DEPARTMENT OF HEALTH AND HUMAN SERVICES
UNITED STATES FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING
OF THE NONPRESCRIPTION DRUGS ADVISORY COMMITTEE
AND THE
ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

The committee will evaluate data submitted by Merck & Co., Inc., to support the over-the-counter use of Mevacor (lovastatin) 20 milligrams a day to help lower cholesterol which may prevent a first heart attack

Thursday, December 13, 2007

8:00 a.m.

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C O N T E N T S

C O N T E N T S (Continued)

C O N T E N T S (Continued)

OPEN PUBLIC HEARING

C O N T E N T S (Continued)

PARTICIPANTS

Mary E. Tinetti, M.D., Chair, NDAC
Diem-Kieu H. Ngo, Pharm.D., Designated Federal Official

NONPRESCRIPTION DRUGS ADVISORY COMMITTEE (NDAC) MEMBERS
(Voting)

Mary E. Tinetti, M.D., NDAC Chair
Ruth M. Parker, M.D.
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TEMPORARY VOTING MEMBERS

Arthur Flatau, Ph.D.
Stephen P. Glasser, M.D.
Arthur A. Levin, M.P.H. (Consumer Representative)
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INDUSTRY REPRESENTATIVE
(Non-Voting)

Edward B. Nelson, M.D., Ph.D.

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(Non-Voting)

Charles J. Ganley, M.D.
Andrea Leonard-Segal, M.D.
Curtis Rosebraugh, M.D., M.P.H.
Eric Colman, M.D.

P R O C E E D I N G S

Call to Order and Opening Remarks

DR. TINETTI: I am going to start the meeting and welcome you all. I am going to begin by reading a statement.

For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues and that individuals can express their views without interruption.

Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting.

We are aware that members of the media are anxious to speak with the FDA about these proceedings, however, FDA will refrain from discussing the details of this meeting

with the media until its conclusion. A press conference will be held in the Chesapeake Room immediately following today's meeting. Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch.

Thank you.

I am going to have each of the Committee members introduce themselves, but before I do that, I would just want to remind everyone that the open public hearing time has been rescheduled and that will take place at 1:30 this afternoon due to last minute changes in the agenda.

Thank you.

Introduction of the Committee

DR. TINETTI: I will start by introducing myself. I am Dr. Mary Tinetti from Yale University School of Medicine.

I think we will start at this end and everyone introduce themselves.

DR. NELSON: I am Dr. Ed Nelson, Vice President of Martek and the industry representative.

DR. SHRANK: I am Will Shrank. I am from Brigham and Women's Hospital in the Division of Pharmacoepidemiology

and Pharmacoeconomics, and from Harvard Medical School.

DR. PROSCHAN: I am Mike Proschan. I am a statistician from NIAID.

DR. FLATAU: I am Arthur Flatau. I am the patient representative.

DR. PARKER: I am Ruth Parker from the Department of Medicine at Emory University School of Medicine.

DR. TAYLOR: I am Robert Taylor, Professor of Medicine and Pharmacology, Howard University College of Medicine, member of NDAC.

DR. NEILL: Hi. I am Richard Neill. I am Vice Chair and Residency Program Director of the Department of Family Medicine at the University of Pennsylvania and a consultant to NDAC.

MR. LEVIN: Arthur Levin, Center for Medical Consumers. I am the consumer representative.

LCDR NGO: Lieutenant Commander Diem-Kieu Ngo, Designated Federal Official.

DR. PICKERING: Tom Pickering, Columbia University, New York, and formerly on the Cardiovascular and Renal Advisory Committee.

DR. GLASSER: I am Steve Glasser from the Division

of Preventive Medicine, University of Alabama at Birmingham.

DR. ROSEN: Cliff Rosen. I am an endocrinologist from Portland, Maine.

DR. CAPRIO: I am Sonia Caprio from Yale University, Pediatric Endocrinology.

DR. BURMAN: Ken Burman. I am head of Endocrinology at the Washington Hospital Center, and Professor, Department of Medicine at Georgetown.

DR. COLMAN: I am Eric Colman, Deputy Director for Division of Metabolic and Endocrine Drugs at FDA.

DR. ROSEBRAUGH: Curt Rosebraugh, Acting Director, Office of Drug Evaluation II.

DR. LEONARD-SEGAL: Andrea Leonard-Segal, Director, Division of Nonprescription Clinical Evaluation. Good Morning.

DR. GANLEY: Charlie Ganley. I am the Director of the Office of Nonprescription Products.

Conflict of Interest Statement

LCDR NGO: Good morning. I would first like to remind everyone present to please silence your cell phones if you have not already done so. Also, I would like to identify the FDA press contact Ms. Susan Cruzan and Mr.

Chris Kelly. If you are in here, please present yourself. I think they stepped out of the room for a moment.

Also, we would like to remind everyone that there is an overflow room over in the Chesapeake Room down the hall on the left, so in case the room fills up here, we do have an additional room.

Now, I would like to read the Conflict of Interest Statement.

The Food and Drug Administration has convened today a joint meeting of the Nonprescription Drugs and Endocrinologic and Metabolic Drugs Advisory Committees under the authority of the Federal Advisory Committee Act of 1972. With the exception of the industry representative, all members and consultants of the committee are special Government employees or regular Federal employees from other agencies and are subject to federal conflict of interest laws and regulations.

The following information on the status of these committees' compliance with Federal ethics and conflict of interest laws covered by, but not limited to, those found at 18 U.S.C. Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act are being provided to participants in

today's meeting and to the public.

FDA has determined that members and consultants of these committees are in compliance with Federal ethics and conflict of interest laws. Under 18 U.S.C. Section 208, Congress has authorized FDA to grant waivers to special Government employees who have potential financial conflicts when it is determined that the Agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special Government employees and regular Government employees with potential financial conflicts when necessary to afford the Committee's essential expertise.

Related to the discussions of today's meeting, members and consultants of these committees who are special Government employees have been screened for potential financial conflicts of interest of their own as well as those imputed to them, including those of their spouses or minor children and for purposes of 18 U.S.C. Section 208 their employers.

These interests may include investments,

consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves data submitted by Merck & Co., Inc., to support the over-the-counter use of Mevacor (lovastatin) 20 milligrams a day to help lower cholesterol which may prevent a first heart attack.

This is a particular matters meeting involving specific parties. Based on the agenda for today's meeting and all financial interests report by the Committee members and consultants, conflict of interest waivers have been issued in accordance with 18 U.S.C. Section 208(b)(3) and Section 712 of the FD&C Act for Dr. Thomas Pickering.

Dr. Pickering's waivers involve his membership in a competing firm's unrelated advisory board. He receives less than $10,001 per year. The waivers allow this individual to participate fully in today's deliberations.

FDA's reasons for issuing the waivers are described in the waiver documents which are posted on FDA's web site at www.fda.gov/ohrms/dockets/default.html.

Copies of the waivers may also be obtained by submitting a written request to the Agency's Freedom of

Information Office, Room 630 of the Parklawn Building.

A copy of this statement will be available for review at the registration table during this meeting and will be included as part of the official transcript.

Dr. Edward Nelson is serving as the industry representative acting on behalf of all regulated industry and is employed by Martek Biosciences.

We would like to remind members and consultants that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal and imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all other participants to advise the committee of any financial relationships that they may have with any firms at issue.

Thank you.

DR. TINETTI: Thank you.

I think we will start with the FDA introductory remarks. I just wanted to remind the panel that any questions that you might have, please hold until the afternoon session. After each of the talks, only clearly

clarifying questions this morning. Thank you.

FDA Introductory Remarks

DR. LEONARD-SEGAL: Dr. Tinetti, members of the joint committee, good morning again.

[Slide.]

For those of you who don't know me, and some of you I know do, my name is Dr. Andrea Segal and I have the pleasure of welcoming you to this meeting this morning on behalf of the two Divisions. I think we have a very interesting day ahead of us.

[Slide.]

I am going to try to lay a foundation for you for today's meeting, and so in this introduction, I am going to tell you about the history of the development program for OTC Mevacor, the 2006 NDAC meeting that was held, and some of the people sitting at this table attended it, but certainly not the majority, on Consumer Study Design Issues that led to changes in our study design approach.

I am going to talk about the regulatory requirements for nonprescription marketing, and I will end by summarizing today's agenda.

[Slide.]

First, let's turn to the history of this development program.

[Slide.]

Lovastatin is dosed in 10 mg to 80 mg per day and has been marketed by prescription since 1987. It is indicated as an adjunct to diet to reduce elevated total cholesterol and LDL cholesterol in adults and in adolescents. It slows progression of coronary atherosclerosis in patients with coronary heart disease.

[Slide.]

Now, this is the third time that a joint committee of EMDAC and NDAC are meeting on this switch application. Originally, Merck submitted this application in 1999 and the committee met to consider it in 2000. They resubmitted and a committee considered that resubmission in 2005, and resubmitted again, and now we are in 2007.

The proposed labeling for OTC Mevacor has changed substantially from one submission to the next, much data has been submitted and reviewed, and progress has been made along the way.

[Slide.]

The application for Mevacor 10 mg for OTC switch

was based on a total cholesterol label paradigm, and this was the one that was considered in 2000.

The application was considered deficient back then because it did not establish consumer use in accordance with the NCEP guidelines. It did not establish a clinical benefit of 10 mg in the proposed OTC population. It did not establish that consumers could treat their cholesterol to a goal, to a target goal.

