our concern.

The animal studies, which I will explore in some detail, show fetal and neonatal adverse effects in the absence of maternal toxicity. This

is an important distinction because it is felt that the findings in the absence of maternal toxicity are those that are potentially relevant because a responsible physician is not going to dose up to the point of maternal toxicity.

I should state that both CDER and Merck agree that there is no benefit to temporarily treating pregnant women. Therefore, we both agree with the contraindication during pregnancy.

[Slide]

For those of you who may not be familiar with developmental study designs, I will briefly review these in this current slide. Standard reproductive and developmental evaluations are done in accordance with ICH guidelines S5A, which is a guidance to industry. Generally, these study designs fall into one of three categories. I also want to point out that this is considered the minimum for product registration and Merck has clearly, over a 24-year period, submitted a substantial number of these types of studies which exceed the minimum.

For the purpose of discussion just to describe these types of studies, the traditional segment 1 study which you may be familiar with is

really a fertility/early embryonic developmental study. It is performed usually in one species, usually a rat. The exposure is performed prior to and during mating in either males or females. In females the exposure continues from mating through implantation.

The segment 2 studies are set up to asses embryo-fetal development. They are usually done in two species, both rat and rabbit. In this case, exposures are done during organogenesis.

The segment 3 studies, which are peri- and postnatal developmental studies, are usually performed in one species, usually the rat. Exposure occurs from implantation to the end of lactation.

[Slide]

This slide summarizes Merck's interpretation of their reproductive and developmental data. Specifically, they denote that

the developmental toxicity seen consists of rat skeletal anomalies which occur at maternally toxic oral doses, those doses that either equal or exceed 400 mg/kg/day. This is a very high exposure dose.

Moreover, they determined that the skeletal anomalies are a direct function of fetal nutritional deficits which are the result of reduced maternal food consumption and maternal body weight. These factors are a function of maternal toxicity, specifically for forestomach inflammation, which can become progressive leading to hyperplasia of the squamous epithelium. Merck hypothesizes that the forestomach inflammation is due to a local up-regulation of HMG CoA reductase in the rat forestomach. Moreover, the rat forestomach is an organ specific to the rat. Humans just don't have this organ.

They believe that the histopathology is reversible by co-administration of mevalonate. I should note that the actual studies that show HMG CoA reductase up-regulation were performed in hepatocytes, not in forestomach.

Merck feels that these particular skeletal findings are probably not clinically relevant because they occur in a rat specific organ, as I

mentioned, and they occur at a significant exposure multiple compared to the proposed 20 mg clinical OTC lovastatin dose. CDER doesn't necessarily disagree with this interpretation of these findings that are extremely high exposures, but we believe that this interpretation is only part of the story.

[Slide]

One of the differences in interpretation of the data involves the definition of maternal toxicity. According to Merck, maternal toxicity occurs at an exceedingly high dose, at or above 400 mg/kg/day given to rats by oral administration, and it results in the forestomach hyperplasia that I mentioned. But if you actually go back and look at the data, you find that at exposures less than this dose--so between 100 and 400 mg/kg/day--given to rat dams by an oral route during pregnancy, you see that there are maternal decreases in body weight gain of roughly 10 percent and you see decreased

food consumption.

Moreover, when you look at the studies that administered lovastatin to the rats during pregnancy by a different route, by a subcutaneous route in order to avoid the forestomach toxicity, you still see maternal toxicity in that you still see maternal mortality and you also see decreased body weight gain.

This suggested to us that perhaps a more conservative maternal no-effect level, no observable adverse effect level, which is what NOAEL is, could be established at an 80 mg/kg dose which represented about a 60-fold exposure relative to the proposed 20 mg clinical dose.

What we did is, having established this NOAEL effect level, we went back and reviewed the reproductive and developmental data from 1980 and looked to see if there were any fetal or neonatal findings at these doses and below. What we found was that there were fetal and neonatal findings that were observed in fertility, embryo-fetal studies through postnatal developmental study

designs. The results of this analysis are briefly summarized in your briefing document. In the interest of time, I can't go through those specifics. But the results are summarized on the next slide.

[Slide]

This summarizes fetal and neonatal findings at clinically relevant exposures. So, at exposures in rats less than or equal to five times the therapeutic exposure--and what I mean by therapeutic exposure is the exposure that you would achieve following a 20 mg clinical lovastatin dose--you still see fetal findings. You see fetal and pup mortality and you see fetal and pup decreased body weights. In some of these studies we have observed these findings at exposures equivalent to the therapeutic exposure.

If you look at studies where higher doses were used and greater exposures were achieved, you begin to see the developmental delays which involve changes in reflexes, such as the righting reflex, the auditory startle response, and you see effects

in swimming and open field effects. You also see some incomplete skeletal ossification.

If you go at still higher cephalosporins, 25 times, you begin to see these skeletal malformations that I discussed previously. These translate to increased supernumerary ribs and wavy ribs and, in addition, you still see the incomplete skeletal ossification. I want to emphasize that all these findings occur in the absence of maternal toxicity.

[Slide]

In addition to those studies, Merck has also looked at co-administration of lovastatin in the presence of the end products of HMG CoA reductase, specifically, mevalonic acid co-administration or cholesterol co-administration with lovastatin. Our interpretation of these data is that you do see attenuation of the more severe fetal malformations, but you still see wavy ribs and incomplete ossification present, and you still see evidence of maternal toxicity. To us, the results of these series of studies support that the

fetal toxicity is related to disruption of cholesterol biosynthesis by lovastatin.

[Slide]

If I could summarize our interpretation of these studies, it would be that fetal and neonatal toxicity is seen in the absence of maternal toxicity; and that the drug-related fetal and neonatal toxicities include skeletal malformations, mortality and developmental delays. Moreover, some of these fetal findings occurred at exposures that are similar to the clinical exposure, that is, the proposed 20 mg lovastatin OTC dose. And, these findings are potentially relevant to clinical risk assessment. Moreover, our feeling was that the pregnancy category designation is still valid.

[Slide]

A developmental no-effect level can be established in various species, as shown on this slide, for both rat, as you have seen, the rabbit and the mouse. This is a level of exposure where there are no fetal or neonatal findings observed, and that is indicated in this column where the no

observable adverse effect level is indicated. This exposure level is then expressed in this next column, indicated by the safety margin column. This exposure level is, again, expressed as a multiple of the human exposure following a proposed 20 mg lovastatin OTC dose. The comparisons are based on body surface area rather than actual pharmacokinetic or AUC exposure data but they do indicate that there is establishment of a developmental no-effect level, which is comparable across the species but, as you can see, the exposure multiples are relatively low.

[Slide]

In 2004 Merck submitted to us new postnatal neurodevelopmental data. This data was actually requested by the agency to address data gaps in the neurologic development based on limitations in postnatal study design between the species. For example, the major periods of myelination occur in the rat postnatally, specifically weeks two through four, but occur during the second and third trimester in humans.

Our feeling and the advice of our internal experts was that the postnatal developmental study designs may not adequately evaluate this particular

event. Moreover, as you have seen briefly, the prior studies had shown that developmental delays occurred in prior postnatal studies. So, we specifically requested a detailed neurodevelopmental assessment and recommended direct dosing of rats during the critical period of neurologic development. We specified that we would like to see evaluation of exposure, establishment of a no-effect level, detailed brain histology, and certainly adequate behavioral and functional developmental assessments.

[Slide]

The study that we actually received in 2004 was a direct dosing neonatal rat study. The dose selection for the higher dose tested in the actual study was based upon a dose-range finding study looking at acute dosing. The results of that study suggested that at a dose of 20 mg/kg/day there were findings such as a decrease of body

weight gain in these neonatal rats, and some injection site alopecia and scabbing.

Based upon this, in the definitive study the high dose was halved so that a 10 mg/kg/dose was tested. The drug was given subcutaneously from postnatal day 4 in these neonatal rats up to days 41 or 51, depending upon the type of evaluation that was performed.

The results of these studies suggest to us that there was a short-term learning retention decrease. Specifically, there was an effect in the passive avoidance test. Moreover, the functional observational battery also showed an increase in central nervous system activity in the same group. We felt a no-effect level for this particular study could be established at 5 mg/kg/day, which would achieve a rough exposure of 20 times that of the proposed clinical dose based on AUC.

I should point out that this 20-fold sounds like a large exposure multiple relative to the other postnatal studies that I described, but you have to keep in mind that the study design for

this particular study is very different. This study is a neonatal rat study in which the neonates were directly dosed and exposures were based upon known exposures in these neonates. In the previous postnatal studies the mothers were the ones who were directly dosed and so the exposures are based upon maternal plasma exposures.

Moreover, the only way that the neonates could be exposed in the earlier postnatal studies would be through placental transfer--I should say that is how the fetuses were exposed. The neonates would be exposed only through drug that was excreted in the milk.

[Slide]

So, our assessment of the new neurodevelopmental data is that there are decreases in short-term learning retention; increased activity in the central nervous system, at least in high dose females. And, these learning and behavioral findings are consistent with the prior postnatal evaluations. However, we felt, through several discussions with the sponsor, that the

neurologic evaluation was somewhat minimal in that the passive avoidance test, being the only measure of cognitive function, was somewhat minimal. Our reasoning for this was since various tasks could be assisted by different neural systems a second neurobehavioral test had been recommended, specifically a swimming maze.

I should also point out that the histopathology done in the study was focused on neural tissues only. I believe it was brain, tibial and sciatic nerves, and only in the high dose treatment groups compared to controls. Toxicology endpoints in other tissues were not performed, and the neural anatomical and biochemical evaluations according to protocol were only going to be performed if there were lesions that were observed in the high dose group, and since they weren't the evaluations weren't done.

The other part of the assessment is that the study design of this study is to evaluate acute and not delayed developmental effects which were of concern.

[Slide]

So, if I could summarize our interpretation, although I didn't talk about this,

there is clearly an established statin mechanism of action. The extensive developmental studies submitted from 1980 to 2004 show consistent findings with lovastatin exposure. These findings include fetal mortality; decreased fetal weight; skeletal malformations; and behavioral and learning delays. The limited neurodevelopmental neonatal rat study with the delayed learning effects is consistent with the prior postnatal studies.

Some of these findings, as I mentioned, occur in animals at exposures that are similar to the therapeutic exposure, that is exposure that could be achieved in humans following a 20 mg lovastatin OTC dose. Moreover, this was reviewed by our in-house panel of experts on the CDER reproductive toxicology subgroup and there was consensus.

Post-marketing reports of first trimester fetal adverse effects although, as I mentioned,

represent very limited data which results in failure to show cause and effect, certainly don't allay the potential concern.

[Slide]

If I could conclude, based upon the extensive animal data, a potential human fetal risk exists following exposure to lovastatin during pregnancy in women of childbearing potential. The contraindication of statins, including lovastatin, during pregnancy is valid. Thank you.

DR. WOOD: Thank you very much. Merck has asked to respond to this and, in the interest of fairness, I think we should let them do so.

Before we get to that, and I may have been postprandial, help me understand what the data are in humans. You sort of alluded to that but I didn't actually hear that data, I don't think.

DR. DAVIS-BRUNO: I didn't present that data--

DR. WOOD: That is why I didn't hear it!

DR. DAVIS-BRUNO: --because that is not my expertise, although it is summarized in the

briefing document that has been presented to the committee.

DR. WOOD: I understand that. Can you summarize that for us?

DR. DAVIS-BRUNO: If I can get an overhead I can.

DR. WOOD: Well, maybe while Merck is presenting you can be thinking about that because that is obviously key.

DR. HEMWALL: Thank you, Dr. Wood. As you can see, this is a complicated issue. In fact, we agree with the regulatory definition, such as it is, that when there is no benefit to treat during pregnancy the drug should remain labeled category X. But I think we need to put a little perspective on the data. Recognizing the complicated nature of all of these different interpretations, we will have just a few remarks by Dr. George Lankas who supervised the conduct of most of these studies, and then I will have some follow-up remarks after him.

DR. LANKAS: Hello. I am George Lankas

and I am a toxicologist at Merck, and I have been responsible for conducting many of the studies that were just alluded to.

As Dr. Davis-Bruno mentioned, there has been an extensive amount of preclinical reproductive and developmental toxicity data that has been generated with lovastatin over the years, and there is certainly opportunity for reasonable scientists to disagree in the interpretation of many of these findings. But given the potential significance of two certainly key findings that were just mentioned, the developmental effects on body weight and also the fetal death, I thought that those findings warranted closer scrutiny. So, what I would like to do is just briefly review for the committee the differences in the approach of how these data are analyzed and actually show an example of the actual data and the difference in interpretation. So, if I could have slide 766, please?

[Slide]

This is my attempt to summarize for the

committee the differences in methodology with respect to how these data are looked at based upon reviewing the FDA briefing document. The FDA method focuses on actual individual group mean differences between treatment group data and concurrent controls, and tends not to utilize statistical analyses unless the statistical analysis indicates that there is a significant p value. The Merck method, the MRI method, relies on a combination of looking at dose-response relationships, that is, evidence of a dose-related trend in the response that is under analysis, as well as statistical significance and an evaluation of both concurrent and historical control data. The committee has to realize that for many of these data there is tremendous variation in control data in a given species. So, reliance just upon concurrent control data can sometimes be misleading.

In addition, when there are multiple data available from different studies on a given endpoint, we also look at reproducibility of those

findings as further evidence or confirmation of whether there is a treatment-related effect.

[Slide]

On this slide I would like to summarize the FDA's analysis of the data as indicated in the briefing document that was supplied by FDA. This is characterized by FDA's study number 2. This was a rat study in which dosages of 2, 20 or 200 mg/kg/day were administered to rats, beginning 15 days prior to mating and then throughout mating and then throughout the gestation period until gestation day 20.

These are the doses here. The FDA's review indicated that these are the exposure multiples relative to the OTC dose of 20 mg. The check mark indicates that there were findings that were delineated by FDA as being drug related. Note that at the highest dose there is nothing indicated as being drug related, but at 20 mg, the mid-dose group, there were findings of fetal death as well as decreases in fetal body weight.

[Slide]

This slide actually shows the data on which this interpretation is based. So, these are the various groups in the study, control through

high dose, and these are the number of dead pups that were evidenced in this study by control group. You can look at the total number of pups across the groups. It is a relatively high number. You will note that there is really no evidence of any dose-related effect when you look at the concurrent control through the high dose of 200 mg/kg/day. Just to add perspective, this is roughly 25- to 30-fold based on exposure multiples, the proposed 20 mg OTC dose. So, this would be characterized as a relatively high dose.

So, the findings of fetal death are really based upon a finding in the mid-dose of 20, which is really due to the findings from one litter. One dam lost the entire litter, almost the entire litter, 8/14 pups. So, in our view, this does not rise to the level of a drug-related effect and we would discount this one litter as being evidence of a treatment-related finding, particularly when

there was nothing in the high-dose group.

Similarly, if we look at the effects on fetal body weight in these various treatment groups by time--PND stands for postnatal day, these are the days after birth on which these measurements were taken. Please note that the statistical analysis shows absolutely no evidence of any statistically significant effect. I believe that the effect that is being noted as possibly being evidence of a drug-related effect is on postnatal day zero or postnatal day seven, a period which really doesn't indicate any evidence of trend with respect to dose response.

So, our conclusion is that there was no evidence of a drug-related effect on mortality or on postnatal body weight not only in the 20 mg group but the other treatment groups as well.

[Slide]

This is an attempt to summarize for the committee what animal findings look like with respect to other over-the-counter products and also another lipid-lowering agent that is currently

prescription, fenofibrate. So, if we look at cimetidine, fenofibrate, epinephrine--this is actually ephedrine, and ibuprofin relative to lovastatin and we look at the effect on these various endpoints and look at the lowest effect level, that is, the lowest dose at which the reported effect has been observed, and then compare that to the animal relative to the human dose ratio, if this ratio is less than one it indicates that there is absolutely no evidence of a safety margin relative to the human recommended dosage. So, for these various agents you can see that the safety margins for lovastatin are well in line or exceed the margins for these other products.