Consumer comprehension and behavior inadequacies were in the application, and there were safety concerns that were not adequately addressed.

[Slide.]

In 2005, with the resubmission, Merck proposed to bring Mevacor 20 mg instead of 10 mg over the counter, and provided new labeling. This labeling, instead of being based on a total cholesterol paradigm, was based on an LDL label paradigm target population, and that population is described on this slide.

[Slide.]

In 2005, the Advisory Committee agreed that the proposed OTC LDL cholesterol paradigm target population merits statin treatment to lower cholesterol along with an

improved diet.

They also agreed that there was adequate rationale for the use of fixed dose lovastatin 20 mg to decrease cholesterol and heart disease in the target population assuming that consumers adhered to the label.

[Slide.]

That label in 2005 was tested in a label comprehension study to determine if potential consumers could understand the information on the label.

It was tested in an actual-use study to see how people would actually use the product and if they could properly choose to use the product based upon their own medical circumstances. That study was called the CUSTOM study. That is the acronym that you are going to hear spoken many times today. You will hear it by Dr. Hu. You are going to hear it from Captain Shay.

There were deficiencies in label comprehension, self-selection, and use that led to the submission of the new data that we are considering this morning and this afternoon.

[Slide.]

So, 2007 has arrived and Merck has modified the

2005 label to address deficiencies that they heard from the Committee and from the Agency. They have conducted two new label comprehension studies. One is a pivotal study and one is a study that focuses on the muscle warning on the label.

They have used two label paradigms, one an LDL label paradigm, and this one is the same as the one that was used in 2005, and they have used a new total cholesterol paradigm. They have also conducted a self-selection study on these two labels, and you are going to hear a lot about that today.

[Slide.]

What we will and will not talk about. There are issues that have been previously addressed by the joint committees and subsequently by the Agency that we will not revisit today.

The purpose of today's meeting is to consider the data in the 2007 resubmission that Merck provided to address the issues that remained after 2005.

[Slide.]

I am going to mention the issues for deliberation over the new few slides, but here they are in a nutshell.

First, the label paradigms. Today, we will not

ask you to address the merits of the OTC target population defined by the LDL cholesterol paradigm since that population is unchanged from 2005 and is considered acceptable.

We do request that you consider the merits of the target population defined by the alternative total cholesterol paradigm label.

[Slide.]

In 2005, the Committee recommended that baseline liver function testing and liver function monitoring for Mevacor 20 mg were not needed. Generally, the Committee found that the risk of liver toxicity with statins was low, and they were not excessively concerned with the use of lovastatin 20 mg by those with an undiagnosed liver problem.

[Slide.]

Today, we will not ask you to discuss the need for LFT monitoring in those with normal livers because we are comfortable with the previous committee advice.

At Agency request, Merck provided additional data on use in those with liver disease. So we request your views as to whether those with asymptomatic liver disease can safely use lovastatin 20 mg without LFT monitoring and,

if not, could labeling minimize the risk to this population.

[Slide.]

In the CUSTOM actual-use study, 75 percent of subjects who developed unexplained muscle pain made a correct decision about stopping Mevacor use.

FDA requested that labeling be developed to accomplish a higher rate of adherence with the muscle warning and that label comprehension testing should document this improvement.

Today, please provide your views on the comprehension of the new label muscle pain warning.

[Slide.]

I am going to talk about pregnancy now.

In rodents exposed to very high lovastatin doses, there were fetal skeletal abnormalities in the pups. There have been reports of congenital anomalies with human use, but no causal inference, trend, pattern, or association with lovastatin has been established.

As with all statins, lovastatin is Category X, because safety has not been established in pregnant women and there is no apparent benefit to therapy during pregnancy. The prescription labeling recommends counseling

adolescents who are put on lovastatin by their physicians about contraception.

[Slide.]

The majority of Committee members in 2005, 18 of 23, thought that lovastatin is not so potentially toxic to the fetus as to prevent OTC marketing. All recommended that the pregnancy warning should be improved.

Today, please provide your views on the adequacy of the new label pregnancy warning.

[Slide.]

Today, you are going to hear what is known and not known about whether there is a connection between statin use and amyotrophic lateral sclerosis. We are interested in your thoughts on what role the state of our knowledge about this issue should have in making a decision about OTC statin availability.

[Slide.]

We will turn to self-selection. In 2005, the majority of Committee members felt that the self-selection data were insufficient to show that OTC consumers can use lovastatin 20 mg safely and effectively without physician guidance.

Members expressed concerns about the ability of consumers to self-manage their cholesterol with regard to self-monitoring and drug interactions.

[Slide.]

Today, please provide your views as to whether new data demonstrate that consumers could make an appropriate self-selection decision giving consideration to treatment guidelines, those already taking a statin and, as a related issue, whether data support adequate comprehension of the muscle pain warning.

[Slide.]

Now, there are differences between the CUSTOM actual use study label and the two labels used in the SELECT self-selection study.

We seek your advice today as to whether the CUSTOM results that did look at behavior related to LDL follow-up testing and behavior when muscle pain develops remain meaningful considering the label differences.

[Slide.]

Now, I am going to turn your attention to another bit of history, which is the 2006 NDAC meeting on consumer study design issues. Some of you were at that meeting and

some of you were not. This meeting led to changes in the way we approach self-selection analyses.

[Slide.]

In 2005, for the CUSTOM study, the actual-use study, we applied strict label eligibility criteria to define correct self-selection, which was also looked at in that study, with regard to decision making. We looked at each component of the lipid panel, the risk factors for coronary heart disease, and contraindications to use.

Ten percent of those study participants who correctly self-selected, "yes, it is okay for me based upon my own medical circumstances to use this product," did so based upon these criteria. After listening to the Committee member discussion, we wondered if this had been too stringent an analytical approach.

[Slide.]

We had a lot of other questions about how consumer studies are designed, so we took this entire basket of questions to NDAC in 2006. With regard to the self-selection analysis, NDAC discussed that it would be reasonable to change our approach.

They recommended that we pre-define a hierarchy of

critical label elements based upon risk and benefit--in other words, "deal breakers." A consumer must correctly decide whether, based upon these "deal breaker" elements, it is okay for him or for her to use the product. Correctness for other elements on the label would be optional.

Prioritizing these label elements can be very difficult. Sometimes, speaking from personal view, it is somewhat brain twisting, but we have been doing it and we do feel that there is merit in doing it.

Since the NDAC 2006 meeting, we have been recommending the hierarchy approach to sponsors of a variety of different types of products.

[Slide.]

Now, in 2006, as this committee was meeting, the Mevacor SELECT and LC studies were in progress, so there are no predetermined hierarchies for this application. Today, however, you will see several post-hoc self-selection hierarchy analyses.

Please consider what elements could constitute an appropriate hierarchy for statin self-selection. We are very interested in your views on this.

You will hear a discussion of hierarchies when Dr.

Hu talks to you about the self-selection SELECT study.

[Slide.]

So, the issue for today is: Does lovastatin 20 mg meet the regulatory requirements for nonprescription marketing?

[Slide.]

What are those requirements?

[Slide.]

In 1951, the Durham-Humphrey Amendment to the Food, Drug and Cosmetic Act was passed. This Act formally differentiates prescription from nonprescription drugs. It lays out criteria to carve a niche for prescription drugs, so those drugs are the ones that can be used safely only under supervision because of their toxicity, their other potentiality for harmful effect, their method of use, or collateral measures necessary to their use. Otherwise, the drug should be available without a prescription.

[Slide.]

Now, those criteria generate questions in our mind that we always ask ourselves when we consider a switch application. The questions are as follows:

Does the product have an acceptable safety

profile? Is there a low potential for misuse and abuse? Is there a reasonable therapeutic index of safety?

Can the condition to be treated be self-recognized?

When used under OTC conditions is the product safe and effective?

Do the benefits of this product outweigh the risks in the OTC setting?

[Slide.]

So, with that foundation, let's think about what we are going to do today.

Next, we are going to hear from Dr. Hemwall and his colleagues at Merck. Then, there is going to be a break.

Then, the FDA team will make their presentations. We will have lunch, an open public hearing, and then we look forward to the discussions and questions.

I thank you for your attention and I am going to turn it back to you, Dr. Tinetti.

DR. TINETTI: Thank you.

We will now move on to the sponsor presentation. Before Merck's presentation, I would like to remind the

public observers at this meeting that, while this meeting is open for public observation, public attendees may not participate except at the specific request of the panel.

Thank you.

Applicant Presentation

Introduction

DR. HEMWALL: Thank you, Dr. Tinetti.

[Slide.]

Good morning. I am Ed Hemwall and I am representing the Merck Mevacor Daily Development team along with our partners, which now include GlaxoSmithKline.

Today, we are seeking your recommendation for approval of lovastatin as a nonprescription option to lower cholesterol and reduce the risk of heart disease and death. This is a real opportunity to help tackle our nation's number one public health problem.

As you know, in 2005, this panel did vote favorably on the questions of safety and efficacy, as Dr. Leonard-Segal explained. However, they wanted to see more data around the question will the right consumers do it, will they use it right.

Since then, we have worked with FDA, with their

input, to design and conduct new studies to answer those questions.

[Slide.]