So, it is our conclusion, our firm conclusion that the findings that are noted with lovastatin are non-specific findings, not indicative of a direct fetal toxic or teratogenic effect and that lovastatin certainly has an adequate safety margin relative to other over-the-counter products.

DR. HEMWALL: We do have just a little bit

more here. I want to put this in some perspective. First of all, my conclusion is that these studies are really complicated and it is tough to ask the committee to make some kind of judgment on what they just saw, but I want to try to put this into a little bit more context.

Let's go back to the pregnancy categories that we were looking at and the definitions, and let's remember--let's have the first slide--

[Slide]

--that our position is that lovastatin is not a teratogen. There are certainly some findings in animal studies that put it in a situation where it has to be judged to either be category C or category X, and it has been put into category X because of the fact that the fetal risk that is seen is enough to outweigh possible benefit, and we have all established that we agree that there is no benefit to treating a woman with a lipid-lowering drug during the period of pregnancy. The very fact that there are other drugs that have very similar findings but are listed category C is because they

do have benefit. Drugs used in diabetes; drugs used in asthma; drugs used in hypersecretory conditions are all category C with very similar findings, but that is because they have benefit when given to a mother and a doctor is asked to make that decision as to whether or not the risk outweighs the benefit, and they are called category C. In fact, a heartburn drug approved by NDAC just a couple of years ago has a category C label with animal findings and even sporadic reports of fetal abnormalities in human exposures. Next slide, please.

[Slide]

But let's take a look at what the human exposures actually are. These are numbers from the IMS database that show the number of women of childbearing age that have been prescribed lovastatin. To be exact, it is the number of prescriptions that have gone to women of childbearing age.

Let's just look at 2004, and you can see the numbers are increasing. About 19 million

prescriptions were written in 2004 for a statin. Of these, about 100,000 were women of 21-30 years; 480,000 were prescriptions for women of 31-40 years; and the numbers start to rise dramatically as you get into the older age group but still technically of childbearing age. Over two million prescriptions were written for statins for women of childbearing age in 2004, and there is a cumulative number of prescriptions obviously written over the years. Next slide, please.

[Slide]

In our own database we have, as you have heard many times and will remember it after today, the 27 million patient-years of exposure. We do have 105 reports of pregnancy in our WAES database. The majority of these are in the first trimester. There are 67 cases where the actual report is prospective. That means that we got the report before the pregnancy went to term so we were able to follow the pregnancy--or the reporter was able to follow the pregnancy to term. Then, 38 reports were retrospective. That is, once an anomaly was

found, often these reports come in and they are more commonly seen. So, in those 38 reports we do have 7 congenital abnormalities, and the specific pattern of defects in those reports is very diffuse. There is no pattern which would suggest something is going on that would be representing a mechanistic cause. Next slide.

[Slide]

So, our conclusions are that the reported experience with lovastatin exposure during pregnancy is limited, and that is because of the labeling and that is appropriate and we would want to reinforce that message in anything we do with an OTC product to minimize the potential for women of childbearing age to actually use the product. And, there is no evidence that exposure during early pregnancy is associated with any specific pattern of congenial abnormalities when they do appear.

Also, just to take a quote directly out of your background package that the FDA provided to you, in their Office of Drug Safety Review: A causal association between in utero statin exposure

and identified birth defects cannot be made based on the current information. So, we are not talking about a teratogen. This is not thalidomide; this is not Accutane where true fetal toxicity is known. We are talking about a drug that has a signal that is consistent with a category C drug but, simply, the history has been that there is no benefit for treating women during pregnancy so, by definition of the categories, that puts them in category X.

[Slide]

This is also looked at in a computerized, well recognized teratogenic tracking system, called the TERIS database. We have provided the actual printout from the TERIS database to everybody at the table here. This is something that accumulates all the animal data and all the human data and puts it into a computer-based system, and then it is reviewed and there is consensus by a group of clinical toxicologists. They group them into three broad categories, either no risk, minimal risk or unlikely, a small risk or risk undetermined. Next slide, please.

[Slide]

In the TERIS database, and you can read it in the handout you have, lovastatin is listed among

only 6.4 percent of drugs which are actually listed as unlikely to pose teratogenic risk in human pregnancy. About 90 percent of the drugs have not enough information. They have actually viewed that the lovastatin information is enough to support that conclusion. They have also noted that the non-minimal or unlikely category is equivalent to the FDA use of the pregnancy category A or B. Last slide.

[Slide]

So, just in summary, it is labeled category X because of the lack of clinical benefit and the potential risk that we have seen from these animal studies. We are not disputing that there are findings, and we can have our dueling experts going back and forth about which is the level and which is not the level, but there are findings that are consistent with category C. There is no evidence that we have seen in our databases that

exposure during early pregnancy is associated with increased risk of any specific congenital anomaly, and the TERIS database supports this, listing it as unlikely. That is why we believe that the risk to a mother who has an inadvertent exposure, however much we try to minimize the frequency of that event, is very low, especially compared to the overall benefit to the large population of people that should be getting this drug, lowering their cholesterol and lowering their risk of cardiovascular disease.

DR. WOOD: Karen, do you want to say anything in addition to that?

DR. DAVIS-BRUNO: To address the Chair's question about what the actual findings were in those limited human experiences, this table that I am going to present is also in your briefing document.

DR. WOOD: That is fine. Just tell us where it is and then keep going.

DR. DAVIS-BRUNO: It is at Tab 4, around page 4 or page 3, in the beginning of my review.

DR. WOOD: Okay, keep going.

DR. DAVIS-BRUNO: Well, I am done with my presentation, unless you want to entertain

questions.

DR. WOOD: Let's keep the questions until the end and let's go straight on to the next presentation, which is from Capt. Laura Shay.

Label Comprehension Study

CAPT. SHAY: Well, good afternoon.

[Slide]

This is switching gears quite a bit from the last talk. My name is Capt. Laura Shay. I am a consumer safety officer for the Division of Over-the Counter Drug Products.

[Slide]

The purpose of my presentation this afternoon is to provide a summary of my review of the pivotal label comprehension study for Mevacor OTC. First, I will provide a description of basically what label comprehension studies are; followed by a description of the Mevacor study design. Finally, I will provide a summary of the

study results.

[Slide]

The purpose of a label comprehension study is to evaluate whether or not consumers can comprehend important communication objectives on the label. It is important that both literate and low literate populations are evaluated, and that a diverse population is evaluated that is representative of the United States population.

[Slide]

Generally, label comprehension studies are performed prior to the behavioral or actual use study. This is in order to optimize the label before placing it into a naturalistic setting. It is important to note that low comprehension may be predictive of poor results in the actual use setting. However, as has been mentioned previously, high comprehension does not necessarily guaranty success in the actual use setting.

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For the pivotal label comprehension study the primary objective was to evaluate consumer

comprehension of the label used in the CUSTOM actual use study.

[Slide]

Secondary objectives included were to determine how well respondents correctly respond to questions designed to try to measure self-selection; to evaluate low literacy respondents; and to evaluate non-Caucasian respondents.

[Slide]

The key communication objectives are provided in your FDA background package under Tab 6, page 1. But I will provide more detail on them as I present the results of the study.

[Slide]

It is important to note that in the Code of Federal Regulations an OTC label must be likely to be read and understood by the ordinary individual, including individuals of low comprehension, under customary conditions of purchase and use.

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So, how do we assess comprehension? There is no defined numerical value for acceptable comprehension. Ideally, we would like everyone to

understand everything on the label 100 percent. However, realistically we understand this concept is not possible. However, the more clinically significant a communication objective is, the close to 100 percent comprehension is desired. For example, for the consumer's ability to understand that they need to stop Mevacor OTC if they experience unexplained muscle pain, we would like to see high comprehension. For other communication objectives we might accept a lower score. A good comparison would be a driver's manual. After someone reads a driver's manual you can test them on their comprehension of the manual, and you would like to see comprehension for understanding the need to stop a car at a red light. If someone doesn't comprehend well the need that you need to park at least 10 ft from a fire hydrant and not 8 ft, this would not be viewed at the same level of importance as the red light. In the process of

developing and testing a label judgments have to be made on the areas that need to be fixed and what areas can be left alone, even if they are not even close to 100 percent.

[Slide]

Everyone at this point I think is familiar with the label. This is the principal display panel that was tested and also used in the CUSTOM use study.

[Slide]

This is the drug facts label.

[Slide]

The study design was as follows: Recruitment was done when subjects were selected if they were found to be cholesterol-concerned respondents. They were shown a concept board and they were asked if they were interested in lowering their cholesterol. If they were concerned or would like to lower their cholesterol, they were asked to participate in the study. And, they were paid $20-$25 for participating and essentially to cover the cost of their time.

[Slide]

The study was conducted in 25 shopping malls across the country in a very diverse

population.

[Slide]

The total number of study cohorts was 696. Of those, 203 tested at low literacy. The definition for testing at low literacy--and they used the REALM test which also was mentioned. That stands for the Rapid Estimate of Adult Literacy in Medicine test. That is if they test less than or equal to an 8th grade reading level. And, 493 were considered adequately literate; 207 were non-Caucasian; and 489 were Caucasian.

[Slide]

The gender breakdown, 44 percent were male. Of the males, 51 percent were greater than or equal to age 45, which is the target population for this product, and 56 percent were female and 35 percent of those were greater than or equal to age 55, the target population for this product.

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The questionnaire design was testing one label. They used structured interviews, and the respondent was allowed to refer to the label throughout the study. The questions were primarily multiple choice, and there were many scenarios used in order to test key communication objectives and

to test decision-making ability based on information found on the label.

[Slide]

An example of one of the scenarios is one for unexplained muscle pain: Diane has been taking Mevacor OTC for several weeks. She didn't do any unusual physical activity and isn't feeling sick, but she has started to feel pain in her leg muscles.

[Slide]

On the drug facts label there are two areas that explain to consumers what they should do if they develop unexplained muscle pain. Under warnings it states "stop use and ask your doctor. If you develop any unexplained muscle pain, weakness or tenderness stop immediately. This can

be a sign of a rare but serious side effect."

Under directions, it is also stated a second time. Unexplained muscle pain--:stop using immediately and talk to your doctor if you develop unexplained muscle pain, weakness or tenderness. This can be a sign of a rare but serious side effect."

[Slide]

According to the protocol, the answer definitions were as follows, a correct answer would be if a respondent's answer adhered to the label. An acceptable answer is if a respondent's answer did not specifically adhere to the label but would not pose a safety risk.

[Slide]

The answer selection for the unexplained muscle pain is the following, the choices they had and the results are going to be listed right now: They were told to stop using the drug. Must talk to a doctor. That was considered correct. They could select continue to use but must talk to a doctor. This was considered acceptable. Stop

using; does not need to talk to a doctor--also acceptable. Continue to use and does not need to talk to a doctor--incorrect. And don't know would be considered incorrect.

[Slide]

The breakdown of the scenario results according to correct--and that would be, again, just strictly adhering to the label, the results were between 74-81 percent. When acceptable answers were factored in the results were 98-99 percent.

[Slide]

Another scenario is for liver disease. Barbara has liver disease.

[Slide]

On the drug facts label the issue of liver disease is under one area in the warning section and it states liver disease--"do not use if you have liver disease."

[Slide]

The answer options for this scenarios--this person should not use at

all--correct. Before using, this person needs to talk to a doctor--acceptable. This person could start using right away--incorrect; And, again, don't know is considered incorrect.

[Slide]

The results of this scenario, for the correct answers, adhering to the label, the range was 65-71 percent. When acceptable was factored in the range was 99-100 percent.

[Slide]

I will now present the study results. There was little difference between the cohorts of the low literacy, normal literacy, Caucasian and non-Caucasian. Therefore, I will present only the total representative sample, and I will only present the correct answers, which were those answers in which respondents strictly adhered to the label.

[Slide]

Ninety-nine percent understood what the product was used for; 99 percent, dosage and dosing information; 95 percent, the need to consult with a

healthcare professional prior to use if on a prescription drug. Ninety-two percent understood the active ingredient; 87 percent, time frame for cholesterol testing. Eighty-six percent understood the need to have diet and exercise before taking the medication; 82 percent, that evening was the best time of day for dosing; and 78 percent, the need to fast before cholesterol testing; and 50 percent, that the cholesterol will go up if Mevacor OTC is stopped.

[Slide]

The percent of correct answers according to the label for scenarios that indicate the need to stop Mevacor OTC with multiple scenarios and the range of correct answers were 47-90 percent. Of most clinical significance was the unexplained muscle pain at 79 percent.

[Slide]

The percent of correct answers according to the label for self-selection scenarios was a range of 37-81 percent, with an average of 54 percent. Of most clinical significance, allergy to

lovastatin 72 percent; and in the scenario they listed a prior history of muscle pain on cholesterol-lowering medicine and the correct answer for that according to label for that was 42 percent.

[Slide]

The percent of correct answers according to label listed under the warning section of the label, "do not use if...," 74 percent for pregnancy; 77 percent for breast feeding; 69 percent for liver disease.

[Slide]

The percent of correct answers for false positives--and what these were was the sponsor did a nice job of integrating scenarios that may not necessarily be on the label but forced the responder to have to think in a decision-making manner, sort of common scenarios such as if you developed a cold, you were taking Tums for indigestion, you have poison ivy, you have gas from food or constipation. The correct answers according to label, the range was 64-72 percent.

Again if acceptable was factored in the range was 94-98 percent.

[Slide]

Self-selection was also looked at. Respondents were asked if they could start Mevacor OTC today. This was after they had a period of time to look at the label and it was asked at the very beginning of the study. This answer was then compared to the self-reported medical history questions and demographic data in order to validate if the response was correct.

[Slide]

Of the 696 total respondents or total representative sample, 461 reported that they could not start Mevacor OTC today; 209 reported that they could start Mevacor OTC today; and 26 respondents were unsure.

[Slide]

The results, of the 461 that responded that they could not start today, 100 percent of them were correct. All 461 had a contraindication on the label that they discussed in their

self-reported medical history. Out of the 209 respondents who reported they could start Mevacor OTC today, three, or one percent, self-selected correctly according to the label criteria. That brings a total of 67 percent, or 464 out of the 696 total respondents that self-selected correctly according to the label.

[Slide]

In summary, this was a well-designed study in that it covered a diverse population and included non-Caucasian and low literate subjects. The questions were non-leading and well constructed. And, the study was able to distinguish varied levels of comprehension.

[Slide]

The areas of clinical significance that adhered to the label strictly, for unexplained muscle pain 70 percent; for breast feeding 77 percent; for pregnancy 74 percent; allergy to lovastatin 72 percent; liver disease 69 percent; and explained muscle pain 47 percent.

This point of unexplained muscle pain is

not a clinically significant issue but it does point to the fact that respondents had a difficult time understanding the difference between explained and unexplained muscle pain. Although, again, not clinically significant in that we would rather see someone stop and ask a doctor if they are uncertain, it does point to the complexity of this label in that it attempts to convey medical information to the consumer that is more complicated than what is seen in current OTC labeling.

[Slide]

In summary of the self-selection, the total number who self-selected correctly according to the label was 67 percent or 464. Of those who said they could start Mevacor OTC today, one percent or 3 out of 209.

[Slide]

Now, the issue of correct versus acceptable, when acceptable answers were factored in the answers increased most scores to greater than 90 percent. In some situations factoring in

acceptable responses could actually be considered correct if these issues or scenarios fell under the sub bulletin in the label that states do not use; ask a doctor of pharmacist, or under the sub bullet do not use unless directed by your doctor. However, the acceptable answers often contained "ask the doctor" even when not indicated to do so on the label. It is important to note that respondents often had a greater than or equal to 50 percent chance, or a three out of five chance of selecting either a correct or an acceptable answer.

The sponsor chose to use both correct and acceptable answers to assess comprehension of this label. This method potentially creates an elevation of the scores, resulting in an overestimate of a consumer's ability to comprehend the label. Should the acceptable answers that contain "ask a doctor," even when not directed to do so on the label, be factored in? Did they truly assess the ability to comprehend the label or are they attempting to predict the behavior? Did the respondents choose an answer that contains "ask the

doctor" rather than the answer "I don't know" because it was more comfortable? These are important questions to ponder.

Again, it is important to remember that the label comprehension study cannot predict consumer behavior. Even labels with high test scores for comprehension can do poorly in the actual use setting. As previously described, this label was tested in the CUSTOM actual use study. A review of this study will now be presented by Dr. Daiva Shetty.

DR. WOOD: Just before you leave, on page two of your briefing document and also on your slides you get to the total number who answer a question correctly by adding the numbers who couldn't start with the numbers who could start and, it seems to me these are not equal questions. So, getting the question wrong that you could not start and, therefore, not starting is a quite different outcome from getting the question wrong that you could start and starting. And, only one percent of the people who could start got the

question right whereas a large number who could not start got the question right and that is what gives you this 67 percent answer. So, it seems to me, that is like asking people if it is all right to jump out of the plane and the people who did jump out of the plane, only one percent of them got it right because they had the parachute on--

[laughter]

--and, you know, the ones who said it wasn't time to jump out of the plane, all of them got it right so that was all right, we will just add the two together. Well, I am not so sure that is right. So, could you comment on that? I mean, that seems to me an extraordinary addition to make.

CAPT. SHAY: You want me to comment on that?

DR. WOOD: Yes, please. I mean, only one percent of the people who jumped out of the plane got it right.

CAPT. SHAY: True, but I think it is important to look at the entire balance and, in all fairness, when a person goes and selects a product

you also want to make sure that they are not selecting appropriately if they shouldn't. So, we always factor that into the whole decision-making process. But I agree with your scenario in that of the 209 who did self-select correctly and the one percent, or three, that got it right--that is of concern.

DR. WOOD: So, I am reading that right? All right.

DR. GANLEY: Alastair, could I just add to that a little bit?

DR. WOOD: Sure.

DR. GANLEY: I think the analogous situation is when you look at the actual use study and you have the purchasers and non-purchasers. Those non-purchasers, they did have to make a decision whether to select to use the product and they chose not to use it for various reasons. And, many of the answers there were correct answers. So, you can't really ignore that.

DR. WOOD: No, I am not ignoring it.

DR. GANLEY: That is why we have broken it

up like that and not just given you 67 percent.

DR. WOOD: But I just wanted everybody to be sure they understood where that 67 percent came from. Let's move along to the next talk.

CUSTOM - Actual Use Study

DR. SHETTY: Good afternoon.

[Slide]

My name is Daiva Shetty. I am a medical officer in the Division of Over-the-Counter Drug Products.

[Slide]

My presentation today will briefly cover some aspects of actual use studies; actual use issues that are important to address for Mevacor over-the-counter marketing; and the results of the actual use study submitted to support the prescription to over-the-counter switch of Mevacor. My presentation and the results will focus on the analyses that strictly adhere to the label criteria.

This morning Merck presented multiple analyses that looked at ways to view the data.

Some of them were prespecified and some of them were not prespecified. Most of them assess data from the benefit to the population point of view.

[Slide]

Before presenting data from the CUSTOM study, I would like to mention a few words about actual use studies in general. Actual use studies attempt to simulate over-the-counter use. Recruitment is usually done through print and broadcast media directed toward the general over-the-counter population targeted for use of the drug. Study sites are usually located in areas where consumers would seek to purchase over-the-counter medications, such as pharmacies and grocery stores. The studies have very few exclusion criteria and ideally should not have recruitment pre-screening and minimum interactions between the participants and the study personnel. As much as they try to mimic over-the-counter use, these studies are not perfect. There are procedures, such as informed consent, information gathering and diaries that always involve

interactions between the subjects and the study personnel, and participants usually are compensated for their participation in those studies.

[Slide]

The objectives of an actual use study depend on the specific product and concerns related to that product, such as self-diagnosis, which refers to a consumer's ability to diagnose the condition for which the over-the-counter product is indicated; self-selection, which refers to a consumer decision to use the drug or not to use it. De-selection refers to a consumer's decision to stop using the drug in cases such as not achieving a benefit or development of an adverse reaction to the drug. They also assess compliance, the dosing and duration of use; off-label use; safety and sometimes efficacy in over-the-counter use population.

[Slide]

In the actual use study there are several important behavioral issues for the nonprescription Mevacor marketing. First of all, are consumers

able to self-diagnose hypercholesterolemia? Did they know their own cholesterol values? And, did they understand serum cholesterol values? Are they able to identify risk factors for coronary heart disease? And, do they understand how many of those risk factors they should have or should not have to qualify for the treatment? Are consumers able to self-select appropriately based on the label eligibility and the contraindications for use?

[Slide]

Are consumers able to self-treat hypercholesterolemia? Are they able to follow label directions for dosing and duration of use? Do they follow directions for when to get follow-up cholesterol tests or when to see a physician? Do they understand the treatment goal? And, are they able to identify risks during therapy and de-select? For example if they develop muscle pain or start new medication that may have a drug interaction with Mevacor, or do not achieve goal cholesterol levels, would they stop using the product?

[Slide]

Now I will switch my presentation to the data of the actual use study submitted to support

this application. The study, as you have already heard, was called CUSTOM, Consumer Use Study of OTC Mevacor.

[Slide]

I will start from the label used in the CUSTOM study and tested in the label comprehension study which is identical to the proposed label for over-the-counter marketing. According to the proposed label, there are four conditions that determine correctness of the self-selection. The order that consumers have to go through in their thought process when looking at the label is as follows: To be eligible for treatment with Mevacor, the consumer must be a man at least 45 years of age or a woman at least 55 years of age; must have LDL cholesterol between 130-170 mg/dL; must have at least one of the following risk factors for coronary heart disease, smoking, low HDL cholesterol, family history of coronary heart

disease or high blood pressure, and also must be free of conditions that may put him or her at increased risk from using the product.

[Slide]

The study did not evaluate self-selection as the primary endpoint. Rather, it assessed the decision to purchase Mevacor. It is obvious that purchasing the product can be construed as self-selecting a product. A total of 3316 subjects participated in the decision to purchase Mevacor and 1205 decided to buy the product and 2111 did not. The majority of both those who purchased and those who did not purchase stated that they needed more information to make a decision to buy or to use the product. The most common reason among purchasers needing more information was to obtain their cholesterol numbers. Non-purchasers commonly cited a need for personal health information or to talk to a physician. The reasons for not purchasing the product were evaluated. We believe that the majority of non-purchasers may have made a correct decision not to use the product.

[Slide]

In the next few slides I will show the self-selection decision results based on the four

previously mentioned label criteria, age, cholesterol levels, risk factors and the warnings listed on the label. It does not include the physician override concept. Since the raw data were submitted late into the review process, the numbers I will present today will differ a little bit from what you have in your background packages.

There were a total of 1061 subjects in the study who not only purchased but also used the product. Two were excluded because of protocol violations. Of all the users, 797 subjects met the age criteria. That means that they were men at least 45 years of age or women at least 55 years of age. Of those who met the age criteria, 281 had LDL cholesterol levels between 130-170. Of these, 206 had at least one risk factor for coronary heart disease. The majority of them were men. Only 69, out of 430 women were in this group meeting the first three labeled criteria.

[Slide]

A further three subjects with underlying liver disease, which is contraindicated in the contraindications for use, were excluded and 18 subjects with a history of muscle pain or weakness from using statins, and we are left with 185

subjects.

[Slide]

Then, there were 22 subjects who had only one risk factor for coronary heart disease, in addition to age, and a high HDL level above 60 which did not qualify them for treatment. Finally, there were 53 users with high triglyceride levels, over 200. The final numbers of correct self-selection according to the strict label eligibility criteria were 110 users, 33 women and 77 men, which is 10 percent of all the user population. This does not include the physician consultation.

[Slide]

It is important to look at the demographics of the users. Among the 1061 subjects

who purchased and used the drug, there were 430 women. Of the 430 women who used the drug, 37.4 percent were less than 55 years of age, below the targeted age by the label. The breakdown of women users by age was as follows: 11 percent were less than 45 and another 26 percent were between 45-54.

[Slide]

The actual use study suggests that women of childbearing potential may select to use the product. Over 20 percent of all women users were less than 50 years of age. Consequently, because during the first trimester of pregnancy women may not realize that they are pregnant, it is important to understand the risk to the fetus if women of childbearing potential are going to use the product in an over-the-counter setting and determine what mechanisms could decrease that risk.

[Slide]

Now I would like to show the study results on whether the users knew their LDL cholesterol value at the time of purchase. The knowledge of cholesterol value becomes important in an

over-the-counter setting especially if there is not access to testing.

The rows in this table represent user self-reported cholesterol values and the columns show the results of LDL cholesterol at baseline. Highlighted in yellow are the numbers of subjects who knew and correctly identified their LDL cholesterol. Around two-thirds of those who thought they knew their LDL cholesterol correctly identified it. It comprises 47.7 of all user population.

It is important to note that over a third of all users did not know their LDL cholesterol value or their values were missing. Given that the label states that you should know your cholesterol, why would these subjects purchase Mevacor without knowing their cholesterol? There could be two reasons. First, they could get a physician override, and I don't have data on which of those 318 plus 27 subjects consulted their physician. Or, they could have purchased a test at the site. Everybody in the study had an opportunity to buy a

test at the time of purchase. However, out of 318 who did not know their cholesterol, 67 decided to buy a cholesterol test on site in order to find out their cholesterol.

[Slide]

Another important fact that could be learned from this table is that a significant number of users had a baseline LDL cholesterol below the targeted level. That means that they may not need to be treated. Even though the correlation between the self-reported and measured LDL cholesterol values was high in the subgroup, 87 out of 122, knowing that their cholesterol is low, chose to use Mevacor; 168 out of 265 subjects who had higher than targeted LDL cholesterol also incorrectly chose to use Mevacor.

[Slide]

This is the summary of consumer knowledge of their LDL cholesterol values based on the data from the previous table, 30 percent of the users did not know their LDL cholesterol and chose to use product; 47 percent of all users actually correctly

identified their LDL cholesterol value; 71 percent of users who correctly identified their cholesterol is less than 130 chose to use Mevacor; and 75 percent of those who correctly identified their cholesterol above 170 also chose to use Mevacor.

[Slide]

The sponsor analyzed the self-selection in more than one way. One of those self-selection assessments was based on the number of risk factors for coronary heart disease, ignoring whether the user cholesterol values were within the labeled range of 130-170. The results of this study showed that 42.7 percent of users did not have at least two risk factors and used the product even though they did not meet the label criteria.

[Slide]

Now I would like to explain how the sponsor assessed the correctness of self-selection and why our results are so different. The original definition in the study protocol defined correct self-selection as according to label, or AL, which represented a decision that is entirely consistent

with the product label. Or, if not according to label, the consumer achieves LDL cholesterol goal after six weeks of treatment.

In the middle of the ongoing study the sponsor redefined the categories and the major difference that was introduced for assessment of self-selection is the physician override concept, which means that if a consumer failed self-selection for any reason but stated that their physician approved the use of Mevacor, they were classified as correct self-selectors.

There is nothing wrong if people consult their physicians to make a better decision for self-treatment, however, in this study the contact with a physician or the information discussed was not verified and we don't know why the majority of users in the study failed the label criteria and were approved by their physicians despite the risks or no benefits for the treatment.

[Slide]

The sponsor also introduced two additional categories for assessment of correctness of

self-selection. The first one was called "closely adhered to the label" and included users who did not meet one or more of the criteria for age, risk factor profile, and had LDL and HDL values outside the targeted range for treatment. But because they knew their lipid profile; did not have elevated triglycerides; did not substitute Mevacor for their prescription lipid-lowering medication; and did not have diabetes, heart disease or stroke, they all were assessed as correct self-selectors.

[Slide]

In addition, the sponsor reevaluated subjects who failed the previously mentioned definition, "closely adhered to label" benefit criteria, and looked at the subject's 10-year risk profile for myocardial infarction or coronary death. This approach allowed them to reclassify the users who failed self-selection according to the label if they did not know their lipid profile, if they had elevated triglycerides, substituted Mevacor for their prescription lipid-lowering medication, or had diabetes, heart disease or

stroke but were eligible for study therapy by ATP III guidelines based on the calculated more than 10 percent 10-year risk for myocardial infarction of coronary death.

[Slide]

These are the sponsor's results of the correct self-selection, 484 self-selected correctly according to the label or medically acceptable for self-management definition; 68 of those self-selected on their own without a physician's input. An additional 202 subjects who closely adhered to the label were added to the correct self-selection group. Finally, the sponsor states that although 357 did not adhere to the label benefit criteria, 258 of this cohort were eligible for statin therapy by ATP III guidelines, thus raising the correct self-selection rate to 89 percent or 944 subjects.

These analyses are not based on subject self-selection decision but, rather, on the retrospective analysis of their baseline characteristics. When consumers are picking up the

package from the shelf they should be able to make the right decision by reading the label.

[Slide]

There are several relative contraindications for the use of Mevacor listed on the proposed label. Of the 1061 users, 55.5 percent had at least one or more contraindication specified on the label. In addition, 2.2 percent subjects' data was not known due to missing information. This brings the number to 42.3 percent of users who did not have any relative contraindications for using Mevacor. The majority of those users with relative contraindications were classified by the sponsor as correct self-selectors because they stated that they spoke to their physician. Even if we assume that some participants in fact discussed their particular risk condition with their personal physician, a significant proportion of users with those contraindications remain who did not get physician clearance.

[Slide]

A listing of these non-clearance users is shown on this slide and 37.5 percent of those who substituted prescription lipid-lowering medication

with OTC Mevacor did not consult the use of Mevacor with their physician; 64.5 percent of those with high LDL or high triglyceride levels used Mevacor without physician clearance; 37.5 percent of those taking potentially interacting drugs; 41 percent of diabetes; 41.5 percent of subjects with coronary heart disease; 51.6 percent with a history of stroke; and 61.6 percent of subjects with a history of previous muscle pain while taking statins also used Mevacor without consulting with their physician.

[Slide]

Another consumer behavior aspect that was assessed in the study is the self-management or compliance with treatment and de-selection. Over the next two slides I will show you how users in the CUSTOM study behaved after the initiation of therapy.

Thirty-seven percent, or 393 subjects did

not get any follow-up cholesterol test after they started using Mevacor, and the majority of them, 277, continued therapy; 63 percent, or 666, had at least one follow-up cholesterol test.

[Slide]

Of those who had at least one follow-up cholesterol test, 7 discontinued the treatment and 659 continued on therapy. Of those who continued on therapy, 375 were at goal for LDL cholesterol goal on their follow-up test; 160 subjects were not compliant with their label treatment because they were not at goal, and their cholesterol was above 130 or their follow-up cholesterol values were missing and they continued on therapy. The rest complied with the label treatment criteria according to the sponsor because they either continued with physician override or discontinued because they were not at goal.

[Slide]

By the end of the six-month study a lipid test was not optional but required by the protocol. There were 548 subjects among the 878 tested with

LDL cholesterol below 130 mg/dL. However of those, 160 subjects had LDL cholesterol less than 130 at baseline and for 39 subjects baseline LDL cholesterol values were unknown. So, we don't know what benefit, if any, these 199 subjects received from the therapy. There were 349 with LDL cholesterol values above 130 at baseline who achieved goal by the end of six months of the study.