First, let's look at the population we have already agreed could benefit from using the product. Lovastatin 20 mg daily is proposed with the indication to help lower cholesterol which may prevent a first heart attack.

The target population is based on the national guidelines for cholesterol reduction and it includes men 45 and over and women 55 and older who have moderately high LDL within the range shown here.

They should also have one additional heart disease risk factor, such as family history, smoking, or high blood pressure.

Now, just like the national guidelines for physicians, the OTC label elements are also guidelines. They act to screen for consumers who could optimally benefit. They certainly should not be viewed as sharp boundaries outside of which there is no benefit.

In fact, FDA has asked us to not only look at how consumers follow these label guidelines, but also to

demonstrate that they understand the concepts upon which they are based.

Today, we will present findings from the SELECT study that was designed to gather both the quantitative and the qualitative information on how close consumers come to meeting these guidelines and how and why they make those decisions.

[Slide.]

A major emphasis of our program has always been that Mevacor Daily appeals to a certain type of consumer. Our research tells us a great deal about the unique consumers interested in using a nonprescription statin.

They are health conscious and motivated to take care of themselves, and they regularly see a doctor and generally have had a recent cholesterol test. As you will see today, they may not all know their specific numbers, but they do know and have learned from their doctor that they have a cholesterol problem.

Our data also shows that these people are committed to the important lifestyle changes of diet and exercise. Some already are using a range of consumer products for heart health, some with proven benefit like

aspirin. Regarding cholesterol, many are using foods and supplements, but are reluctant to take a prescription and would prefer a more effective option in that middle zone.

[Slide.]

In 2005, the Advisory Committee votes were highly favorable on the questions of target population, efficacy, and CHD risk reduction and the important safety questions regarding liver, muscle, drug interactions and use in pregnancy.

Although your predecessors encouraged us not to give up on this important initiative, they did not vote for approval and suggested that improvements be made in the labeling and the program elements. FDA has agreed that the target population defined by the label guidelines can benefit from treatment and that 20 mg of lovastatin has an appropriate safety and efficacy profile.

They also agreed that the actual use seen in the CUSTOM study was satisfactory with participants achieving cholesterol lowering with appropriate ongoing use, behavior regarding goal, follow-up lipid testing, diet and exercise, daily use over the long term and interaction with a healthcare professional when appropriate.

[Slide.]

To complete the picture, the FDA asked us to revise our label and conduct additional label studies and a self-selection study, maintain the strong safety behavior already seen in our CUSTOM label, and strengthen our pregnancy and muscle safety warnings

They also asked us to improve the directions to reduce use by women under 55 and by consumers with a lower risk of coronary heart disease.

Finally, the Agency asked us to provide additional details on how the consumer support program would be implemented and monitored once Mevacor daily was on the market.

To help summarize where we are today, this chart lists the key criteria we have been asked to address for a non-prescription statin. Many of them we generally agree were addressed in 2005.

[Slide.]

Today, we will mainly focus on what we have done since 2005 to address the key remaining issues.

[Slide.]

We will look at two major studies, consumer

behavior studies, one our actual use study CUSTOM first presented in 2005. This allowed consumers to purchase and use Mevacor Daily with the consumer education and support program in place for up to 6 months.

Since then, we have worked with FDA to design the SELECT study, a self-selection study aimed at looking at what consumers decide and understanding why they decide to do it. We also performed two major label comprehension studies which the FDA will be reviewing for you later this morning.

[Slide.]

Before moving on, we need to acknowledge that providing access to a lovastatin without a prescription truly represents a shift in how we make life-saving medicines available to American consumers. This is a significant step. We are committed to doing it responsibly and with our partners, GlaxoSmithKline, who have a great deal of experience in this area.

If approved, Mevacor daily will be part of a comprehensive education and support program. Key components of this program have already been evaluated with consumers in the CUSTOM study and enhanced based on those learnings.

There has been recent discussion about behind the counter status for certain products. This category does not exist. So, we developed a program that helps consumers manage this on their own, and our studies have demonstrated that they can do it. But we also recognize that there would be a need sometimes for consumers to want to consult a healthcare professional, so we are proposing that Mevacor daily be sold on the open shelf but only in stores with pharmacies.

This approach offers an excellent balance of greater access and having a pharmacist available for assistance for those who want it and, in this way, we can increase awareness of lipid management and optimize this important public health opportunity.

[Slide.]

Here is our agenda for today. Dr. Burroughs, an endocrinologist, will explain why we think now is the time for this public health opportunity, and Dr. Adamsons will review the safety and efficacy profile which led to the positive decisions in 2005.

Jerry Hansen will review the key results of the CUSTOM study, and I will present the results of SELECT, the

new consumer behavior study.

Dr. Shiffman will outline the education and support program and how we will monitor use in the marketplace, and George Quesnelle, of GSK, President, North America, will discuss how we will market the product responsibly.

At the end, I will return to briefly summarize.

[Slide.]

We also have several experts today that are available to answer your questions and provide perspective as needed on their areas of expertise.

I would now like to turn the presentation over to Dr. Valentine Burroughs who will discuss the unmet need and the potential public health benefit for a low dose statin.

Public Health Opportunity

DR. BURROUGHS: Thank you, Dr. Hemwall, and good morning. I am here today because, like many of you, I see firsthand the toll that cardiovascular disease is taking in this country and it frustrates me, as I am sure it does you. With all best intentions we are still failing to prevent this epidemic.

It is time to take bolder action, to try new

approaches. I believe broadening access to low-dose statins over the counter is one such strategy and, as I will show you, low-dose, over-the-counter statins can help bring treatment to those who are not being treated.

[Slide.]

This could have a significant public-health impact by preventing tens of thousands, or even hundreds of thousands, of cardiac events. This approach can make a real difference because cardiovascular disease remains the number-one cause of death in the United States, killing more people than the next three causes of death combined.

[Slide.]

More than half of us have cardiovascular disease by the time we are in our mid-50s, and it turns out the risk for women is as great as it is for men. As a group, women have been undertreated for years. Efforts, such as the Red Dress Campaign, are increasing awareness among women and encouraging them to take action to prevent heart disease.

[Slide.]

As we know, one of the biggest risk factors for heart disease is high cholesterol. But there is an enormous gap between those who need cholesterol-lowering treatment to

prevent heart disease and those who receive it.

In fact, 50 million Americans are at risk for heart disease because of high cholesterol, 20 million at moderate risk, and 30 million at high risk and, according to guidelines, all of them should be getting therapy.

[Slide.]

But only a third of the moderate-risk people are being treated, and this is the population for whom an over-the-counter statin is intended. Mevacor Daily can help close this gap and can have a substantial positive impact.

[Slide.]

Of the 30 million people at high risk of heart disease who should be taking prescription statins, only half of them are being treated. Now, these people may not be candidates for over-the-counter statins. However, based on the data detailed in your briefing book, the attention that over the counters would bring to cholesterol treatment has the potential to drive them into their physicians' offices where many of them will receive prescription therapy.

Clearly, what we are doing isn't working, and we have got to make a change. What would be the impact of allowing people better access to low-dose statins? In fact,

this potential benefit can be quantified.

[Slide.]

Dr. Eric Brass, a professor of medicine at UCLA and a former chair of this advisory committee, calculated conservatively that Mevacor Daily would prevent between 23,000 and 33,000 coronary heart-disease events per million users over a 10-year period.

This calculation was based on the results of the CUSTOM study of over-the-counter Mevacor and reflects the consumer profile likely to use this in an over-the-counter marketplace.

Another recent estimate looked at events prevented over a 5-year period. The authors calculated that access to an over-the-counter statin in the United States could prevent close to 185,000 coronary heart-disease events in a moderate risk population.

So, two different approaches, different results. But, as we can see, in both cases, the potential public health benefit of an over-the-counter statin can be substantial.

At this point in my presentation, you may be wondering, if people are not taking prescription statins,

why would they take one if it is non-prescription.

[Slide.]

Well, a recent survey was conducted among consumers at moderate risk of heart disease who were not taking statin therapy. They were asked whether they would prefer an over-the-counter statin or a prescription statin.

They were preferred an over-the-counter statin by a margin of 3 to 1. Among the main reasons, they said it would be more convenient and easier to buy, as you would expect with any over-the-counter medicine.

[Slide.]

But there was also an unexpected important insight. These consumers said over the counters were more suitable for people who take charge of their health, like themselves, and that prescription drugs are for people who are sick.

Now, those of you who see patients may not find that surprising--I know I don't--because many of my patients are already taking nonprescription products in an attempt to lower their cholesterol and reduce their risk of heart disease.

[Slide.]

I see them taking everything from Red Rice Yeast, to garlic, to green tea, but the fact is most of these products are at best unproven, and at worst unsafe. I would rather see them taking a safe, efficacious FDA-approved over-the-counter option to lower their cholesterol.

[Slide.]

Here are clinical data showing that access to an over-the-counter statin could have a profound impact on public health. This slide shows the distribution of baseline LDL values among consumers who used Mevacor Daily in the sponsor's CUSTOM study.

[Slide.]

Now, here, the yellow bars show very graphically how the LDL curve shifted in a favorable direction by the end of the trial. This could dramatically decrease the risk of a first heart attack in the target population, and that can lead to an important improvement in the public health.

[Slide.]