Since there were some questions about the compliance and how consumers in the study complied with the treatment, I want to mention that the median number of tablets that the users purchases in the study was 122, which is approximately a four-month supply for the treatment.

[Slide]

Despite many self-selection errors, there were no safety signals reported during the study and 17 percent of all users reported at least one drug-related adverse experience and only one of those was assessed as a serious event. That was an allergic reaction to lovastatin. No other serious

drug-related adverse events were observed during the study.

[Slide]

In summary, based on the information I have presented, the actual use study showed that the majority of the participants, those who purchased and those who did not purchase Mevacor, needed more information to make a decision. Although approximately one-half of the users correctly identified their LDL cholesterol, approximately one-third of all users did not know their LDL cholesterol values and chose to use Mevacor.

[Slide]

There were some self-selection errors and 37 percent of women users were less than 55 years of age; 26 percent of users met the age and baseline LDL cholesterol range; 19 percent of users met the age, LDL cholesterol and the risk factor for coronary heart disease criteria. Based on our assessment 10 percent of all users self-selected correctly by the strict label eligibility criteria

without a physician override. It is not clear whether the complicated paradigm of treatment of high cholesterol, or the label used in the study, or both led to such poor self-selection results.

[Slide]

Forty-two percent of the users did not meet the label eligibility criteria for the number of risk factors for coronary heart disease. More than half of the users had at least one relative contraindication for the treatment with Mevacor.

[Slide]

There was relatively good compliance with follow-up cholesterol tests, 63 percent; 35.6 percent of users achieved the target LDL cholesterol goal of less than 130 at follow-up testing. Data was not presented, as the sponsor already mentioned--those who used Mevacor had lowered their cholesterol approximately 21 percent and 25 percent lowering in those who had fasting cholesterol values. Even though testing at the end of six months showed that over half of all users had LDL cholesterol less than 130, one-third of

them started at a level below 130 or their baseline values were missing.

[Slide]

There were no serious safety signals observed during the study, but if Mevacor becomes available over-the-counter, based on the study results, it is likely to be used by women of childbearing potential, consumers with contraindicated conditions, consumers with no risk or low risk for coronary heart disease, and consumers at high risk for coronary heart disease who can potentially be under-treated. This ends my presentation. Thank you for your attention.

DR. WOOD: Thank you very much. Let's take a break.

[Brief recess]

DR. WOOD: Dr. Koenig will now talk about simvastatin use in the United Kingdom.

Nonprescription Simvastatin in the United Kingdom

DR. KOENIG: Good afternoon.

[Slide]

I am Michael Koenig, an interdisciplinary

scientist in the Division of Over-the-Counter Drug Products.

Over the next 15 minutes or so I am going to be providing some additional information about what you have heard referred to earlier today as OTC simvastatin in the United Kingdom. This is currently the only statin available without a prescription anywhere in the world. Simvastatin in 10 mg tablets has been marketed in the United Kingdom as Zocor Heart-Pro since July of last year, just a little under six months.

The information that I will be presenting comes from the Internet and has been vetted by colleagues at the British Medicines and Healthcare Products Regulatory Agency.

[Slide]

My presentation can be divided into three parts. First, I will describe how medicines are classified in the United Kingdom. Second, I will outline the process by which medicines can be reclassified or switched between classes, which is the process that we are going through here today.

This is part of that same type of process. Third, I will bring up some of the issues that were considered in the United Kingdom in considering specifically the switch of simvastatin from prescription to nonprescription status.

[Slide]

As in the United States, medicines in the United Kingdom can be broadly classified into two categories, prescription and nonprescription. Prescription medicines are also known as prescription only medicines, or POM medicines, and they are in this class because of safety concerns. The British feel that the medicines in the prescription only medicine class present a direct or indirect danger to human health if they are not used under a doctor's supervision. Additionally, these medicines may contain a substance or substances requiring further investigation or they require injection. All new medicines, and by that I really mean all new chemical entity-containing medicines, are initially placed in this class, prescription only medicines.

[Slide]

Unlike in the United States, the nonprescription classification of medicines can be

further broken down into two different subclasses. The first of these that I am going to talk about are those in the pharmacy, or P class of medicines. These are available in pharmacies and only in pharmacies, and they are administered under the supervision of a pharmacist or the pharmacy staff who have been trained to work with this medicine. In the United States we would refer to this type of medicine as behind-the-counter if we had such a class but we currently do not. There is no legal behind-the-counter classification. Simvastatin falls in the pharmacy class of nonprescription medications.

More like our OTC drugs are those listed on the general sales list. These are available on pharmacy shelves, open pharmacy shelves. They do not require the assistance of pharmacy staff. They are also found in supermarkets, and they include medications such as analgesics and cough-cold

medications. As I indicated, the comparable class in the United States is what we refer to as OTC or over-the-counter drugs.

At this point I would like to point out what you may have seen in the literature, and you have already heard referred to this morning. You have heard simvastatin referred to as OTC simvastatin. All nonprescription drugs, that is both classes, pharmacy and GSL, are considered and are sometimes referred to as OTC medications. So, there is that distinction that I wanted to bring out.

[Slide]

Let me now talk about the reclassification process itself, or the switch from one classification to another. I am going to focus specifically on the reclassification from prescription only to pharmacy type of medicine because that is the one that is involved with simvastatiin. It is also possible to reclassify medicines from pharmacy to GSL but medicines in the United Kingdom do not jump directly from

prescription only to what we would consider OTC to GSL.

The first thing that goes into the application, as you would expect perhaps because it is included in any NDA, new drug application for a switch in this country, is the safety profile for the drug. This includes reports of adverse reactions; the results of post-marketing surveillance studies; published literature supporting the reclassification; and safety reviews that may be available. Additionally, the application includes patient information which is the proposed labeling for the product. In the case of a medicine being considered for switch to the pharmacy class, the applicant must show how the pharmacists and their staff are going to be trained. Finally, the application includes a detailed evaluation by a clinical expert and, of course, since the application comes from the sponsor the clinical expert is provided by the sponsor.

[Slide]

The process itself can really be broken down into five steps: First, the application containing the information I have just talked about

is submitted to the Medicines and Healthcare Products Regulatory Agency, or MHRA, a body that is directly comparable to our FDA. The MHRA takes this application in for review.

In the case of simvastatin and most other switches from prescription only to pharmacy, the MHRA likes to include the Committee on Safety of Medicines, or CSM. This is analogous to you, to the advisory committee members. These are experts from around the United Kingdom who come together to advise the MHRA on what they think, or contribute their thoughts on the advisability of making the switch.

Upon completion of the review, a consultation letter is prepared which contains the findings and tentative conclusions of the MHRA in conjunction with the CSM, the Committee on Safety of Medicines. This is then sent out to the different health agencies for comment and for their

response. Whether the MHRA is leaning toward a switch or against a switch, the information goes out for public comment, and that is probably not terribly different from what we will be having tomorrow morning when we have the open hearing--the same type of public input. This meeting is public as well.

The responses are received back at the MHRA. In this case the respondents were given 60 days to respond. They are then reviewed to determine whether or not any new issues have come up that the MHRA feels must be addressed. Then, in the final step, the MHRA takes some sort of action, either approving the switch or not approving it. In the event that it is not approved there is the right of appeal.

[Slide]

In the specific case of Zocor Heart-Pro, this medicine was reclassified as a nonprescription pharmacy type medicine in July, as I said, of 2004. I would just like to briefly go over some of the labeling. You have heard extensive talks about the

labeling both from the sponsor and from my colleagues in the FDA. But let's look at the labeling briefly for Zocor Heart-Pro, and I will be going into some more detail on this a little later in my talk.

This labeling is available in your Merck background package right at the very end. For this particular label the display panel is on page 343 of the Merck background package. You can see that, just as labeling in this country, the labeling indicates the proprietary name, Zocor Heart-Pro, as well as the active ingredient.

What I wanted you to see is the primary indication. In the United Kingdom Zocor is marketed to reduce the risk of a heart attack. On the back of the package there is the same sort of information that you might find in this country, although not in drug facts format. I want to point out that Zocor Heart-Pro is for people who have a moderate risk of coronary heart disease. So, I believe that is the same indication that Merck is seeking.

But in the United Kingdom patients are advised or would-be purchasers are advised that the pharmacist can advise them further and help them to

identify their risk level. Merck has already said that will be the case with Mevacor. Here it is actually a requirement. That is a specific designated nonprescription class.

[Slide]

Additional labeling that consumers are exposed to includes the questionnaire which must be filled out in the pharmacy itself and is assessed by the pharmacist or his staff or her staff to determine whether the patient qualifies to receive this medication.

[Slide]

Then, if they are able to obtain the medicine, once they get home and open their package detailed patient information is provided in this patient information leaflet, and I will be referring to this in somewhat more detail just a little bit later on.

[Slide]

I would now like to get to the real meat of what I hope to present to you today, and I would like you to consider some of the issues that were considered in the United Kingdom when they were thinking about switching simvastatin to a pharmacy status.

[Slide]

The public consultation letter, as I said, contained all of the issues considered by the MHRA. I have just picked six of these for a little deeper presentation to you, a little bit deeper discussion. The MHRA considered the potential for myopathy and rhabdomyolysis. They also looked at the potential for liver toxicity in consumers who would be taking this product. They were concerned about possibly use by pregnant women--if this sounds familiar, it should. They were concerned about whether or not consumers could adequately self-diagnose that they were at moderate risk of a heart attack, again with the assistance of a pharmacist. They addressed the issue of whether consumers even needed to know their LDL cholesterol

numbers or not. And, for this medication which is, again, a pharmacy medicine, the MHRA considered the adequacy of training materials provided to the pharmacy staff.

[Slide]

With regard to the potential for myopathy or rhabdomyolysis, the MHRA felt that this was a sufficiently rare condition that they were not particularly concerned about it, especially since they considered the warnings on the labeling to be adequate.

So, now if I take you back to that patient information leaflet which is included in the package, there are four things I would like to point out here that all deal with myopathy and rhabdomyolysis on the labeling. First, consumers are advised not to take these tablets if they have had muscle problems in the past after taking a cholesterol-lowering medicine.

Secondly, consumers are advised to stop taking the tablets immediately and check with their doctor if they develop generalized muscle pain,

tenderness or weakness unless it is an explained pain. That is, unless it is clearly the result of flu, unaccustomed exercise, recent strain or injury.

Thirdly, consumers are advised that they should not be taking certain medications concurrently, those being cyclosporin or other prescription cholesterol-lowering medicines, as these may cause problems if they are taking Zocor at the same time.

Finally, and this is not on the labeling in this country, the British pointed out that consumers should not drink huge quantities of grapefruit juice, more than a liter a day; 250 ml was fine.

[Slide]

Now, regarding the potential for liver toxicity, the MHRA concluded that this was an extremely rare condition and that routine testing of liver function was not required. Again, they felt that the warnings included in the labeling were adequate.

[Slide]

Again looking at the patient information leaflet, we see the following three items: First,

consumers are told not to take these tablets if they know they have liver disease or they have been told they have had abnormal liver function blood tests in the past. Secondly, do not take these tablets if you drink excessive amounts of alcohol. Third, stop taking these tablets and see your doctor if you develop the symptoms of hepatotoxicity--it doesn't say hepatotoxicity but yes.

[Slide]

What about the possible use by pregnant women? This has come up today I think. It was not a concern to the folks at the MHRA. They pointed out that the labeling clearly specifies, right at the very outset, that it is only to be used by women by 55 and over. Furthermore, again they felt that the warnings in the labeling were adequate.

Again, if I could refer to the patient information leaflet, there is this directive: do

not take these tablets if you could become pregnant, are pregnant, are planning to become pregnant or are breast feeding.

[Slide]

What about the consumer's ability to self-diagnose that they are at moderate risk of a heart attack? The MHRA concluded that with pharmacists' assistance patients should readily be able to identify whether or not they are at moderate risk based on age and the risk factors. This is included in the questionnaire which the pharmacist goes over with the would-be purchaser, as well as in the patient information leaflet.

[Slide]

On the questionnaire, right at the top, patients are asked if they are of a certain age. I would just like to point out because this came out earlier today too, females ages 55-70, and if you are female, have you reached menopause? Yes/no?

They are also asked about four risk factors, and these are similar but not identical to the four risk factors on Mevacor. Smoking is the

same. Family history of early heart disease I think is very similar to what is on the Mevacor label. But not on the Mevacor label, and of concern to the British regulatory agency, was whether the consumers were overweight and whether or not they were of a family origin from South Asia.

[Slide]

The same information is on the patient information leaflet. You are likely to be at moderate risk based on age criteria as well as those same risk factors. So, there is plenty of exposure to determine if they are at risk for coronary heart disease. This, by the way, as in the United States, is the leading killer of adults in the United Kingdom, coronary heart disease.

[Slide]

What about do consumers need to know their LDL cholesterol levels? The MHRA pointed out that reducing the level of LDL cholesterol or bad cholesterol reduces the risk of a heart attack, and you have heard that described already today.

Therefore, the MHRA felt that there was no specific requirement to know initial LDL cholesterol levels or to monitor these levels after starting. Consumers that are found to be at a higher risk--and this is based on the answers they give to that questionnaire--would be identified by the pharmacy staff and would be given opportunities to determine their LDL cholesterol levels. These people could then be referred to a doctor for further studies.

[Slide]

Finally, what about the MHRA's feeling on the adequacy of pharmacy staff training? It doesn't really apply in this case but to complete the major issues. The MHRA felt that this had been prepared in consultation with national pharmacy bodies and was adequate; would be distributed to pharmacists and medicine counter assistants throughout the United Kingdom; and the education specifically included understanding of pathophysiology of coronary heart disease and major risk factors; contraindications, precautions, and

possible adverse effects of taking Zocor, as well as alternative interventions including, for example, lifestyle changes--diet and exercise.

[Slide]

The consultation letter went out in November of 2003 and was sent to over 250 different health service agencies. Of those, they received 100 responses. Most of these came from national health service trust organizations, but they also got significant input from pharmacy bodies, royal medication colleges, medication bodies and academia. Additionally, there was input from industry and from patients.

[Slide]

Well, what did people think? Of those 100 responses, 9 percent said unequivocally yes, we feel this should be switched to pharmacy status; 24 percent said yes, they felt it should be switched but they had issues they felt warranted further consideration; 21 percent said neither yes nor no but stated that they had issues that they felt should be addressed; 11 percent responded with no

comment; and 35 percent said no, it should not, either statins in general nor Zocor in particular should be switched to pharmacy status.

[Slide]

I will just briefly and quickly go through the major concerns raised in response to that consultation letter. At least 50 of the respondents indicated that they felt the dose of Zocor 10 mg was too low to be effective, and pointed out that there were no clinical trials at this dose so it was not clear how the MHRA had reached a conclusion that it was efficacious.

At least 27 felt that, although the MHRA did not feel this way, there was a need for cholesterol testing, arguing that since this is an asymptomatic disease, a chronic asymptomatic disease, how could people know if it was effective if they had no way of seeing anything or measuring anything?

At least 21 felt that there was a need for liver function testing, something that you will remember the MHRA did not feel is necessary. The

argument was that preclinical only medicines require liver function testing so it was not clear to these respondents why it shouldn't be required for pharmacy class medicines.

At least 21 respondents raised the issue of the potential for ignoring lifestyle changes. In other words, people might forego changes in their diet or exercise regimens in favor of taking Zocor Heart-Pro.

Another 21 brought up the issue of the cost of OTC statins. That is not an issue that we worry about in the FDA but it was an issue that came up over there. Zocor costs about 12-15 pounds per package. That is a 28-day supply, taken once a day, usually in the evening. That equates to about $24-30 and that is about $360 a year. So, there were concerns that there would be a disparity between the ability of those who could afford it to buy it and those who really couldn't afford to buy it.