There is no question that it is easier to maintain the status quo than to make a change. There are always many reasons not to take an action, but we have to take advantage of novel opportunities like this one. There are

approximately 500,000 new heart attacks and over 150,000 deaths due to heart attacks each year in the United States.

This is a chance, an important one, to help turn the tide. We will need many bold moves to get there and I hope this won't be the only one, but we have an opportunity right here, right now, to make a difference in people's lives. I hope you will take it.

Now, I would like to turn the presentation over to Dr. Adamsons, who will review the key clinical data supporting the efficacy and safety of lovastatin therapy.

Dr. Adamsons.

Lovastatin: Efficacy and Safety

DR. ADAMSONS: Good morning.

[Slide.]

Dr. Burroughs has reminded us of the burden of cardiovascular disease and of the treatment gap that exists in the United States today. He pointed out the significant consumer interest in a nonprescription statin, as well as the potential public health benefit of such a treatment option.

I will now review the efficacy of statins and the efficacy and safety of lovastatin in particular.

[Slide.]

The value of statin therapy in decreasing cardiac events in both primary and secondary prevention has been demonstrated in numerous clinical trials. The studies included on this graph are from primary prevention studies; in other words, they enroll people who had not yet had a cardiac event. This is the same population for which Mevacor Daily is intended.

[Slide.]

As shown on the graph, the lower the LDL-C, the lower the incidence of cardiac events. This information, along with additional epidemiologic information, led Dr. Scott Grundy and co-authors to conclude that no matter what one's LDL-C, lowering it will decrease the relative risk of coronary heart disease.

Importantly, as shown on this graph, the change in log relative risk is the same for any given change in the LDL-C level no matter how high or how low the starting LDL-C level was. So, lowering your LDL-C will lower your cardiac risk and statins have been shown to do both.

[Slide.]

In fact, statins are one of the most studied drug

classes in history. Mevacor or lovastatin was the first statin approved by the FDA. In the 20 years since approval, it has been estimated that there have been more than 35 million patient treatment years with lovastatin.

Besides extensive marketed use, lovastatin has been carefully studied in many large clinical trials including two landmark trials, namely, the 48-week trial known as EXCEL, and the multi-year endpoint trial known as AFCAPS.

[Slide.]

EXCEL confirmed lovastatin's efficacy in significantly lowering LDL-C. In line with treatment guidelines for high cholesterol, this study began with a 6-week run-in period during which all patients were treated with appropriate diet. Then, at baseline, patients were randomized to placebo or to one of four doses of lovastatin including 20 mg daily, or continuing to follow an appropriate diet.

This graph shows that 20 mg of lovastatin lowered LDL-C by an average of 24 percent. This degree of reduction in LDL-C was very similar to that seen in the consumer-use study of Mevacor Daily, which Jerry Hansen will discuss

later.

[Slide.]

In addition to effectively lowering LDL-C, lovastatin has also been shown to significantly reduce the risk of a major coronary event. AFCAPS was a 5-year study which enrolled middle-age and older men and women with high cholesterol, but without heart disease. Dr. Antonio Gotto of the Weill-Cornell Medical School, who was instrumental in AFCAPS, is available today to answer questions related to this study.

This graph shows the cumulative incidence of a first acute major coronary event over the course of the study. The solid yellow line represents the patients randomized to lovastatin and the broken yellow line represents the patients randomized to placebo.

The results showed that lovastatin begins to reduce the risk of a first major coronary event after just one year of treatment. After five years of treatment, there was a 37 percent reduction in the risk of a major coronary event in the lovastatin group compared to placebo.

[Slide.]

There has been a post-hoc analysis of the AFCAPS

patients who would have been eligible for Mevacor Daily, and the benefit observed for the entire cohort was clearly maintained in this subgroup.

The solid orange line on the graph represents the lovastatin patients who would have been eligible for Mevacor Daily, and the broken orange line represents the placebo patients who were similarly eligible.

The benefit realized by this lovastatin subgroup closely paralleled that for the entire lovastatin group. AFCAPS clearly demonstrates that lovastatin is very effective as primary prevention of coronary heart disease.

[Slide.]

And importantly, this safety profile of lovastatin was also excellent. Both the 20 and 40 mg doses were comparable to placebo in all side effects. This table shows the data for key muscle and liver side effects.

Because of the low hepatic risk reflected in this table, the physician prescribing information for prescription lovastatin was updated in April of 2005, and liver enzyme testing is no longer recommended for doses lower than 40 mg.

[Slide.]

AFCAPS has also provided important and reassuring information about potential drug interactions. At the time of AFCAPS, we didn't appreciate the effect of CYP3A4 inhibitors, so such medications, which are now understood to slow the metabolism of lovastatin, were permitted in this study.

As shown in this table, the incidence of muscle adverse events in study patients receiving these inhibitors was the same whether they were receiving 20 or 40 mg of lovastatin or placebo.

This information is very reassuring. Nevertheless, the Drug Facts label for Mevacor Daily advises consumers to speak with their physician if they are receiving these medications in order to further limit the potential for the safety concern.

[Slide.]

The FDA briefing document asks you to consider two points related to the safety of lovastatin. The first is safety in consumers with chronic underlying liver disease. The FDA briefing document includes assessment of a large retrospective cohort database study evaluating patients with pre-existing liver dysfunction or disease. Fourteen percent

of these patients had received lovastatin.

The study found that exposure to lovastatin was associated with a substantially reduced risk for a number of adverse hepatic outcomes. As shown on this slide, the FDA concluded that there was sufficient evidence that patients with common asymptomatic liver disease could safely use Mevacor Daily.

[Slide.]

The second point that you have been asked to consider is amyotrophic lateral sclerosis, or ALS, and statin exposure. This concern has been carefully assessed by the FDA and is summarized in their briefing document.

The FDA did not find an increased incidence of ALS in placebo-controlled clinical trials of statins. Neither did they identify any increase in the incidence in the United States during the past 20 years when statin use has been widespread.

We reviewed clinical trials for lovastatin that were at least 6 months in duration for any reports of ALS. In these trials, no cases were identified in either the lovastatin or placebo-treated patients.

[Slide.]

Thus, in summary, lovastatin effectively lowers LDL-C and decreases the risk for coronary heart disease. It also has an excellent safety profile. Furthermore, the safety and efficacy profile has been demonstrated with the proposed nonprescription dose and in a population similar to the proposed nonprescription consumer population

I would like to now turn the presentation over to Jerry Hansen, who will discuss our pivotal 6-month actual-use study.

CUSTOM Study Overview

MR. HANSEN: Good morning.

[Slide.]

I have worked on the Mevacor Daily program since its inception 10 years ago, and have led the development and testing of the label and consumer support program. Today, I am going to review the top line results of CUSTOM, our pivotal actual-use trial which demonstrates how consumers used Mevacor Daily in a real live setting over a 6-month period.

These data provide an important context in reviewing additional consumer behavior data that will be presented next by Dr. Hemwall.

[Slide.]

The objective of the CUSTOM study was to determine if consumers could appropriately self-select and use Mevacor Daily over the long term. Another key objective was to determine the amount of LDL reduction people could achieve in this real life setting.

But the study also provided other important information including how people complied with therapy, how well they did with diet and exercise, and, when appropriate, how they interacted with their physician.

[Slide.]

CUSTOM was conducted in a simulated OTC setting. More than 1,000 consumers purchased Mevacor Daily and then used it as they would in the actual OTC marketplace over a 6-month period.

This included allowing consumers to return to purchase more medication and assess their cholesterol while on treatment. As part of the OTC offering, they could also access our consumer support program.

Later in the presentation, consumer behavior expert Dr. Saul Shiffman will detail this program and discuss further enhancements we are proposing for the

marketplace, but here is a quick overview of the program to help you better understand the CUSTOM results.

[Slide.]

The Mevacor consumer support program utilized a two-step approach. It helped people decide whether Mevacor was right for them by aiding them in the store and providing ongoing support after they made their purchase. This focus on educating and supporting consumers every step of the way makes it clear that Mevacor Daily is not just a pill, it's a comprehensive program.

In the study, more than 90 percent of the users used elements of the program in addition to the label. So, the key question is: Did the label and program work in driving appropriate behavior? And the answer is yes.

[Slide.]

What you will see on this slide are the CUSTOM results compared to benchmark studies in the prescription setting.

[Slide.]

In CUSTOM, 62 percent of consumers reached their LDL goal, and 62 percent persisted on therapy for the entire 6 months.

[Slide.]

Importantly, these results are very consistent with what you see in the prescription setting.

[Slide.]

It was this behavior that resulted in people reducing their LDL cholesterol by an average of 21 percent, which is also comparable to controlled clinical trials.

[Slide.]

Another important question is: Will an OTC statin provide an excuse for people to cheat on diet and exercise? The actual data shows the opposite to be true. Consumers were directed to eat a healthy diet and exercise before using Mevacor Daily, and continue diet and exercise while on therapy.

In CUSTOM, a combined 98 percent improved or maintained their dietary habits with 40 percent improving, and a combined 94 percent improved or maintained their exercise patterns with 24 percent improving.

Clearly, the Mevacor Daily program promotes healthy lifestyle changes.

[Slide.]

So, CUSTOM showed that consumers in our target

population can successfully manage the Mevacor Daily program on their own, but our program also encourages them to discuss their use of Mevacor with their doctor and to have regular health check-ups.