[Slide]

At least 16 raised the issue of the burden

on the pharmacist and the pharmacy staff and the training that would be required. We felt that either the training wasn't completely adequate or they felt that training and the time spent counseling potential purchasers would be too great a burden on the pharmacist.

Another 16 were concerned about record keeping and patient management. The feeling here was that since the pharmacy had one set of records and the doctors had another set of records there might be a disconnect between the two and the left hand doesn't know what the right hand is doing. So that was an issue.

Ten felt that interactions with other medications warranted further consideration, and 10 felt that the side effects, for example the rhabdomyolysis and the liver toxicity, merited further consideration as well.

[Slide]

In summary, as I said, this was reclassified as a pharmacy medication in July of last year because the medicine does not produce, in

the view of the MHRA, a direct or indirect danger to consumer health without medical supervision, but only if it is given with the advice of a pharmacist and supported by a comprehensive pharmacy training package. Again, this type of behind-the-counter classification does not currently exist in this country. There is no legal basis for it at present. Thank you.

Questions from the Committee

DR. WOOD: Thanks to all the presenters for sticking to time. I guess now is the period for the committee to ask questions and we will entertain questions. DR. WOOLF: A couple of questions. The system in Great Britain has been in place for six months. Do we have any idea, in this short period of time, how well it has worked?

DR. WOOD: The question was it has been in place for six months in the U.K., how well has it worked?

DR. HEMWALL: Yes, as you noted, it has only been on the market for six months in the U.K. We don't have a good handle on how well it is

working yet. I do have Dr. Steve Mann, who actually was the person who took the application through the MHRA, here and he can answer a lot of your questions about this. Maybe you have a comment now, Steve?

DR. MANN: Thank you. Firstly, I want to thank Dr. Koenig for what I thought was a fair characterization of the process in the U.K. As Ed said, it is a little early to judge exactly how well this is working, although we are committed to monitoring how the system works.

We did pilot the questionnaire that is used in pharmacies before or actually during the process of the application and showed that it works well, with pharmacists being able to use it adequately, and actually, a fair proportion of people being able to fill in the questionnaire without any pharmacy help.

Perhaps the only comment I would make on the process is that the Committee on Safety of Medicines was heavily involved in approving this. It is not just the MHRA. The Committee on Safety

of Medicines, as Dr. Koenig pointed out, is an independent body of advisers to the government.

The only comment I would take slight issue with is we do encourage people to test their cholesterol. It is just simply not mandatory for them to know their cholesterol level going in. The view of our experts and of the Committee on Safety of Medicines was that if people have a risk level that justifies treatment, whatever their starting LDL cholesterol level, there is evidence that they will benefit, and that it is important to know that their cholesterol is reducing, and that they don't have a high level on treatment. That really is the place of cholesterol testing is the current view in the U.K. I hope that was helpful.

DR. WOOLF: The second question is for the FDA. On page 2 at Tab 4 of our briefing document it states that there were 195 cases of women who were pregnant who received a statin. We only have the data on the 25 who had lovastatin. Do we have the information for the remaining 170 who took a different statin and what was the outcome in those

pregnancies?

DR. DAVIS-BRUNO: That particular data was obtained from an Office of Drug Safety consult that we requested. I don't know of Jocelyn Swann is here but she is the one who actually did the consult and could specifically address that question. I don't have slides on the other statins.

DR. WOOD: Well, while you are up there, if my recollection is right, Merck said there were seven fetal abnormalities in your database, and on page 2 and 3 of your Tab 4, are these overlapping or are these additive, or what is the story there?

DR. DAVIS-BRUNO: If you are referring to the pharmacology/toxicology briefing document, that table with clinical findings--

DR. WOOD: I am referring to Tab 4.

DR. DAVIS-BRUNO: Right. Those particular human findings are relevant only to lovastatin.

DR. WOOD: No, no, I understand. These are the numbers from the AERS database.

DR. DAVIS-BRUNO: Correct.

DR. WOOD: And in the Merck database there are seven, they said. I was surprised, first of all, that the seven didn't seen to be reported to

the AERS database and the question was did these seven that they have include these five, or are there really 12, or what are the numbers? I thought they had an obligation to report all the numbers, so how come there are less?

DR. LEVINE: I am Jack Levine, with Merck. The five that are there are included in our seven--those six are included in our seven.

DR. WOOD: Okay, and what is the seventh?

DR. LEVINE: There was one aborted fetus that the FDA refers to, and we have two where there is actually a question of whether they are the same case.

DR. WOOD: All right. So, the total universe is seven including 1/2.

DR. LEVINE: Correct.

DR. WOOD: Thanks. Dr. Parker?

DR. PARKER: It seems that there was some valuable information obtained from the label

comprehension study, as well as the use study, about the bottom line of people who would use this drug, their ability to understand what they need to know. I am wondering if the insights gained from the label comprehension study, however you slice the pie, were used to modify the label for the use study. In other words, what is the exact timing of the label comprehension study and the use study, and whether or not the results from the label comprehension were used to make the label better in the use study?

DR. HEMWALL: As you saw in one of the slides that Jerry Hansen showed, we did research for about three years, and the total amount of research going even further back that that was with about 30,000 consumers, studying every possible element of the label in focus groups and in pilot label comprehension studies. So, once we had the label that we were confident was well understood, we did the studies, the CUSTOM study and the label comprehension study simultaneously, knowing full-well that the next study would be one with

input from this committee and from the FDA, having reviewed and commented upon the results of not only the label comprehension study but the CUSTOM study, to help further refine that.

DR. WOOD: Mary?

DR. TINETTI: I have a few questions related, first of all, to label comprehension, and this would be both for the FDA and Merck. First of all, I was sort of interested that it had an 8th grade comprehension level. I wonder if anybody knows what the median comprehension level for the older population is. I guess the last I heard, it was closer to 5th grade. I am curious. In this population there is only 35 percent for women, for example, who are over 55 and probably few of those are over 70. My concern is that there is a large number of those people who are going to have many of either the contraindications or most likely the indications for discussing it with their physicians. So, I wonder if there was any sub-study looking specifically at that population, and whether the people we are most concerned about

understand the label, and could they, indeed, do it.

I am also concerned about the size of the print for the older population. Finally, I was sort of curious. It sounded as if people understood that if you stopped the medicine your cholesterol would go back up. But do they really understand the question that we are interested in, that once you start this medicine you are only going to get better if you take it forever and taking it in fits and starts is not going to be particularly helpful. I wonder if there were any questions related to that and, if not, what do we think the repercussions of not having that information are.

CAPT. SHAY: There were no questions in the label comprehension study that addressed that but, I agree, that would have been an important element to come out in the study.

DR. WOOD: Let's go on to Dr. Follman.

DR. FOLLMAN: I wanted to talk a little more about pregnancy. In the sponsor's analysis

that they showed on the screen a little while ago, my recollection was that they talked about 67 reports of statin use during pregnancy and that nothing happened as a result of this, no toxicities or problems, or anything. But in their briefing document they talk about these 67 and note that in 34 of these pregnancies that were reported during statin use outcome data was available, and in this table they note that three of these 34 with known outcome data ended in elective abortion; one in a spontaneous abortion and one in fetal death.

So, I wanted to, I guess, set the record straight in terms of what they said earlier that, in fact, there were some untoward events during those pregnancies.

I also have a couple of comments about the analysis of the mice data. One was that the sponsor's analysis sort of disparaged what the FDA did and noted that one of the litters had, I think, 8/8 fetal abnormalities. So, all of the abnormalities were in one litter and that seemed to be sort of over-counting. I don't know exactly

what statistical analysis the FDA did but there are certainly analyses that I trust the FDA did which take into account the fact that outcomes in a litter are likely to be similar. So, just the fact that you used litters in your analysis doesn't necessarily mean that it is incorrect.

Another point I wanted to make was that in the weight loss analysis they had a table which showed various outcomes in the control group and then weights at different times for the three different doses of statin, and they said these were all non-significant. But if you look at them, in each instance, except for one of the 12 I believe, the weight was less in the lovastatin-fed mice than it was in the control group. So, to me, if you would combine that it would suggest something more consistent with what the FDA said, which was that there was concern about weight loss with lovastatin.

Finally, there was some comment about disparaging the use of concurrent controls and that historical controls would be better. I have never

heard that argument before; it is kind of mystifying to me.

DR. WOOD: Does the sponsor want to respond to that as these were in their presentation? No? All right.

DR. DAVIS-BRUNO: Can I just clarify? I just want to make sure that it is clear that the FDA looks at both concurrent controls and also historical control data when we do our analysis.

DR. WOOD: Okay. Dr. Watts?

DR. WATTS: I would like to hear from Merck. You have one of your products now approved at the pharmacy level for use in the U.K. and you are asking us to approve or recommend approval of a different drug in the same class for use in the U.S. I wonder why you picked simvastatin to use in the U.K. and lovastatin to use in the U.S.

DR. HEMWALL: There is a fairly simple answer. Lovastatin was never approved for prescription marketing in the U.K. so simvastatin was our only option for switching in the U.K.

DR. WATTS: But why not simvastatin here?

DR. HEMWALL: Well, as you have heard today, we have done an awful lot of work on lovastatin, including additional investigative

animal work, and this has been our project I think since about 1997. It would have been difficult to switch in midstream to simvastatin. Secondly, in keeping with the data-driven determinations that are made by this committee and the FDA, lovastatin is directly tied to a study, AFCAPS, which showed risk reduction in the primary prevention target population that we are considering for OTC. Simvastatin has many excellent long-term studies but they are in different risk level populations although the HPS study was certainly a basis for approval in the U.K. without needing to know one's cholesterol level.

DR. WOOD: While we are talking about the comparison between the two, you obviously went with an approval in the U.K. without an LDL measurement, and you are going here with an LDL measurement. Do you want to comment on why you made that distinction?

DR. HEMWALL: I think I will ask Dr. Mann to comment on the thinking that was considered in the U.K. In the U.S., of course, we are trying to be as consistent as possible with the NCEP guidelines.

DR. MANN: Yes, if I could comment, in the

U.K. we faced a very different situation I think to what prevails in the U.S., in that there has not, in the U.K., been an extensive cholesterol awareness campaign over many years, and I think it is fair to say that the level of consumer knowledge about cholesterol risk factors for coronary heart disease and the connection between the two is not very high in the United Kingdom. We were faced really with a quite different setting I think from what prevails here.

Our expert panel and the Committee on Safety of Medicines concurred with this view and felt that the current state of knowledge about cholesterol dictated that intervention should be based on someone's absolute risk of coronary heart disease and, if that risk justified intervention,

then the person would benefit from reduction of cholesterol whatever the starting level of LDL-C. I think you saw earlier today that Dr. Pasternak presented those data, suggesting really that the benefit is there throughout the line of what the starting cholesterol LDL-C is.

It is also the case in the United Kingdom, and I think it is probably true to a similar degree in the United States, that with these age and gender categories there are very few people who have what is characterized as a desirable LDL-C level and, on that basis, it was felt that not having to know the LDL-C at the start of treatment would discourage fewer people in the United Kingdom from taking part because really the knowledge of those numbers didn't exist. But knowing what their LDL-C was on treatment is something that would be encouraged both to motivate and to continue but also to pick up those who are inadequately treated.

DR. WOOD: Dr. Fincham?

DR. FINCHAM: I would like to preface my question with just perhaps a comparison between

pharmacy in the U.K. as opposed to pharmacy in the U.S. If you look at the sheer numbers of pharmacies in the United States, there are probably four times as many pharmacies in the U.S. as there are in the U.K. But, yet, because of the population difference, if you look at it as a pharmacy per unit of population, residents of U.K. have probably twice the opportunity to see a pharmacist perhaps as we do in the U.S. Plus, the types of pharmacies that you see in the U.K. are vastly different from what you see in the United States, and there is some penetration of chains much more recently into the U.K., and certainly it is dominant in the United States. So, the size of the pharmacies is perhaps different. Thank you for allowing me to say that.

The question is it appears, when looking at the training materials either for consumers or for consumers and pharmacists, that the process in the U.K. seems to be driven through a pharmacy by a pharmacist or a trained technician to aid the consumer, whereas, in the United States what has

been proposed, or at least what I have seen in the documentation, indicates that it is much more of a consumer-driven process within a pharmacy and, by the way, you can ask a pharmacist in the United States should you need to. And, I would just like to have an answer to the question why is there a difference in how this is being marketed to consumers through pharmacies in the different countries.

MR. HANSEN: Maybe I will have Steve comment on access to pharmacists in the U.K. versus the U.S. My understanding, after being over there several times, is that it is pretty similar to the U.S. in that two major chains do have about 50 percent of the market share--but I will let Steve confirm that--and the rest are independents, which is similar to what you see in the United States--

DR. FINCHAM: However, one of those pharmacies traditionally has been a major player, and it is Boots, and Boots has always had smaller pharmacies as the norm as opposed to the opposite.

DR. HANSEN: Yes, it is not true anymore.

They look more like a CVS or a Walgreens than they do the old Boots that you remember. In fact, they even have a dentist's office in a lot of them. So, they have expanded over the past few years. I was actually surprised. So, we can debate whether they look the same or not the same.

But I think the key question is why the difference; why aren't we putting it behind the counter here and putting it behind the counter in the U.K.? And, the key difference, as Dr. Koenig from FDA said, is that there is no third class, legislative third class in the United States.

DR. FINCHAM: That is a great answer but I don't think it answers my question. The question is that driving the product for consumer use appears to be vastly different between the two models. My point is that in the U.K. you are driving it through consumers to go through the pharmacist in a pharmacy, whereas here, at least in what has been proposed and what is on the boards, etc., it appears that this is driven by the consumer in the pharmacy who may or may not have a

consultation with the pharmacist.

MR. HANSEN: Yes, I think the difference is the hallmark of our program, that the consumer can do it on their own here, in the United States, because you have to consider worst case, that they are not going to talk to the doctor; they are not going to talk to the pharmacist and, therefore, we developed a system for them to do it on their own. That is number one.

Secondly, understanding the type of consumer who is interested in using this, we know that most of them see their doctor on a regular basis. Most of them consult with a pharmacist. So, we want to make sure we facilitate that and we want to make sure that they do have that option in a pharmacy so that it is there. It is not mandatory. It is not behind the counter because there is no legislation for that, however, we do want to make it easy for consumers to avail themselves of that as well.

DR. WOOD: Also, I would not oversell what actually happens in a U.K. pharmacy when they are

behind the counter.

MR. HANSEN: I was going to stay away from that!

[Laughter]

DR. WOOD: Right, you may be reluctant to say that what happens is the consumer goes up to the girls who stands behind the counter and says they would like that, and the sales person waves it at the pharmacist who says okay, and then it gets issued. Is that fair?

DR. MANN: I think it is probably fair for acute symptomatic treatments. They take it much more seriously with the newer medicines that are becoming available, and I think simvastatin is probably the first of a new class and is very much recognized as having to have a different approach.

One thing I would add to what Jerry said is that access to healthcare professionals in the U.K. drives to a large extent how people get their medical care, and primary care doctors are under a huge amount of pressure in the U.K. just by virtue of the numbers. So, people are used to accessing

care in pharmacies. However, the model that is applied in pharmacies in the U.K., particularly for simvastatin, is relatively simple and certainly our experience with piloting the questionnaire is that many consumers can do that without pharmacy assistance although the pharmacist is always there at the point of sale.

DR. FINCHAM: But there are really some sophisticated materials that are provided in the U.K., a pharmacist training guide, medicine counter assistance training guide, Zocor Heart-Pro consumer questionnaire pad, concise guide to when to recommend, BMI height/weight chart, customer counter leaflets--

DR. KOENIG: If I could just add something, I pointed out, I thought, during my talk that the reason this is a pharmacy medicine is that you can't go directly from prescription to GSL, or what we would call OTC, in the United Kingdom. You go sequentially and usually you stay in each class at least five years so that a sufficient safety record can be built up. So, simvastatin doesn't

have the option of being sold as we would do it in this country; it has to be sold as a pharmacy medication under those regulations.