In addition, because Mevacor Daily is not intended for higher risk cardiovascular patients who need physician oversight, we developed the High-Risk Referral System. This system is designed to identify higher risk patients and refer them to their doctor for more aggressive treatment.

With regard to physician interaction, the data are also very strong.

[Slide.]

Among all the users in CUSTOM, nearly 60 percent talked with their doctor during the 6-month trial.

[Slide.]

269 users had not discussed cholesterol with their doctor in the past 2 years, but a third of those saw their physician and discussed cholesterol during the study. So, despite the concern that an OTC statin will take patients away from their physician, the program had the opposite effect and actually drove many people to see their doctor who might not have done so otherwise, and these data are

even more dramatic with high-risk users.

[Slide.]

In CUSTOM, 3 out of 4 higher risk patients saw their doctor. We conducted a follow-up survey in a subset of those people who were directed to their doctor by the High-Risk Referral System.

The majority discussed cholesterol with their physician and more than half of them were put on prescription therapy. This demonstrates that the program not only benefits those in the specific target population, but also has the added benefit of funneling higher risk patients to their doctor.

[Slide.]

So, in summary, Mevacor Daily, along with the consumer support program, worked. Consumers were able to reduce their cholesterol, comply with diet and exercise, and talk to their doctor when appropriate.

We are committing to offering this entire program and more in the actual marketplace, and it clearly spelled out these commitments to the FDA.

Now, I would like to turn it over to Dr. Ed Hemwall who will present our new self-selection data.

SELECT Study Results

DR. HEMWALL: Thank you, Jerry.

[Slide.]

This is going to be the long part of the presentation, because this is really where the meat of our information is. I am going to review the improvements we have made to the outer carton and the label, and review the results of the SELECT study.

[Slide.]

The SELECT study, to remind you, was designed with input from FDA with some specific objectives in mind; first and foremost, to maintain the high safety self-selection results we saw in CUSTOM and to improve the self-selection, especially in women under 55 years old and those of childbearing potential, and in people at the lower end of the risk continuum for developing coronary heart disease.

Now, before I take you through some of the key labeling changes, I want to emphasize that the basic directions and warnings have not changed from the label used in CUSTOM. What we have changed is to increase the prominence of the key messages and the format in which they are presented. So, let's take a look at that.

[Slide.]

We changed the outer carton to specifically emphasize the age requirement right on the front of the box for men and women.

[Slide.]

We also added a new back panel that clearly states that consumers must have tried diet and exercise first before they buy the product, and they need to know their cholesterol numbers which should be within a target range.

[Slide.]

In addition, we created a unique four-step decision tree separated from the Drug Facts section of the label, and some of you on the committee have samples of this box around the table.

[Slide.]

So, first, the consumer determines if their age is correct. If not, they are told not to use it.

[Slide.]

If Yes, the next step tells them to determine if their cholesterol is within the optimal range.

[Slide.]

If it is, the next step tells them they have to

have one of the heart-disease risk factors such as high blood pressure, a family history of heart disease, being a smoker, or having a low good cholesterol HDL.

[Slide.]

If all these are Yes, they are directed to read the entire Drug Facts label before using the product.

[Slide.]

Now another area that we targeted for improvement was to expand the pregnancy warning to exclude, not only women who are pregnant or breast-feeding, but also those who think they may become pregnant, and we provided additional language to explain why this is so important.

You will see this worked extremely well when I show you the SELECT results.

[Slide.]

So, the new label was tested in comprehension study, and there was also a specific study focused on the muscle safety warnings, and the FDA will review those results for you later this morning.

We appear to be in general agreement with FDA on their conclusions that this label does have strong scores in the key safety areas and in cases where the scores were

generally lower involved ongoing use--that is, areas which are more thoroughly explained on the materials inside the carton, and not part of the outside carton label.

Similarly, the enhancements made to the muscle safety warnings on the materials inside the box were successful in communicating the importance of what to do in the case of unexplained muscle pain.

So, before we look at how this label performed in the SELECT study, let's review some of the objectives in the design of that study.

[Slide.]

We had two main objectives. The first was to collect the self-selection data and do that in two ways, by having participants judge whether or not the product is right for them, and this is called self-assessment or SA. You will see that abbreviation.

Next, we asked participants to decide whether or not to purchase the product. This was the purchase decision or abbreviated as PD. This was the endpoint that was used in CUSTOM and provides another measure of what the consumer might actually do in the real marketplace.

Now, the second objective was to understand why

they made the decisions they did, and this was especially important because many of the participants applied the label directions to their own personal individual circumstances and often made logical informed decisions.

So, let's look at the main features of the study design.

[Slide.]

In order to obtain a diverse population, we conducted the study at two locations in each of seven U.S. cities. We recruited participants through television and radio ads in both English and Spanish. The ads simply announced a cholesterol study in the area with a phone number to contact.

We did not provide any information about the product or the target population in the ads, and this is very different from what we are committed to doing in the marketplace where all advertising will clearly explain who this product is for.

[Slide.]

Participants were directed to one of the two simulated retail sites in their area where they expected to purchase and use the product. At the site, they were asked

to review one of two carton labels, as you heard, but, importantly, there was no additional material included as there would be in the marketplace, just the carton label.

As in CUSTOM, we tested the label based on the traditional established LDL-cholesterol paradigm, but we also tested the label based on the total cholesterol numbers.

[Slide.]

As I explained a minute ago, each participant was asked to make two self-selection decisions, self-assessment followed by purchase.

[Slide.]

After they answered the questions, we interviewed each consumer using a carefully worded script to obtain more information that allowed the deeper understanding of their reasons behind their decisions, and then we also recorded their medical history, took blood pressure and gave them a cholesterol test.

So, let's take a look at who participated in this study.

[Slide.]

We had nearly 1,500 participants with an even

gender split. The median age was consistent with the population that is concerned about cholesterol. The low health literacy numbers were typical for a sample like this in the U.S. population.

We had an ethnically diverse cohort with a household income consistent with the national average. So, let's look at the specific label elements that we asked them to evaluate.

[Slide.]

We took a very comprehensive approach to this label, asking people to consider 15 different elements within three categories; absolute safety, which are the Do Not Use warnings, and the relative safety category, which are the Ask a Doctor Before Use warnings, and then the benefit guidelines, which define the conditions for the optimal benefit.

So, looking at the label, like this, with multiple self-selection criteria organized in these categories, helps us assess the overall benefit-to-risk relationship for both the individual and the population at large.

Now, it is no surprise that most participants did not strictly follow each and every one of the 15 label

elements. Such a level of perfection is really unrealistic, but probably not a necessary benchmark, and that is why FDA has asked us to examine the label behavior using a hierarchy. And this committee, some of you were there in 2006, reached a similar conclusion.

So, in this way, we look at the label at the relative importance of each label decision, especially with regard to the consequence of not heeding the label. Heeding the safety criteria is most important, followed by the benefit guidelines by which there can be more leeway.

So, as long as the safety warnings are heeded, the benefit associated with the label, and the lipid reduction that comes with it, can be positive almost always but may vary while the relative risk remains minimal.

[Slide.]

With that in mind, let's look at the 456 participants who judged this product to be right for them and they followed on average at least 13 of the 15 label elements. When we looked at just the safety warnings, they followed on average 6.9 out of 7, which is very high, and this is what we have consistently seen in this high level of safety behavior in all of our studies.

As we expected, most of the veering from the exact label guidelines occurred on the benefit measures because this is where participants were most likely to apply their own personal situation.

So, in general, this big picture approach is very reassuring that the safety decisions are nearly always correct. But let's take a closer look at the specific label elements beginning with safety.

[Slide.]

Here, we see the participants affected by one of the absolute Do Not Use safety warnings. The values under the bars represent the numbers of participants with these conditions, and the bar heights indicate the high percentage that correctly judged that Mevacor Daily was not appropriate for them. This included women who were pregnant or breast-feeding or thought they may become pregnant, and people allergic to lovastatin.

[Slide.]

And if we look at the purchase decision, all three of the women who were either pregnant or thought they may become pregnant did not want to purchase for those very reasons, and this purchase decision is very important. It

shows another way people think about themselves actually using this product.

Usually, it is the same as the self-assessment decision, but it often reveals another layer of their true intent. In this case, we see that 100 percent did not want to use it, and these are the absolute safety warnings.

[Slide.]

So, if we look at the relative safety warnings, these participants affected by one of these warnings are the warnings that said the product was not appropriate for them, but they should check with a doctor.

These warnings direct them either to talk to a doctor or pharmacist if they are possibly taking potentially interacting medication, already on a prescription lipid medicine, or with a history of liver problems.

So, the label is working well to discourage use in this group, but what about those who said it was appropriate?

[Slide.]

The orange bars on top show just as the label directs, that many who said Yes wanted to check with a doctor or pharmacist before using Mevacor Daily. Then, when

we interviewed the participants about these decisions, we find, as shown by the additional green bars, that several, most, actually did have good explanations for their seemingly incorrect decision.

These reasons have been termed mitigations or mitigating factors. We were conservative in applying these mitigations and, in most cases, FDA reviewers agreed with our approach.

Now, again, it is important to consider the purchase decision especially for those already taking lipid lowering medications because some of these people logically thought Mevacor would be appropriate for them. But we see with the purchase decision that the correct decisions are often even higher. So the label worked very well on the relative safety warnings.

As we know from the clinical safety data presented by Dr. Adamsons, for the small fraction who make a mistake, the probability of a serious adverse outcome is extremely low. So, we have very good safety behavior to support the lipid-lowering benefit that this product provides.

[Slide.]

And, as we set out to do with the new label, we

maintained or improved our strong self-selection for the safety warnings as we did in CUSTOM.

Remember, in SELECT, to be conservative, we required consumers to make these decisions based on the carton label alone without the help of the in-package materials available in CUSTOM and the in-market education and support program that Jerry mentioned earlier, and you will hear more about later.

We also see opportunity to improve the carton label, especially regarding the message not to use if already taking a prescription medicine. So, now, let's look at how we did on the benefit guidelines in the label knowing that the potential for safety concern is extremely low.

[Slide.]

Now, you know the benefit guidelines were established to generate a population that can optimally benefit from 20 mg of lovastatin. For example, the ages are those around which experts agree that heart disease risk begins to substantially increase. The target cholesterol ranges are also consistent with medical guidelines and again, for optimal benefit, consumers should have one additional CHD risk factor.

So, these guidelines are intended to produce a user population within a benefit sweet spot, so to speak, not firm boundaries beyond which there is no benefit, and we want to avoid consumers with a prior history of heart disease, stroke, or diabetes, and direct them to a doctor.

The results of SELECT indicate that consumers do understand this concept. Although the label worked well to drive away most consumers that did not match up, some did not heed exactly all benefit guidelines. But in most cases, consumers had reasonable health conscious reasons for their decisions.

[Slide.]

To illustrate this, let's just look at the mean values for those who thought the product was right for them. Clearly, the label produced a population centered right within the target zone. Men and women with an average age in their mid to late 50s, with mean LDL levels in the mid-150s, and an average of two risk factors.

Yes, these are means and there are outliers, but they are just that; they are outliers who will still benefit and will be exposed to little risk and, if appropriate, will likely be directed to proper care by the Mevacor Daily

Support Program.

[Slide.]

But before we look at the specifics of the behavior around these benefit guidelines, let's look at the behaviors the FDA reviewers were concerned about regarding adherence to these benefit guidelines.

These included the women who were under the recommended 55-year age guideline, the participants who thought the product was appropriate despite being outside the optimal lipid range, those with a history of heart disease, stroke, or diabetes and, finally, the percentage of people with a calculated Framingham risk score of less than 5 percent, most of whom were women.

The rest of my presentation will focus on the behavior benefit, and it will help to put into context these FDA concerns when examined in the light of the overall decisions and the good safety behavior that people exhibited in SELECT because all of these people will receive a lipid-lowering benefit by using this product.

[Slide.]

First, we see that, for each of the main benefit guidelines, participants made appropriate decisions about 75

to 85 percent of the time. The majority of these people realized that they were too young, had lipid values out of range or no risk factors, and they correctly self-assessed that the product was not right for them.

But what of the remainder, the ones who self-assessed Yes?

[Slide.]

Again using the concept building with the orange bars, these are the people we take into account who said, as the label directs, they wanted to talk to a doctor. So, with that, we have at least 80 percent following the label for these benefit guidelines.

[Slide.]

Again, when we factor in the reasons they provided for not heeding the label guidelines, we start to approach the 90 percent level for appropriate decisionmaking.

These are the mitigating factors obtained from the interviews that showed they made informed decisions, reasons like I had a family history, of being told by their doctor they have a cholesterol problem, or knowing that they are quite close in age or lipid levels. So, we see that the label alone, without the educational materials, does quite

well with regard to the benefit guidelines.

[Slide.]

Now, I want to take the same approach to the participants who reported that they had a history of heart disease, stroke, or diabetes. The label is written to help them recognize that their lipids should be managed by a doctor, and we see that 50 to 70 percent of the participants reporting one of these conditions made initial decisions consistent with those guidelines.

[Slide.]

And the numbers increase substantially when you add in those who said Yes but correctly wanted to check with their physician as the label directs.

[Slide.]

Again, when you add the mitigations--and as we saw from the other benefit guidelines, the level of the appropriate decisions continues to rise when we account for the participants who gave acceptable informed reasons or these mitigating factors for their decisions.

Around 80 percent made appropriate decisions with a prior history of heart disease, and well over 90 percent did so with a history of stroke or diabetes.

[Slide.]

And the picture looks even better when we examine the purchase decision and we find this highly encouraging, especially when we consider again the behaviors being driven by the information on the outer carton alone, and later you will see that most of this group were not on any lipid-lowering therapy and should be.

So, we have a net benefit with this higher risk group. Now, you have seen how the entire SELECT population performed on each of the main label elements. I would like to now take you through some of the subgroups of particular interest to us and the FDA, starting with women at the age guideline of 55 years.

[Slide.]

We see the label successfully turned away 89 percent of women under the age of 55, and 88 percent from wanting to buy it. This is a major improvement from the 76 percent who did not want to purchase in CUSTOM.

For the women who said Yes, and it was appropriate for them, they appeared to have good reasons and, if we look at these 42 women, they reported that they knew they had a cholesterol problem, a worrisome family history, or knew

their age was close. And, of the 42 women under 55, they had additional considerations. Three-quarters were at least 45 and many had one or more risk factors, such as elevated LDL values, and one-third knew that they should be talking to a doctor.

So, with the correct decision combined with those who wanted to check with the doctor, 93 percent were consistent with the label.

[Slide.]

We also wanted to look at how the label worked with people at lower CHD risk. One way to do this is to examine those with LDL values below the label guideline of 134 mg/dl.

Again, as with the younger women, well over 80 percent said Mevacor Daily was not appropriate for them, and did not want to purchase. Of those who did say Yes, they all had at least one risk factor and almost 90 percent had two or more.

Forty-two percent were within 20 points of the guideline LDL level, and could still benefit from additional lipid lowering, and others wanted to speak with a doctor or expressed good reasons for choosing to not heed the label's

benefit guidelines. Again, adding those who wanted to check with their doctor, 91 percent were consistent with the label.

[Slide.]

Another approach to this question of low CHD risk is to examine those with lower Framingham risk scores. Of this group, this is a score in SELECT where consumers did not know their Framingham score. But it is a useful tool.

You will note some experts agree that it may underestimate risk in some people especially women. So, with the label acting as a screen or a filter for CHD risk, we see it turned away nearly 80 percent of the participants in this lower risk group with a Framingham 10-year risk score less than 5 percent, and when we look more closely at those people, we see that most were within the label guidelines.

Most had an LDL over 130 or a total over 200. 91 percent had at least one risk factor for heart disease and half had at least two including family history, which a Framingham calculation does not even consider.

Most were within the age range or close, and again it was clear from the interviews that these participants

thought carefully about their decisions to want to take Mevacor Daily. So, the label clearly worked to reject people with lower risk, and those that did want to use the product could still benefit.

[Slide.]

We also looked at higher risk CHD risk in three different areas. Among those with Framingham 10-year risk scores above 20 percent, about half wanted to buy the product.

Remarkably, though, none of these were on any treatment for cholesterol-lowering therapy, and of the people with pre-existing heart disease, stroke, or diabetes, most said No. But of the 35 percent who said Yes, two-thirds were not on treatment despite guidelines saying they should be.

Likewise, those with cholesterol numbers above the label guideline said No in most cases. But of the 38 percent who said Yes, almost 90 percent were not receiving any treatment.

So, in all of these instances, and the others we just looked at, the only consequence of not heeding the benefit guidelines is that they will obtain a 20 to 25

percent reduction in LDL cholesterol, which is far better than no treatment at all, and we have a tremendous opportunity to engage these higher risk people, most of whom are not being treated, so that the High-Risk Referral Program, which worked so well in CUSTOM, will direct them to their doctors.

[Slide.]

So, to recap, the SELECT study results that show that the revised label improved appropriate self-selection decisions, and we maintained the high scores in all areas of safety, among the absolute safety warnings no women who are pregnant, breast-feeding, or thought they may become pregnant chose to buy the product among the relative safety warnings.

Similar high scores were achieved on the liver and concomitant medications, so the safety risks are extremely low.

Turning to benefit, when we look at the populations of key interest, we substantially reduced use by women under 55. Eighty-eight percent did not want to use it compared to 76 percent in CUSTOM, and we find that nearly 80 percent of the people with lower CHD risk are not interested

in the product.

Again, these consumers veered from the label when they made the informed decisions about that. So, together, with the overall safety profile of the 20 mg dose, the benefit-to-risk relationship for Mevacor Daily really becomes a function of the degree of benefit, and the overall benefit remains favorable even if some are not perfectly in the center of that benefit sweet spot where the label guidelines are followed exactly to the letter.

Let me show you a more graphic depiction of this point.

[Slide.]

When we look at the people in SELECT who decided to purchase Mevacor Daily, we see that about half of them are in that optimal sweet spot and exactly followed guidelines or gave mitigating responses for their decisions.

What about those that did not exactly heed the label guidelines?

[Slide.]

This next grouping represents those at higher than optimal CHD risk. We want these people to see a doctor for evaluation, however, none of these people were receiving any

treatment, so at the very least, they will get a substantial lipid lowering from Mevacor Daily and many will be directed to their doctor as we saw in CUSTOM.

[Slide.]

The next group represents those at the lower than optimal CHD risk category. While most in this category were properly turned away by the label, the smaller subset that did want to buy Mevacor Daily could still benefit from the lowering of their cholesterol.