MR. HANSEN: The only point I was going to make is that exactly the same materials, at least as they apply to the United States, would be available here. In fact, a lot of the materials used in the U.K. were actually adopted from the U.S. because we have been working on the program longer here than they have in the U.K.

DR. WOOD: Neal?

DR. BENOWITZ: I wanted to just follow-up on some of the differences between the U.K. and the U.S. trials. First, I just wanted to be sure that we had data on primary prevention, that lowering cholesterol below--or treating someone with cholesterol below 130 is still a benefit because we saw that a lot of people who are going to be taking this drug will have cholesterols that don't meet the entry criteria. I would like to know is it in fact of shown benefit in primary prevention.

A second thing I am curious about is why

the U.K. criteria did not include hypertension which is one of the major cardiovascular risk factors. Was there some concern about why hypertension should not be one of the indications for use in the U.K.?

DR. WOOD: Tony?

DR. GOTTO: Tony Gotto. The log linear plot of LDL was relative risk reduction showing an intercept of 1 and LDL of approximately 40 mg/dL where risk was not increased. There is nothing magic about 130. The sponsor has very carefully tried to make these recommendations consistent with the NCEP guidelines to avoid causing further confusion in the case of the person who is trying to follow the directions or the physician. So, they are very consistent with the guidelines but there is nothing magic about 130.

In fact, the recommendations of the National Cholesterol Education Program, ATP III guidelines were that the optimal LDL level for all patients is less than 100. I realize that in the CUSTOM study there were people with LDLs less than

130, a third or so, who followed the program, but it is very unlikely that you would do harm and, in fact, some people with levels in that range will get down to the optimal level. Only 23 percent of the adult population in the U.S., based on the current NHANES data, have an LDL under 100. So, it is very unlikely that you will get down to very low LDL levels.

As has been said before, there has been much less cholesterol education in the U.K. and a great deal of impetus for the Zocor OTC there, I believe, came from the Heart Protection Study where the investigators very strongly believed that you treat risk levels, not cholesterol levels. As they said in the presentation when HPS was presented at the American Heart Association, if a patient is in a high risk category we give 40 mg of Zocor regardless of what their LDL level is because it is too high for them. The OTC program in the U.K. and in the United States is aimed at a moderate risk category. So, based on the prevailing conditions, lack of cholesterol measurements and education in

the U.K., they have gone a different route but here we have been very closely tied to the numbers, spending huge amounts of time and funds trying to educate the public and physicians about the guidelines. So, there certainly is benefit in trying to have the guidelines as closely as possible in sync with what is being recommended to avoid confusing the public and the doctors.

DR. WOOD: Tony, before you sit down, what you are saying has great importance for interpreting the labeling studies because the HPS study and other studies really suggest that most people in the groups that are under study here will benefit. So, the studies of label comprehension and so on, my sense is, don't allow people to be treated who wouldn't derive some benefit based on most of the studies. Is that correct? Do you want to develop that a bit because that is relevant to understanding these studies and whether they matter.

DR. GROTTO: Well, I think there is no question that the patients are people who would

fall into this category with LDL between 130 and 170 with the age criteria and additional risk factors. These were the patients that we studied in AFCAPS/TexCAPS. Only 17 percent of those patients would have qualified for statin treatment by the guidelines at that time. We saw no diminution in treatment. We were aiming at trying to get LDLs down as low as 110 and the mean was 115 in the group on lovastatin. But we saw no breakdown or no diminution in benefit going down to the lower levels. The relative risk or the absolute risk is related to the LDL level so you have to treat more patients, obviously, at the lower risk range in order to see benefit. But it was a very robust result and indication for primary prevention was given based on a single study. So, I think going by the data that are available from clinical trials, patients below 130 would benefit.

DR. WOOD: My point was also that if you have patients who haven't had an LDL measured and who fit the other criteria for risk, the proportion of patients who won't benefit in that group is

relatively small. Isn't that right?

DR. GROTTO: That is absolutely correct.

DR. WOOD: So, that is relevant to interpreting the apparent disparity in the labeling studies.

DR. GROTTO: Yes. I completely agree. That is a good point. Thank you.

DR. WOOD: Frank?

DR. DAVIDOFF: Yes, I have a question about the issue of cost in the U.K. because, as we have heard a number of times, cost is not considered by the FDA in its decisions here. But the British system of financing medical care is obviously very different since the NHS pays for virtually all healthcare in the U.K. including medications.

I notice that there were editorials both in the British Medical Journal and in the Lancet apropos the decision to go to over-the-counter statins, which took up the issue of cost as a very major one. The BMJ more specifically pointed out that if all those patients who were at moderate

risk were actually treated with statins, and most of them currently are not, it would actually consume 10 percent of the total NHS budget.

The arguments can go either way because it was also pointed out by Lancet that going over-the-counter would mean that those people who could afford to pay what it cost to buy the over-the-counter drug would do so and those who couldn't would not, and that this would actually increase the disparities in health care.

So, my question is whether in the regulatory process, approval process, in the U.K. cost is actually formally considered because it clearly, from the NHS point of view, could make a huge difference in making the decision to go over-the-counter.

DR. MANN: It is not explicitly a criterion for whether something goes over-the-counter or not. However, it clearly has a considerable impact on how people behave. The joint British societies that issue our guidelines on treatments of coronary heart disease have always

recognized that levels of risk, more moderate levels of risk--that there is very good evidence that treating them is beneficial. That has been in the guidelines since 1998. But the thresholds for treatment under the NHS are governed entirely by socioeconomic factors. The new joint British guidelines which are shortly to be issued and have already appeared in some abbreviated formats do suggest treating at lower levels of risk, going down to 15 percent, or broadly the equivalent to 15 percent 10-year coronary risk. So, there is a shift gradually downwards within the National Health Service as resources allow--I think those are the weasel words to be used.

I think the recognition here is that the OTC approach is entirely complementary to what is available on the National Health Service, and that people should have the option to take that should they wish to. Obviously, people then have choices whether to spend their money on healthy lifestyles or reducing their cholesterol.

DR. WOOD: Dr. Neill?

DR. NEILL: Earlier this morning Dr. Ganley discussed what constituted the OTC and we reviewed a little bit of that today in terms of the

fact that this is a consideration that includes a condition that meets few or none of the classic OTC conditions. In a prior NDAC meeting, in discussion of non-sedating antihistamines, it was interesting to listen to a company have to answer why a medicine should not be made OTC since it was safe and effective, and I believe it is still the case that it is incumbent upon the FDA to make something available in the OTC setting if it is for an OTC condition and if it is safe and effective for use in the OTC setting. In other words, a company cannot simply decide to make it prescription if all of those things are met because they would like to. Rather, the FDA may compel them. And, it is my understanding that that in part informed the discussions between health plans in California and the manufacturers of some of the non-sedating antihistamines.

So, with that background in mind and given

that we are talking about a new OTC condition that you already have approved in the U.K. a different product from your company, I am anxious to hear, if you are willing to reveal, how you would respond to a health plan provocation to encourage you to take other safe and effective statins OTC at some dose, number one and, number two, perhaps for FDA, to what extent is it in the public interest to make these over-the-counter statins available across product lines and across companies if, in fact, we reach a decision--and I don't know what will happen tomorrow--that this is an OTC type condition and we are okay with that, and that this is a safe and effective medication.

I am confident that we could sit here for months discussing the individual dose for Zocor--list all the statins--and we could discuss how or whether they were safe and effective. But that is a dichotomy that I think requires some explaining. In other words, if the default is that these must be OTC, why aren't they?

DR. WOOD: At the risk of sounding

cynical, it usually happens when the patent expires.

DR. HEMWALL: I am not sure if that is a question that has a straightforward answer. It sets forth a number of hypothetical situations. I think that we have been trying to develop the data to convince the Food and Drug Administration and your committee that a product like this should be OTC for about seven or eight years.

DR. NEILL: We should approve Zocor as well, and you should be compelled because the issue here for me, in my mind, is that this is an issue of compulsion. It is the FDA's duty to make these medications OTC. That is the default. The only reason to have them Rx is if they are not safe and effective.

DR. WOOD: Hang on, hang on. We are here to discuss Mevacor and that is probably more than we can cope with before five o'clock. So, although these are all very reasonable and interesting points to discuss in the bar on Friday night, I think we need to focus on Mevacor right now and

just stick to that. I don't mean to cut you off but I think I have bitten off as much as I can chew with that right now. Your point is noted. Leslie?

DR. CLAPP: I have a brief observation to share with Merck about the packaging, and that is, as my eyes mature I have increasing difficulty seeing small print. But additionally, the script that is in red on the label that is supposed to be more important is very fuzzy and blurry. The only one I can see in terms of red is "test at two weeks." So, if you can consider emboldening the red script, perhaps it will be easier for aging eyes to see. That is just an observation.

But now I have more of a question for the FDA. I would like to have some clarity about pregnancy category labeling. As was stated previously, Mevacor is pregnancy category X and the components that seemed to go into that determination is the clinical benefit of a medication, as well as the human and animal fetal risk. I don't know if there is any weighting that has been done in terms of a perspective from the

FDA as to category X for Mevacor, but I heard some comparisons from Merck as to those medications that were category C. I am wondering if the perspective we might be encouraged to feel is that Mevacor could be a category C because of the lack of risk--I think that is what Merck is touting as a fact, that there is very little or negligible risk. Whereas, the final statement on Dr. Davis-Bruno's presentation certainly does mention that, based on extensive animal data, potential human risk does exist following exposure to lovastatin during pregnancy. So, I am not sure if there is a weighting that the FDA has to risk for the medication from the human and animal fetal component versus the benefit to the mother or the woman of childbearing age taking the medication.

The other question I do have is are there any other OTC medicines that are category X?

DR. MEYER: I will take the first part of that question. I guess, to make it clear, under the wording of the regulations as they stand for the pregnancy categories, if one is to advise that

the drug not be used in pregnancy because the risks outweigh the benefits, then it is a category X and you can get to that calculus because of large risks in the face of benefits, or you can get to that with a smaller risk in the face of no perceived benefits.

I think that you have heard from the sponsor, and I am not sure we would very loudly disagree with it, that that is more the case with lovastatin, that we are in a situation where the animal data suggests there are in fact some risks. The human data don't really answer it at this point. So, the temporary or short-term treatment of the mother during her pregnancy does not outweigh the potential that we feel the animal data suggests might exist for the fetus. The decision about the category obviously was made some time ago and data continue to accrue both with the post-marketing experience and otherwise.

I would urge the committee not to focus a whole lot on whether it is category X or not. I would ask you to consider the data that we have

presented and that the sponsor presented and look at whether you think that represents a significant risk and, if so, does the labeling that the sponsor has undertaken help minimize that risk? That is really the question because when you get to the OTC setting pregnancy categories have no relevance.

DR. CLAPP: Yet I do just wonder whether or not there are any over-the-counter medicines that have been switched, that were category X as prescription medications that are over-the-counter now.

DR. ROSEBRAUGH: We have considered category X drugs. We have drugs that are OTC that do have teratogenic effects. The poster child is probably nicotine replacement.

DR. WOOD: Dr. Parker?

DR. PARKER: I just wondered if you could comment on the Zocor warning about alcohol use and the fact that that is not there for Mevacor. Did I miss that?

DR. HEMWALL: That is simply a matter that that was something that was requested by the U.K.

It seemed like sound judgment to warn against alcohol use, and certainly we would consider that for the U.S. as well, but it is not because there is any evidence that people with alcoholic liver disease are at any greater risk. But, again, it is meant to be more of a safety net and to keep the risk to a minimum.

DR. PARKER: I guess that was a part of the discussion that went on at the time.

DR. HEMWALL: In the U.K.?

DR. PARKER: Yes.

DR. MANN: In the U.K. we submitted this to the expert opinion about the need for liver monitoring and concluded that it was not necessary and probably unhelpful. However, we started with a Zocor label that said that people with preexisting liver disease should not receive the drug, and we really didn't feel we had evidence to say that we shouldn't do that. Therefore, we have excluded people with known liver disease and I think that is just a precautionary principle. On that same basis, people who have used alcohol and therefore,

potentially at least, have the risk of liver disease were also excluded, again, on a precautionary principle, not on the basis of any great data that those people are at special risk.

DR. PARKER: Could I just ask do we have from CUSTOM alcohol use? Was that a variable that was captured?

DR. HEMWALL: No, we do not.

DR. WOOD: Does the Tylenol label have an exclusion for liver disease?

DR. GANLEY: I would have to check on it but I am not sure that it does right now. I don't believe it does.

DR. WOOD: It would be worth knowing because it is relevant to this.

DR. GANLEY: It has an alcohol warning.

DR. WOOD: I actually was asking for prior liver disease. Jack?

DR. FINCHAM: I know we are not supposed to talk about cost but it is hard not to think about it in the context of at least the tradition in the United States. When a drug is switched

insurance coverage ceases whether it is managed care or whether it is Medicaid or soon to be Medicare. In the U.K. previously, at least according to pharmacy informatics organization, the consumer paid in effect a third co-pay for a month's supply of simvastatin, an equivalent of $10 for a $30 prescription. Now they pay between $19 and $30 and the government doesn't pay anything. There can be no question that these drugs are important to take. I just wonder what the result will be, and this may be a rhetorical question but I just wonder what the result will be when this burden is forced more and more on consumers, not as an opportunity to help themselves but, yet again, another decision that they have to make relative to how they spend limited resources.

DR. WOOD: Do you have that question to address to somebody?

DR. FINCHAM: I don't have the answer to it. If somebody else in the room does, I would sure like to hear it. I think it is a concern that is not addressed in any of our materials, nor

should it be.

DR. WOOD: Dr. Snodgrass?

DR. SNODGRASS: Just a couple of brief comments around the birth defects, the fetal adverse effects issue. One has to do with sharing medications. If Susie buys it and shares it with Sally and Sally turns out to be pregnant is an issue. The comparison I will make is not, obviously, a very good one at some levels but it is a real one. Many years ago, before the current procedure for Accutane in a physician's office to fill out the long forms, Ed Lammer, in California, had shown by epidemiologic data that there were at least 1000 malformed infants in the United States--this is well over 10, 15 years ago--with a drug that had been marketed with a black box warning about teratogenicity, realizing that it is a very well characterized potent teratogen. So, that occurred under prescription circumstances with a black box warning.

The other comment is about the folate receptor in in vitro studies. When you lower

lipids around that receptor it doesn't work as well. It doesn't take up folate; it doesn't respond as well, and we know the relationship between folate and neural tube defects.

DR. WOOD: We have gone round and round on this pregnancy issue so maybe we should try to reach some sort of closure on that. If I can summarize where we are, nobody disagrees that it shouldn't be taken by pregnant women. So, the question really evolves into--were this to be approved and we are not there--have we got sufficient confidence in the methodology to prevent it being taken by pregnant women? That seems to me the issue rather than debating the biology, which I suspect we have neither heard enough about to really deal with adequately today, nor do we have sufficient time to do that. Is that fair? I mean, are people comfortable with that? If people have further comments, let's deal with that issue and then put it away. Neal, is your comment on this issue?

DR. BENOWITZ: Yes. Let me say that I

don't think you can make it quite that simple because if we are talking about Accutane, then we want to be very, very, very sure that no pregnant woman takes it. If we are talking about a low theoretical risk, then you might be more willing to have a little bit of an error. So, I do think there is a quantitative issue here.

DR. WOOD: Do you want to address what you think the quantity looks like? I mean, are you suggesting you think this is Accutane?

DR. BENOWITZ: No.

DR. WOOD: Okay, good. So, help us understand that. I mean, where do you think this fits in the quantitative level?

DR. BENOWITZ: I certainly can't answer that. To me, it looks like it is low in terms of evidence in human exposure levels but I wouldn't want to have a woman take it if she is pregnant if I could help it.

DR. WOOD: Right, I think we would all agree nobody wants this to be taken by pregnant women, but that would be true of most drugs that

don't have a benefit in pregnant women. So, the issue then is can we avoid it and how do we avoid it being taken by pregnant women? You are raising a new issue--well, tell me what the new issue is.

DR. BENOWITZ: No, it is not a new issue. It is how large is the risk. If a pregnant woman absolutely takes it and the risk is really substantial, then you want to make sure absolutely and do everything possible to make sure no pregnant woman ever takes the drug. If it is a theoretical risk or very obscure risk, then if there are some exposures it is not going to be of as much consequence for the population so we may be a little bit more willing to say let's have a little bit of leeway. Now, I don't have the parameters for that in terms of numbers for risk. It seems to me that the risk in humans has not been demonstrated at something equivalent to a 20 mg dose. That is not to say it couldn't happen in some case. But I think it is important in terms of how strong the barriers have to be to prevent any woman who could possibly get pregnant from getting

the drug.

DR. WOOD: Does the company want to respond to that issue? Oh, I am sorry, we will let Dr. Makris talk first.

DR. MAKRIS: Thank you, just a few thoughts. It seems that there is pretty much agreement I think between FDA and the sponsor that what has been seen so far in human incidence data really doesn't indicate that there is a real concern for birth defects when there has been accidental or unintentional exposure. So, there is agreement on that.

It seems that there are some disagreements in terms of how to characterize the animal data, developmental data and having sat on a number of peer review committees, I know that if you put three toxicologist in a room you get seven opinions--

[Laughter]

--about how to interpret the data. Usually you have to go back to the individual animal data and look at it a whole lot more

carefully to be able to weed things out, and I don't know that that is really an issue here or something that we need to be addressing.

But there is something that I do see in the data that was presented that, you know, raised some concerns with me. It had to do with some of the functional assessments that were done. I believe it was the seg. 3 study that characterized a number of functional deficits in the pups and a number of different parameters. And, there was a follow-up study done that was a neurodevelopmental study that dosed from postnatal day 4 through somewhere around 41 or 50 of age, and did a number of additional tests. The evaluation of that study by FDA indicted that there were still some concerns or that they felt that the endpoints that were assessed in that study weren't enough to truly characterize what they were getting at.

But even that being said, I think that the original functional assessments that were done that raised the concern were not addressed in quite the same way in that second study because it was

looking at different stages of development. It is possible that the functional deficits seen in the first study may have come from in utero exposure; may have come from postnatal exposures, and you can't determine that from these types of studies.

The follow-up study that was done was essentially trying to mimic human exposures in late gestation and early postnatal and maybe even through almost adolescence. But the early in utero exposures were not captured in that study and that seems to be what some of the concerns are here, what happens when a woman who just finds out she is pregnant is taking the drug and those early gestational exposures are the ones of concern. So, they haven't, I think, been characterized fully. So, there are some uncertainties I think in terms of whether or not there might be developmental exposures that could result in some kind of functional outcome in the fetus or child.

So, I am not sure that there is any way to address that with the data that have actually been collected, and there is nothing that I see in any

of the human or epidemiological data that would suggest that maybe that is an outcome, but I think we need to at least recognize that lack of information.

DR. LANKAS: I would just like to make a brief comment relative to your comment, and that is that the neonatal toxicity study where the animals were treated beginning on postnatal day 4 was done expressly to, hopefully, try to ally some of the concerns that FDA had raised that a statin-like drug could affect myelination as a function of its effect on lipid metabolism. As Dr. Davis-Bruno pointed out, rats are quite different developmentally than humans with respect to the time of myelination. So, the specific study was done to address the issue of when myelination occurs the exposure to lovastatin was initiated, and in the rat it is during early postnatal development and in humans it is basically during the latter part of pregnancy, during the second and third trimester. So, that was the reason for that study design.

Again, there are differences in interpretation but I think Dr. Davis-Bruno's characterization, a conservative one, indicated

that there was a clear no-effect level at the middle dose group of 5 mg/kg which, in terms of an exposure, would far exceed any exposure that a human fetus would receive because we were dosing the pup directly as opposed to any in utero exposure or lactational exposure.

DR. MAKRIS: Yes, I understand that and the study was not designed specifically to follow up the effects that had been seen in the previous study. It did have a completely different intent and was designed to assess that.

DR. WOOD: I think Neal Benowitz's question still needs to be addressed. Are you going to do that?

DR. HEMWALL: Yes, if I can remember back to the beginning of the discussion, you are concerned about some of the behavior in CUSTOM. There were 12 women who were pregnant or breast feeding that came to the study site and evaluated

whether or not to use Mevacor OTC. All 12 of those women elected not to use it, and there were no pregnant women that took the product.

DR. BENOWITZ: What I was talking about really was the number of women of childbearing age who took it and, obviously, could have become pregnant without knowing it.

DR. HEMWALL: Yes, that is correct. I think what we want to be able to do is be stronger in the labeling about the potential for childbearing. Again, we don't believe that there is a significant risk at all, but we do want to minimize as much as possible the use of the product by women who are of childbearing age, and labeling that has been used for other products that have the same problem, such as nicotine replacement which is obviously used by women of childbearing potential--we would extend that to Mevacor and work with the agency or with committee recommendations on the best language.

DR. WOOD: I thought, Neal, you also had the question about getting some quantitative

measure of the risk in humans.

DR. BENOWITZ: Well, I was trying to.

DR. WOOD: Right. Well, let's see if they can respond to that.

DR. HEMWALL: We don't have a quantitative measure of the risk in humans. We have examined in an abstract the number of prospective and retrospective pregnancies, both in the lovastatin and simvastatin database, and there is no clear signal that rises above the level of background. However, you can't rule out a certain multiple of background just because of the pure statistics.

DR. GANLEY: Alastair, could I just interject something?

DR. WOOD: Yes?

DR. GANLEY: We have obviously been thinking about a lot of this internally, and I will give you my perspective and others can chime in. But I don't think I am as concerned about pregnant women using this product. Remember, this has to be a highly motivated population who would want to use this and understand that they are going to get some

benefit from this. If a woman knows she is pregnant, I think most women are very careful--I may be wrong in that assumption--and I think the evidence from the CUSTOM study where 12 women actually showed up and chose not to use it, which was the correct thing to do--well, that makes a lot of sense.

Now, if these neurodevelopmental issues are second and third trimester issues and a woman may know she is pregnant by her second or third trimester, well, I don't think she is going to necessarily choose to take this drug. So, I don't have this much concern about that.

I think the issue that I have is this childbearing potential and what really is the risk in that first trimester. I think, going back to the CUSTOM study, what is difficult for us, or for me at least personally, to understand is that clearly someone knows their age, and if it is said that this is for a woman greater than 55, well, why did women less than 55 take it, other than being overridden by a doctor?

Merck had some survey data at the end of the study and I don't know if there is something within that that could help us understand, well,

what was it that women did not understand there that caused them to take it. Did they have their tubes tied or was there something else in there that gave them a comfort level? Because, clearly, if 100 percent of the women in this CUSTOM study were greater than 55, we probably would not be having this discussion right now.

So, I think that is how we sort of have to think about this, what went wrong there? Or, if a lot of it was physician override, the prescription labeling for Mevacor says if women of childbearing age are going to be put on this, they should be instructed about not getting pregnant, or they should have some other type of birth control, or something to that effect. But women still got pregnant while on Mevacor.

So, that system failed in itself. The system is not perfect whether it is prescription or OTC so we are not going to get perfection. But I

think we need to understand a little bit why, you know, there was such a high percentage less than 55 that chose to take it. Until we can understand that I am not sure--you know, that may help us get closer to the perfection part of it here. So, I don't know. I know they had a survey, a certain percentage of people were surveyed at the end of the study to better understand their behavior. But I think it would help us sort of consolidate this issue and we could, you know, possibly address that by some other mechanism and understand the risk in the first trimester.

DR. WOOD: Well, it seems to me there are two issues on the table. One is the one you just articulated, how do we avoid them getting it and how do we understand why they took it. If they all had a hysterectomy, for instance, you know, that would be different.

The second one that I am surprised nobody from the agency or the company responded to directly is, you know, if there are seven cases in the database of adverse outcomes in pregnancy, just

by the seat of the pants, to me that seems extraordinarily low. I am surprised, therefore, that no one has offered us that kind of assurance because it would seem to me that, given the number of abnormalities in pregnancy that occur by chance, that seems a pretty small number. So, it would be interesting to know what the data are for--you know, pick a drug. I am surprised that Merck and no one else has told us because that is clearly the issue that Neal was getting at. You know, he says is this Accutane? It is clearly not Accutane and we need to be clear on that. David?

DR. ORLOFF: Actually, I do think Merck did answer the question in their own presentation in this regard by concluding that, while they believe there is a theoretical risk to exposure with regard to fetal exposure in the first trimester specifically related to potential teratogenicity, they think, based on everything that they know, that the risk appears quite low.

Again to reiterate what Dr. Meyer said and what Dr. Davis-Bruno said, there are some animal

findings that suggest a theoretical risk. Although there is nothing in the spontaneous reports of exposures during the first trimester, there is nothing that obviously stands out as a pattern, as a clear pathological presentation that seems to describe a syndrome of lovastatin fetal exposure, nor do those reports completely allay any concerns.

So, nobody here can give the answer. You have given an answer that says, flying by the seat of your pants, you think it is relatively low. Merck has not been so--you know, they don't fly by the seat of their pants and they think it is relatively low. I think the FDA has to conclude that, on balance, it seems like it must be a relatively low risk. But nobody actually can tell you exactly what that is.

DR. WOOD: So, the FDA calls "the seat of their pants" "on balance."

[Laughter]

Mary?

DR. TINETTI: My question has to do with the long-term use of this medication. As we heard

today, this is really a new direction for over-the-counter towards long-term use for primary prevention. I think it is a very exciting opportunity, but still playing by the old rules, particularly with the actual use studies which I think are still predicated on short-term use for symptomatic conditions, my question to the FDA is, is there any interest in having actual use studies that will now more actually match the long-term use of long-term medications if we are going to start putting them over-the-counter?

My question to Merck is, regardless of whether you will be required, is there going to be some long-term monitoring if this does go over-the-counter to make sure that as people's cholesterols do go up after six months, do they continue to monitor their medication if they now take on new conditions such as diabetes that they get more aggressive care and are not in a situation of under-treatment?

MR. HANSEN: Can you bring up slide 1824?

[Slide]

As you have seen, both us as well as other sponsors of OTC statins have done a lot of use studies, and we really feel like most of the

questions, at least in that environment, have been answered. So, we are very committed, if this product is approved, to do post-marketing surveillance and we have given a lot of thought to this. The key issues we would be looking at are, first of all, do consumers use it safely once it is more available in the broad market and, secondly, is their use consistent with the label.

So, here are the methods we have used with other OTC medicines, and they would be extended further in the case of Mevacor. The methods would be that, first of all, we do surveys, toll-free number, hotline, websites and third-party data collection, and we would do this both among consumers and healthcare professionals because both of those would be important on how this product is being used in the marketplace. Then, obviously, we would want projectable samples to the population.

We think it is important to do a

pre-launch study because we want to understand baseline measurements of awareness and attitudes so we can see if this product, in effect, is having the greater population benefit that we are proposing. So, before the product hit the market we would want to look at the number of untreated people at risk and Rx users and understand their attitudes, awareness and insight prior to being put on the market.

As far as a post-launch study, we would look at OTC users in addition to these untreated at risk and Rx users, again, to see what kind of dynamics there are with the OTC. We would use predefined measurement frequency. What we frequently do with OTCs is at six-month intervals is data pulls to look at large populations to see where we can modify the program. So, it actually leads to actions which, first of all, if something happened that we didn't anticipate or something that we didn't see in the use trial, and if we do see that, whether it is safety or behavior, to take corrective actions in the marketplace.

DR. WOOD: Dr. Orloff points out that Charlie Ganley's question didn't get answered and I am just going to reiterate it, if I can, and let

you think about that while we are going through the other questions. The question was, what are the characteristics of the women who took the drug while they were under 55, and tell us about the characteristics of these women.

MR. TIPPING: Bob Tipping, from Merck, again. Dr. Ganley, I believe your question was about the younger women and how many women under certain ages were actually using drug in CUSTOM. I guess to answer that, first of all, I would remind the committee that the age cutoff on the label for women was driven by the risk factor approach, not so much a concern about pregnancy.

But some of the information about the women in CUSTOM from the user population--there were 430 among the users in CUSTOM and 81 percent of this group met the age criteria or did have the interaction with a doctor. I think most importantly, only 24 of those women were under 45

and didn't speak with a doctor. So, if we are talking about a concern within an age group where pregnancies do occur and then are happening within the context of an interaction with their physician, there are low numbers within CUSTOM that that is actually happening.

Then, one final point, while there were 37 percent of women in CUSTOM less than 55, less than that age cutoff, if you look at the non-purchaser population, 57 percent of that group were. So, we can argue whether 37 percent among the users is too high, but the label messages do seem to be working in that, you know, there is a 20 percentage point drop in the actual women who were using the product as opposed to evaluating it in that age category.

DR. GANLEY: Do you have any data that tells you why a physician would tell someone less than 45 it was okay and did they provide them information about potential risk if they become pregnant? Because that is what the prescription label says a physician should do.

MR. TIPPING: In no part of our program

did we confirm what actually took place in a physician's office. We are assuming that that discussion did take place.

DR. GANLEY: In your first survey you could have asked the woman what did the physician talk to you about.

MR. TIPPING: Right. We did not do that.

DR. LEWIS: Let me address that because I see these women every day in my practice. There are very few premenopausal women for whom I would recommend lipid-lowering therapy but there are a few because of the very high risk group that would take special attention and really don't fit in this CUSTOM category. But if you look at the CUSTOM age breakdown, there are a lot of women that are in this 45-55 group who may be postmenopausal and maybe they have two risk factors so that the doctor's evaluation could look at them and say, yes, you are right, you fit NCEP criteria; one risk factor plus age 55, you don't fit that but you do fit by other criteria and, yes, give it a try. There are large numbers of women in that 45-55

year-old age group that are spreading their 10-year risk very quickly.

One of the things we looked at was the comparison of the age spread from the CUSTOM women to the age spread from the women in the CARE study and the curves are almost identical, with about a 5-10-year break, pretty much predicting that this is a group of women that is at risk and the risk is maybe 5-10 years later than the men, who have not been getting aggressive risk factor management.

DR. WOOD: Dr. Schambelan?

DR. SCHAMBELAN: Well, I think that this was alluded to, the reason for the age selection here is that, as you say, it is efficacy driven, not avoidance of pregnancy. Nowhere on the label does it mention anything about being concerned about becoming pregnant. It says if you are pregnant or breast feeding you shouldn't be taking the drug. But there is no reason someone would think about the risk of becoming pregnant from just reading this label. So, I am wondering if this couldn't be alleviated to some extent by adding

that and by having these people take it into consideration because there are lots of people who are going to use this who aren't going to talk to their doctor, and that seems like a pretty simple fix to at least get that to the consciousness level.

DR. WOOD: Dr. Carpenter?

DR. CARPENTER: Yes, if I can divert from the pregnancy issue, otherwise I can come back to it later.

DR. WOOD: Go ahead.

DR. CARPENTER: My question is to Dr. Shetty. I was really struck with somewhat of the discordance between the survey of comprehension versus the behavior information that was somewhat discordant on a number of different categories. My concern in particular has to do with the concomitant medication risk, particularly antifungals, certain antibiotics, and in the over-the-counter setting and potential lack of communication with a physician there is greater potential for such drugs to be concomitantly

administered. Although the comprehension survey indicated that people understood that contraindication of certain co-administered drugs, what was the behavior or the actual outcome in CUSTOM as to the use of other contraindicated medications?