As you have seen from the data, there is clear evidence of risk reduction no matter what the cholesterol starting level is.

[Slide.]

Now, this smaller group at the top are those that were already taking a lipid-lowering medication and either wanted to substitute Mevacor Daily and would have reduced their lipid-lowering benefit, or they reported they would take the 20 mg in addition to their current medication and they may get slightly better lipid lowering. But there is very little impact on safety risk with this dose.

However, this group of people already on therapy do require attention. This is not desirable and we know we

can improve the label to minimize both of these scenarios and plan to make that a priority going forward.

[Slide.]

Finally, since nobody with an absolute safety concern wanted to purchase and only one did not observe the relative Ask a Doctor warning, these bars cannot even be shown on this chart because they are so minuscule.

The net is that the great majority of people who said they wanted to purchase Mevacor Daily, 92 percent using this hierarchical approach stand to benefit while overall risk is very minimal.

Finally, as I have said repeatedly, this was all achieved with just the outer carton, and we are confident that the complete education and support system with the in-package materials will improve user decisions in all these areas.

[Slide.]

Now, to think of that particular consumer support and monitoring program, we know from our long history that we are not expecting any safety problems to arise with the use of the 20 mg dose in the OTC environment, but what we do know is that this is an important step and it requires

careful monitoring and consumer support to make sure that the optimal type of person uses this product.

So, we developed a program with the aid of Dr. Saul Shiffman, who is an expert in this area, and actually has experience with similar types of products, and I would like to introduce Dr. Shiffman now to tell you about that program.

Education, Support, and Monitoring

DR. SHIFFMAN: Good morning.

[Slide.]

As Dr. Hemwall has indicated, taking a statin over the counter is a new and substantial step, and so it requires an equally substantive postmarketing program.

So, in contrast to SELECT, where as you have heard consumers had only the label on the outside of the box to guide their decision, in the marketplace, the sponsors are proposing a robust consumer support program to guide consumers in making decisions about whether to use the product and in using the product appropriately.

This will be backed up by a rigorous surveillance program to monitor how Mevacor Daily is used in the market, and to provide timely data to both the sponsors and,

importantly, to FDA.

So, let me start with the program of consumer guidance.

[Slide.]

The Mevacor Daily consumer program is based on sound behavior change principles and builds upon experience from other ground-breaking OTC switch products including two that I have been involved with, GSK's nicotine replacement therapy for smoking cessation, and GSK's weight loss medicine alli.

These programs can help consumer appropriately select whether the product is right for them, use the product according to label instructions, and change behavior to adopt healthier lifestyles.

[Slide.]

The program is intended to guide consumers through three stages; when they are thinking about whether to use Mevacor Daily, at the point of purchase in the store, and during actual use.

It builds on what was described by Mr. Hansen in the CUSTOM study, but we have added a substantial pre-purchase element to the program to guide people toward

appropriate self-selection, and throughout the program we have added enhanced content and also enhanced the program's interactivity.

[Slide.]

Let me briefly describe each step, in turn, starting with the new pre-purchase step, which begins before the person even enters the store.

Advertising will drive people to a web site or 1-800 number where, based on information individuals provide, they will be told whether Mevacor Daily is right for them per label guidelines.

They can also get an estimate of their cardiovascular risk and advice on how they can lower it. So, that is the pre-purchase guidance, and let's move on to step two in the store.

[Slide.]

Once the consumers are in a store, interactive shelf materials focus on self-selection, asking them should you take it. Now, of course, people will also have the option to consult with a pharmacist if they have further questions.

[Slide.]

Then, once the consumer purchases Mevacor Daily, they will find simple, useful materials inside the package including a Quick Start guide, an in-depth booklet that explains cholesterol and provides tips on diet and exercise, a refrigerator magnet reminding them to watch for unexplained muscle pain, and also information cards that they can give to their doctor and pharmacist to let them know that they are taking Mevacor Daily.

[Slide.]

In addition, consumers would be invited and given incentives to enroll in an interactive support program with the incentives including a free month of Mevacor Daily, an AHA cookbook, and a DVD.

As they enroll in the program, they go through an interactive screening for the label guidelines. Now, realistically, this screening is after purchase so, if a consumer discovers the products is not right for them, they will be encouraged to return the product for a full refund.

[Slide.]

Now, for consumers who are appropriate, the program will provide ongoing guidance on appropriate use of Mevacor Daily and on healthy diet and exercise.

[Slide.]

Now, importantly, this won't just be another web site, but rather a systematic proactive and interactive program based on best practices and behavioral intervention. It takes the consumer through the process of using Mevacor Daily over time, telling them what they need to know and what they need to do and when they need to do it, and it is tailored to individual users because tailoring enhances program effectiveness.

So, for example, the program would remind you of your personal motivation for lowering your cholesterol levels, track your cholesterol levels, and make dietary recommendations based on your personal preferences.

The program is also proactive. For example, it would send you timely reminders when it is time to get your six-week cholesterol test.

[Slide.]

So, I have summarized the program of consumer guidance which will guide appropriate use in multiple ways and at multiple points. But, additionally, to confirm appropriate use, there will be substantial monitoring and surveillance. Now, of course, adverse events will be

tracked and reported to FDA.

In fact, the reporting requirements for Mevacor Daily are the same as for any prescription drug. But the monitoring program goes well beyond traditional adverse-event tracking. It will proactively assess behaviors of concern through multiple series of ongoing studies of Mevacor Daily users as well as surveys to gather data from physicians and pharmacists, and it will be overseen by an independent expert advisory board with results reported to FDA.

[Slide.]

So, these studies of Mevacor users will assess appropriate self-selection and use. Specifically, we will interview panels of Mevacor Daily users to assess endpoints such as are the user's initial cholesterol levels within label guidelines, and are people getting retested and reacting appropriately to the results.

[Slide.]

In fact, the surveillance will track every step of the process beginning with ensuring that the product is attracting interest from the right people--for example, men and women of the right age.

We will do that by conducting consumer surveys, but also by monitoring the profile of people who screen themselves whether by web or phone.

Now, for those who do not qualify according to that screening, who are triaged out, if you will--for example, those who are told to see their doctor for a stronger statin--we will conduct follow-up studies on samples to check compliance with that referral.

[Slide.]

Finally, there will be multiple samples of Mevacor users. The largest will be constructed from a registry that purchasers will be incented to join, and will follow a longitudinal panel from that registry, as well. But we will also collect independent samples of users identified through existing panels to track their purchases and from people who enroll in the consumer support program.

These surveys will be repeated over time to track trends and appropriate use for as long as FDA deems necessary, as we have done for other OTC products. So, that gets us data from users of Mevacor Daily but we also want to understand what professionals are seeing in their practices.

[Slide.]

So, we will also survey physicians to find out if they are seeing any issues of concern with patients on Mevacor Daily and, from pharmacists, we will want to know how often they are being consulted, what sorts of questions consumers are asking, and so on, and these data will help fine tune the pharmacist and consumer education programs.

So, that summarizes the planned guidance and monitoring.

[Slide.]

Importantly, the program will be overseen by an independent advisory board of experts from diverse fields such as cardiology, pharmacy, behavioral science and consumer communication. The board will oversee the program, scrutinize the data for concerns, advise sponsors on how they can improve consumer or professional communication, and send its reports to FDA.

This structure has been used effectively in postmarketing risk-management programs for prescription drugs. So, this is a large, multi-part program. I realize I have covered a lot of information quickly, but I would certainly be glad to give more detail during the discussion period.

[Slide.]

But, in summary, we believe that this comprehensive program embodies the elements and best practices needed to ensure that the right people use Mevacor Daily and that they use it appropriately.

Thank you for your attention.

Now, let me turn the presentation over to George Quesnelle, who is the President for North America of GlaxoSmithKline Consumer Healthcare.

Marketing Plans

MR. QUESNELLE: Thank you, Dr. Shiffman. Good morning.

As you have heard today, the science demonstrates that Mevacor Daily has the potential to help more consumers lower their cholesterol and thus reduce their risk of heart disease. We are proud to have been selected as Merck's partner to bring this important product to consumers.

The question I want to address now is how; how do we help ensure that the appropriate consumer correctly uses Mevacor daily in the OTC setting and thus realizes the benefit of increased access.

We know that Mevacor Daily is for a motivated,

health-conscious consumer, and we are committing to a responsible marketing and support program that will offer tools to help these consumers make important behavioral changes.

[Slide.]

At GSK, we are not strangers to the Rx-to-OTC switch process. As one of the leading Rx-to-OTC switch companies, GlaxoSmithKline has a track record with particularly challenging switches.

These are first in class switches, like Nicorette for smoking cessation, and alli for weight control, and while each switch presents its own unique challenges, our experience with these switches demonstrates that we know how to develop programs to market these OTC switches in a responsible way to maximize the public health benefit.

[Slide.]

The switch of Nicorette from Rx to OTC has had dramatic public health benefit but, back in the mid-1990s, it seemed quite challenging for a number of reasons.

First of all, the active ingredient in Nicorette is nicotine, and nicotine is classified as addictive. There was concern about the potential for misuse and abuse by

teens especially that they might use it as a gateway product into smoking.

There was concern that lack of intervention by a healthcare professional might lead to lower quit rates, and there was concern based on the advertising practices of the cigarette companies about the way we might market Nicorette.