DR. SHETTY: There were a total of 32 subjects that were taking interacting medications, and 12 of them did not consult with a physician. I think 10 of those 12 continued taking medication. Maybe sponsor can confirm that. There was not a large proportion of people that were taking interacting medications.

DR. WOOD: Dr. Parker?

DR. PARKER: I had a question about study personnel, a term that I see on the label seven times. I could say that the word pregnancy is only on there twice but this isn't about pregnancy. I wonder, it is always "doctor or study personnel"--you know, consult, talk to. I also took a look at the little brochure, you know, that helps me get a coupon and, you know, I guess

getting into the study that allows the post-marketing surveillance. I want to direct this to the FDA, to ask you to help me understand for other drugs that have gone to the over-the-counter status, has the study personnel status been a part of labels, and what does that really mean, and could this also be viewed as direct access to buyers of products, and what are the implications of that?

DR. HEMWALL: I think you need some clarification. The materials that you have in your background packages and all the materials, including the box and the internal materials, were actually the materials used in the CUSTOM study. So, in every position where you would see normally "talk to your doctor" it says "talk to study personnel or pharmacist."

DR. PARKER: So, these wouldn't be the ones that would go forward? This was just for the CUSTOM study?

DR HEMWALL: Right, and that is to be distinguished from actually going to their doctor

but in areas about study personnel and adverse event reporting.

MR. TIPPING: Could I come back and just add some additional information on the potentially interacting medications.

DR. WOOD: Sure.

MR. TIPPING: Just very briefly, we agree with Dr. Shetty's number. There were 12 individuals at the beginning of the trial who were on a potentially interacting medication and used Mevacor without a doctor's interaction. Two of those, however, indicated that they had stopped their interacting medication. Then I would add to that that during the course of the study there were only two individuals who were prescribed a potentially interacting medication. In both of these situations the drug was clarithromycin and we didn't get into the actual behavior. We conservatively listed them amongst our 21 but, in fact, the reported behavior from these two individuals was that one discontinued his Mevacor at the time of the clarithromycin and the other one

interrupted his Mevacor dose during his course of clarithromycin therapy. So, small numbers of individuals but I think they were exhibiting exactly the behavior that we would hope the label would drive.

DR. WOOD: Dr. Taylor?

DR. TAYLOR: I guess I was concerned a bit about Dr. Shetty's analyses and how they differed in many respects, not only in terms of the number of pregnant women, the number of individuals who had--for example, 55 percent of users had greater than one relative contraindication according to the label and, yet, even with all those problems--I will call them problems--there were no serious signals that were seen, and perhaps this is related to the relatively small sample that you studied. Nonetheless, in actual practice we violate those categories anyway. So, the argument that the CUSTOM is not sufficiently sensitive may be true but, on the other hand, as a practitioner I see a lot of women who are in their 40s, with some counseling of course, and I think some of that can

be taken as labeling.

So, I just sort of want to put a little balance in there. That is neither a pro nor a con, but in a real functional sense, a lot of things--mistakes, if you want to call them that--that occurred in CUSTOM occur every day and, despite that, the safety record is fairly good.

DR. WOOD: Dr. Watts?

DR. WATTS: I don't want to revisit the pregnancy issue but I do want to visit the next step. I realize that drugs, whether prescription or OTC, are potentially available to children in the household. Prescription drugs typically would come with a child-proof lid. I wonder what precautions you are taking to prevent accidental ingestion of Mevacor OTC by children, and if you can give me some idea of how much drug might pose a problem for, say, an average one year-old or 18 month-old child who might get hold of it?

DR. HEMWALL: Well, first and foremost, the package will be in child-resistant packaging and, obviously, that is something that is done with

prescription drugs as well. We can go to some slides that we can show you but it is almost impossible to overdose acutely on lovastatin. Very, very large doses have been tolerated. It is actually written up in some detail in your background package. We have the data from poison control centers. So, even though we are expecting full child-resistant packaging and that is our plan, if some child were to inadvertently be able to break open a lot of blisters or bottles and get into it, it would be very hard to overdose.

DR. WOOD: Dr. Schade?

DR. SCHADE: There is a portion of this package that is very confusing to me. I understand that the company is targeting the intermediate risk group, but it seems to me they are actively excluding a high risk group. This is what is confusing to me, it says, "do not use unless directed by your doctor if you have...," and then they list six things. Included in those six things are, one, ever had a heart disease (heart attack or angina, and then diabetes.

Now, let me put this in the context of the real world. I come from New Mexico where a very high percentage of our population has no insurance

and the only doctor they ever see is in the emergency room where they come in once a year with their pneumonia or something else even if they are at high risk. Of course, we also have a very high incidence of diabetes. So, I see them reading this and they are not going to see a doctor. Even if they have a doctor, it often takes four months to get in to see one.

I don't understand why we are actively excluding the high risk group when the high risk group, in fact, would probably benefit more from 20 mg of lovastatin than from nothing at all and that is really the alternative here. In other words, in the real world where we have many uninsured people who can't afford to see a doctor, who don't see doctors, this drug might be of great benefit. And, I don't understand whey the packaging here seems to directly try to ward off the high risk population.

Now, Dr. Gotto made a comment with which I

agree, that in the best of worlds all these patients would be put on 40 mg of simvastatin and be followed with their LDLs. Well, the fact is that it doesn't happen in my state and I would like to see this changed to encourage people at high risk, who are unable to see a physician, that this drug might help them, and a statement to the effect that they ought to see a healthcare professional because the dosage may be insufficient, or some other reason, but not to actually ward them off from taking a drug that may be really beneficial to them.

DR. HEMWALL: Yes, we agree with you that people at even high risk could benefit from taking this if they were taking nothing else, but we still want I think to stay within the realm where we are treating the people that could most benefit by this than trying to get the people that could benefit from more comprehensive physician care, treating their diabetes and their post-MI more aggressively with full physician involvement. So, this would be a gap I think in reaching the balance between

trying to attract the right people and then directing the people that are at higher risk to see their physician. But we take your point.

DR. WOOD: Yes, I agree with Dr. Schade. It seems to me that there is a huge problem in listing as a contraindication the patient who needs it most, which doesn't make a lot of sense in any sense, and it also trivializes the contraindications. So, it does seem to me that it is important that patients understand that something is a contraindication, not really a very strong indication which is co-mingled right now. So the strongest indications are also contraindications in your label, which is crazy.

MR. HANSEN: I just want to clarify, it is not a true contraindication--

DR. WOOD: I understand.

MR. HANSEN: --what we say is "do not use unless directed by your doctor." Then within the materials a phrase that has been very helpful and that is that "OTC medicine may not be enough for you. You may need prescription therapy." So,

there is that balance we are trying to make by not inducing high risk people.

DR. WOOD: Neal?

DR. BENOWITZ: A question for the FDA, somewhere I saw mentioned that the marketing material or promotion material is regulated by FTC, not FDA, once it is approved. Is that right?

DR. GANLEY: The advertising is FTC.

DR. BENOWITZ: So, will you be checking out their materials as well to make sure that it is balanced?

DR. GANLEY: We can ask a company for their advertising material and they don't have to send it to us.

[Laughter]

Let me put it this way, and we ask all the time. I have been in OTC quite a few years and I can't remember the last time someone sent me some. It is interesting, you know, usually who we get it from is a competitor.

[Laughter]

But I think the other thing is that we do

have a relationship with FTC, and FTC has a huge market they have to oversee and they are making judgments as to what they are going to put their resources to if they have to take an action because someone is marketing outside the labeled indications.

DR. BENOWITZ: I am sure this will come up tomorrow and I don't know if we will have a chance to talk to the sponsor, but I have a concern about appropriate communication of benefits to people to decide where they are going to spend their money and efforts, and I think it is workable but I think with a lot of drugs there are concerns, as everyone knows, about over-promotion and this could be really over-promoted.

DR. GANLEY: That is what I was trying to point out in my initial discussion because the label is focusing on a certain population, as we discussed at length. Depending on how a drug is marketed or advertised, clearly could pull in a population that was not originally intended. Now, that is taken in the context of, you know, a

company is such a good marketer that they are able to convince someone to buy a drug that treats no symptoms for them for the rest of their life. So, you know, you have to put it in that context too, that someone will really have to want to take this drug. But I think it is important for someone to understand, you know, what is the benefit up front; how long I have to take it; what is the downside to this; and whatever population you are pulling in--you know, if they don't understand the label and they are just going to buy the product because they are very health conscious and they want to control their cholesterol, well, I am not sure that is the best thing but that is the way, you know, people make decisions sometimes.

DR. BENOWITZ: I certainly agree with you. I think the dietary supplement industry is an example where you can market to a lot of people taking medications to allegedly improve their health for many years at a billion dollars of expense. I just think that at some point in time someone should make sure that the benefits to the

individual are really made clear to them so they will know what they are getting, and how long they have to take the medicine, and what it is going to cost them. I just want to be reassured that FDA will be doing that at some level.

DR. GANLEY: Again, if it is an advertising issue we don't have much control. If it is a labeling issue or something to that effect that will adequately convey that message, then we do have control. I think that is why it is important to understand did someone adequately understand the benefit. You raised it earlier in terms of the absolute benefit to them--you know, may be a better way of trying to convey it to someone so they really understand that. I think that is very important.

DR. WOOD: But although the FDA may be unwilling to step into that, this advisory committee could provide very strong recommendations that the FDA should take control of advertising over-the-counter drugs. I am serious--not that I am ever reactionary, right? I mean, we could make

that as a recommendation tomorrow, Neal, if you thought that was important and, you know, we would see probably fewer young ladies skipping through fields of daisies, and so on. Yes, Dr. Woolf?

DR. WOOLF: I have to get back to the question of post-marketing surveillance. The EDMAC committee has probably asked about this at every committee meeting where we have been asked to approve a drug, about how effective it is, and it is certainly an issue that has been in the news the last month or so.

How can we be assured that, in fact, there is appropriate post-marketing surveillance that is carried on despite the promises in this room this afternoon? What teeth are there that six months after the drug has been approved for over-the-counter use, assuming that it is, that in fact data is being collected, being distributed and being looked at based upon that surveillance?

DR WOOD: The short answer is there aren't; there is no assurance.

DR. GANLEY: I am not sure what the

question is. If something happens and someone takes the time to fill out a MedWatch report, whether it is prescription or OTC, we look at those things, as would many companies--look at them seriously.

DR. WOOLF: I understand that--

DR. WOOD: He is talking about Phase IV studies.

DR. WOOLF: Merck has promised a post-marketing surveillance survey to do something far more elaborate and proactive than that, and the EMDAC committee has heard this before, that a company will do that but my understanding is the FDA has a hard time trying to enforce that.

DR. WOOD: He is talking about a Phase IV study.

DR. BRINKER: Excuse me, I didn't mean to interrupt you. I am Alan Brinker from the Office of Drug Safety. Let me just say that if you have a specific concern that you want to raise for the post-marketing environment, then that is engendered to Merck to provide a protocol and we will look at

that. So, you know, we have almost ten years worth of experience in looking at this drug alone, plus all the statins. So, we have a pretty good handle on that. But if you have a concern, then we will follow it up in the post-marketing environment.

DR. ORLOFF: But to respond to your question about how much leverage does FDA have with regard to enforcement of these sorts of commitments on the part of the sponsor, in the absence of a contingent approval, for which there is a regulatory instrument that would not apply here as far as I understand, that is to say an over-the-counter switch, we do not have a legal regulatory handle.

That said, as you yourself have pointed out just for the endocrine and metabolic drug area, across the different drug areas or the pharmaceutical classes that are regulated in the United States, there are multiple such commitments that are essentially described at the time of approval as a matter of public record and there are clear incentives in that alone for the companies to

adhere to or to maintain those commitments.

At some level, it is a gentlemen's agreement, if you will, but from one instance to the next there is no necessary reason for you or for the public to believe that a commitment is not going to hold. So, our job here, and your job, is to think about what sorts of information you think FDA should be concerned about garnering in the post-marketing period, to propose that, and we can take it forward from there.

DR. WOOD: Well, David, a third of the Phase IV studies that are mandated are not started, or weren't started in the last survey. So, I mean, that is not entirely true. Anyway, let's move on.

DR. ORLOFF: But, Alastair, I want to make it clear. I mean, I don't know any other way to state it but on a case by case basis. I don't think we can go into this process with an assumption that no one's word is worth anything or that putting this out in the public domain has no weight. There is experience in the Food and Drug Administration with the pharmaceutical industry of

success in adherence to Phase IV commitments. There is apparently a record that may be overall less than satisfactory, but that doesn't mean that we can't talk about what is necessary now. DR. WOOD: All right. We have one more question.

DR. HEMWALL: I just want to add that Merck Research Lab has a perfect performance record in adhering to Phase IV commitments that we make at the time of approval, and we would expect to uphold that record.

DR. WOOD: Frank?

DR. DAVIDOFF: Just to get back briefly to the issue of pregnancy, it seems to me there are at least two reasons for some reservations about the existing data. One is that, as I understand, the reported number of adverse pregnancy outcomes is really very small. It is 7, or 30 or 40, depending on which universe you are looking at. But given the millions of doses and years that is quite small.

But at the same time, as I understand this, this is all voluntary reporting and voluntary

reporting is well-known to be grossly under-reporting and it is not good sampling. So, it is quite possible that the numbers are larger than that and we really can't make a judgment about that. But to assume that these are all the cases that have happened is not probably appropriate.

The other comment is on the issue of the apparent lack of a pattern of fetal abnormalities and the outcomes of the adverse pregnancy outcomes as somehow being reassuring and that there were no common biological mechanism at work. On the other hand, we are learning rapidly that the statins are not simple agents when it comes to biological actions. In last week's New England Journal there was a very striking article about the apparently cholesterol-independent actions of statins, probably relating somehow to the inflammatory response. So, I think that it is hard to interpret this lack of pattern as meaning that this is somehow not related to the presumed single action of the statins because I think the actions are not single; I think they are quite complex.

I think that that also gets to the issue of assuming that the teratology or the damage to fetuses is going to be related to myelination

because it assumed--somehow the simplistic assumption is made that all they do is to interfere with cholesterol metabolism. I don't think that is fair. It seems to me that there might very well be other developmental abnormalities that have nothing to do with cholesterol metabolism. So, at least in my own mind, I have maintained a little bit of reservation from these data that I have been hearing are being interpreted otherwise.

DR. ORLOFF: Alastair, I would like to clarify. Understand, I am not a toxicologist and, as I said, in terms of absolute risk, unfortunately, all we are left with is hazarding a guess. When I said there was no pattern apparent that would suggest a lovastatin fetal syndrome, yes, there are clearly multiple final mechanistic effects of statins. But I think it is safe, for purposes of at least beginning to conceptualize this, to understand that there is absolutely no

evidence that statins work in any other way except as HMG CoA reductase inhibitors. I mean, that is a hard one to deny. Yes, HMG CoA reductase inhibition itself engenders multiple cellular, biochemical and systemic effects but these are HMG CoA reductase inhibitors first and last.

Now, it may turn out that some of them do have pleiotropic effects beyond HMG CoA reductase inhibition per se but that has never been established. They are designed as such, and I think we have to start at least by considering that that is their mechanism of action.

DR. WOOD: I completely agree with you but I would just caution that what Frank I think is saying is that beta blockers act exclusively by beta blockade but practolol had an effect that was independent of beta blockade. I think that is the point he is trying to make.

But on that note, and the FDA having conceded "seat of the pants" analysis, we are going to stop for tonight and reconvene at eight o'clock in the morning.

[Whereupon, at 5:15 p.m., the proceedings were adjourned, to reconvene on Friday, January 14, 2005 at 8:00 a.m.]

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