[Slide.]

Working together with the FDA, GSK designed an innovative series of post-approval marketing requirements. These included in-market monitoring to make sure that the programs we designed were doing what we said they would do, programs to engage and educate the healthcare professional, so that they, in turn, could help their patients and, finally, comprehensive education, guidance, and support all designed for the appropriate consumer target.

As a result, Nicorette was approved for OTC use in January of 1996 with these commitments as part of the approval letter and conditions of approval.

GSK lived up to all these commitments and we reported them to the FDA every quarter. In 2002, because no signs or signals had emerged on any of these issues, they were no longer necessary, because FDA was satisfied that all

the concerns had been addressed.

[Slide.]

The public health benefit of Nicorette and the other nicotine replacement products that followed has been dramatic. It is estimated the 7.6 million smokers have been able to quit smoking because of the availability of OTC nicotine replacement therapy.

[Slide.]

Similarly, in the recent approval of alli, we worked to address major issues of OTC approval. We knew that alli was not a magic pill. It requires people to follow a low fat diet.

Similar to smoking cessation, our first and foremost goal was to help consumers change their behavior, in this case, to change their way of eating and to manage their own care without the intervention of a healthcare professional.

There was concern about the potential for misuse by teens, especially bulimics and anorexics. There was also concern whether the appropriate consumer in the right range of overweight could properly self-select the product.

[Slide.]

We developed pre-launch and post-launch programs to answer these tough, but legitimate questions, and we are now marketing alli in a responsible way, consistent with the promises we made to this committee before approval.

[Slide.]

Since alli has been approved, 2 million consumers have used this FDA-approved OTC weight loss medicine and have taken steps to move to a healthier lifestyle.

These are just two example that demonstrate our deep experience in responsible marketing of OTC products and OTC switches that can benefit the public health.

Let me now give you examples of how we plan to market Mevacor Daily.

[Slide.]

A core component of the marketing program will be consumer advertising. While we don't have final advertising yet, our ads will target men 45 years of age and older and women 55 years of age and older.

Ads will be placed in publications and aired on programs that are aimed at this population. The people in our advertising will represent the target population. The ads will communicate science-based, yet consumer-friendly,

messages focusing on the importance of lowering cholesterol to lower the risk of heart disease.

They will also give consumers practical guidelines based on the FDA-approved labeling to decide whether or not OTC Mevacor is right for them.

The tone of the advertising will be educational and supportive, and will emphasize to consumers that Mevacor Daily is for a health-conscious and committed consumer.

Our consumer communication will actually start before we begin selling Mevacor Daily. We will be launching a major education initiative and unbranded campaign to educate consumers on the dangers of high cholesterol and the importance of knowing their cholesterol numbers.

We will also emphasize the importance of adopting a heart-healthy lifestyle to help consumers reduce their cholesterol levels. Importantly, this will help consumers to understand what they can do before resorting to medication. The program will make special efforts to reach the medically underserved with focus on women and minorities.

[Slide.]

To drive the success of this program, not only

with consumers, but also through the support of healthcare professionals, we will partner with the American Heart Association on this important effort.

This is a comprehensive program that, like our efforts with alli and smoking cessation, goes well beyond traditional advertising.

It will include an enhanced AHA web site and 800 number to help people assess their cardiovascular risk, educational materials on heart health for consumers, programs for physicians, pharmacists, nurses, and dietitians, and consumer education and screening events, many of which will include cholesterol testing.

We will also collaborate with other professional organizations as we have done in the past to ensure that we have broad access and reach for all of these programs.

[Slide.]

We have learned from our experience with smoking cessation that one of the most effective ways to deliver highly specialized healthcare education is through face-to-face communication. To that end, we are planning on offering one-on-one sessions with trained counselors that will run anywhere from 5 to 20 minutes.

The focus of these sessions will be on encouraging consumers to adopt healthy lifestyle practices including knowing their cholesterol numbers. We will also let them know where they can get cholesterol tests and, at many of the events, cholesterol testing will be offered on site.

We have had great success with a similar program to this with smoking cessation, and these are some photographs from some of these events. Since 2005, we have held face-to-face discussions, one-on-one sessions with over a million smokers, talking to them about the dangers of smoking and the importance of quitting.

This type of outreach will supplement the efforts of our marketing programs to reach out to consumers to deliver responsible healthy lifestyle messages.

[Slide.]

Dr. Shiffman and I have only touched on a few of the consumer support and marketing programs that will be part of the launch of Mevacor Daily. Overall, at the launch of Mevacor Daily, we will support consumers with a comprehensive array of programs to ensure that they can clearly determine whether or not Mevacor Daily is right for them.

We will continue this support after purchase by bringing to life the self-selection criteria on the package. We will communicate with consumers through a variety of methods--one-on-one counseling through the Internet, over the telephone.

These different formats will ensure that we are there with important healthcare information no matter how the consumer prefers to receive that kind of information.

[Slide.]

In summary, we commit to conducting the same responsible marketing for Mevacor Daily as we do with alli and our smoking cessation products. We will educate the consumer about the importance of cholesterol lowering and offer the consumer support and guidance so they can use Mevacor Daily safely and effectively.

We commit to monitoring the results of our programs and adjusting as necessary to ensure that Mevacor Daily is being used by the right consumer and in the right way.

We believe strongly in these commitments and we will abide by them in market and, as proof of our conviction, we have included them in the drug application to

be considered as conditions of approval and enforceable by the FDA.

Taken in total, this comprehensive program of education, guidance, and support has the potential to dramatically impact the public health.

Thank you for your time and I will turn the program back over to Dr. Hemwall.

Conclusion

DR. HEMWALL: Thank you, George.

I hope you understand the importance of our education and marketing program as a critical adjunct to the label that we studied in SELECT, and I think you will see now why we at Merck are so impressed with the proven GSK track record for responsible marketing and why we have chosen them as our partner.

[Slide.]

I would like to go back to the chart I presented earlier, which summarizes the key requirements for consideration of a nonprescription statin, and as before, you see the topics addressed with the earlier data and reviewed by this committee in 2005.

We have noted the topics we have addressed since

then with our new label comprehension studies and the SELECT trial. As you have seen from our last two speakers, the details of a fully developed consumer support and in-market monitoring program.

Clearly, there are opportunities to further optimize the labeling and the support system, and we are ready, with your support, to begin working with FDA immediately to bring this to reality.

[Slide.]

In concluding, I would like to remind you, though, of the large gap that still exists in this country, people who could benefit and are recommended for treatment by national guidelines but are not getting any treatment for their high cholesterol.

The Mevacor Daily program and the awareness that the program generates within the target population will help to close the gap in the moderate risk population and send more consumers to their physicians to help reduce the gap in the high risk population.

[Slide.]

We have seen when it is actually used by our target population that lovastatin 20 mg can substantially

reduce LDL cholesterol and over time it will reduce the risk of a first heart attack and provide real impact on public health. Shifting this curve is the very essence of this public health opportunity and it is one that requires that we accept the outliers who do not fall within the optimal range but for whom the benefits still far outweigh the risks.

[Slide.]

So, we are asking you to recommend approval of this greater access to a safe and effective product so that we can take advantage of the opportunity to reduce the burden of cardiovascular disease in this country. We urge you not to accept the status quo for health-conscious consumers trying to prevent heart disease.

It is a status quo which consists of a choice between dietary supplements and food products or prescription drugs. Let's add something with proven benefit to the middle of that mix, and let's improve the health of those who want it, need it, and can benefit from it.

Thank you for your attention.

That concludes our presentation.

DR. TINETTI: Thank you. Before the break, I want

to remind the panel, do they have any specific clarifying question for any of the industry presentations. Again, we will be having a lot of questions this afternoon, so these only questions if there is something you clearly don't understand about what was presented. Please hold all the rest of your questions until this afternoon.

DR. GLASSER: In the SELECT program, were the labels that the participants viewed the same size as what is on this box, font size and whatnot?

DR. HEMWALL: What you have on the box in front of you is the actual box that was used in the SELECT study.

DR. PICKERING: We haven't heard much about total cholesterol versus LDL labels. What is the situation with that?

DR. HEMWALL: Well, as you heard, we did test both labels, and we presented most of the data in combined form, because we really did not see a large difference between the two labels, but in terms of overall performance and adherence to label criteria.

We did see, as you might expect, that more people knew their total cholesterol numbers, and were at a slightly higher percentage within the optimal target range than they

were with their LDL numbers.

DR. PROSCHAN: On Slide 61, you give the old and the new labels. Do you have that, 61?

DR. HEMWALL: Yes, this is the Slide 61, you can put the slide on. Is this the slide you wanted?

DR. PROSCHAN: Right.

DR. HEMWALL: This is showing the main concepts of the difference between the old pregnancy labeling, which is standard OTC labeling, and the additional labeling. There is also an additional message about why it is so important to particularly heed this message.

DR. PROSCHAN: But I thought the old message, didn't it have all capital letters, and said, "Do not use if pregnant or breast-feeding" rather than this, which has lower case. I mean it seemed more prominent earlier.

DR. HEMWALL: Yes, that is a very good pick-up. There were things that we did in the CUSTOM label that included highlighting, adding color, or bolding or capitalizing.

At the time we did them, we thought that they would work best, and the CUSTOM label did in fact work very well in these areas. But they weren't compliant with what