are the drug facts labeling regulations that make very strict rules about when you can capitalize, when you can bold, or when you can add color to the label.

So, working in conjunction with FDA in developing the new label, you will see that the panel, when you open up the book, the little kind of book back of it, that the right side is the pure drug facts labeling, and that adheres rigidly to the format that is required by the regulations and doesn't allow those things.

The other information is outside of the drug facts, and we are allowed to be a bit more graphic and instructional with the information.

Because we learned that some of the things in SELECT didn't perform quite as well as they did in CUSTOM, and when we looked at them, they are the things that were bolded or highlighted. It is possible that if we go forward with the learnings from both studies, that we have evidence that the bolding or highlighting or capitalizing actually adds additional value, and we would be willing to do that.

DR. TINETTI: Again, just remember these are just purely clarifying questions. The three people that have your hand up, and then we will go for break.

drug, because once they got home and read more of the materials or checked with a doctor, they found out that they weren't appropriate, so not all these people actually took the product for the long term.

It is the slide that follows on this particular graph that shows the reductions that were achieved. So, yes, there were some people on the outlying edges. They are not the people that the label targets, but we do have that type of behavior.

Most of the people that have those lower or higher levels actually are rejected by the label, and we see very good behavior, but that is the full spectrum, and, of course, as you know, shifting that curve to the left is the whole purpose of this product and the opportunity it represents.

DR. TINETTI: Thank you.

Ruth.

DR. PARKER: Slide 68 shows some of the SELECT demographics and I just wondered if you have more--

DR. TINETTI: Can we get that slide up?

DR. PARKER: What I was curious about--and that is for all the participants in SELECT--my question was whether

or not you have further breakdown on gender and age, and who the population really was across gender.

I think I heard in one slide also that 3 to 5 or something of the people in this were pregnant, but do you have the exact number of the people in the study that were pregnant, and then, you know, how that relates to this?

I am looking for childbearing age, as well as how many were pregnant that were in the study.

DR. TINETTI: Maybe I will ask for that this afternoon if Merck can provide us that data during the discussion period, because I think that is a good question.

DR. HEMWALL: We would be happy to do that then.

DR. FLATAU: Since we had the pregnancy warning up, it seems to me that the warning is for pregnant and breast-feeding women, and should say, may cause problems in the unborn or nursing child.

DR. HEMWALL: Yes.

DR. FLATAU: Unborn children are not nursing.

DR. HEMWALL: That is a good suggestion. We could add that for sure.

DR. TINETTI: Thank you.

Before we go to break, I want one other bit of

information that I would ask Merck to present to us this afternoon. Many of your results you showed us, those people who had the answer No, they would not self-assess or purchase. If we could also have the converse information, those who said Yes, and that breakdown, as well, just to prepare for this afternoon.

We are going to take a 15-minute break. We will start right on time. I guess we will make it at 20 after, and just remind the panel to not discuss any of the dealings while we are gone. Thank you.

[Break.]

DR. TINETTI: We are going to start the meeting.

LDL-C vs. TC Labeling Paradigm

DR. CRAIG: Good morning, Chairman Tinetti, members of the Joint Committee, ladies and gentlemen, my name is Eileen Craig. I am a medical officer in the Division of Metabolism and Endocrinology Products.

[Slide.]

I will be discussing our perspective on the two labels proposed by the applicant, one based on LDL cholesterol and the other based on total cholesterol, and how well they reflect the National Cholesterol Education

Program, Adult Treatment Panel Guidelines.

I will start with some background information on the ATP Guidelines. Next, I will discuss the target population and treatment goals for the low-density lipoprotein and the total cholesterol label, and then I will finish with some conclusions and issues that you may wish to consider in your deliberations.

[Slide.]

Under ATP III, treatment approaches, decisions on initiating drug therapy, and goals of therapy are based on calculations of an individual's risk of experiencing a cardiovascular event over a 10-year period.

ATP III uses Framingham point scores in estimating these 10-year coronary heart disease risks with age, total cholesterol, smoking status, HDL, and blood pressure contributing to their total score.

[Slide.]

ATP III also uses heart disease risk factors in addition to LDL, and these include a family history of premature heart disease, hypertension, cigarette smoking, a low HDL, and age, men 45 years and older and women 55 years and older.

Note that diabetes is regarded as a coronary-heart-disease risk equivalent. LDL is not counted among the risk factors listed here, because the purpose of counting these risk factors is to modify the treatment of LDL.

[Slide.]

The coronary heart disease risk factor counts and the Framingham 10-year risk estimates together determine whether an individual falls into one of the following categories.

The high risk category is heart disease or heart disease risk equivalent such as diabetes, and the 10-year risk is greater than 20 percent.

The moderately high-risk category is two or more risk factors for heart disease with a 10-year risk of 10 to 20 percent.

The moderate-risk category is two or more risk factors for heart disease with a 10-year risk of less than 10 percent and a lower risk category is zero to 1 risk factors for heart disease with a 10-year risk of less than 10 percent.

Initiation of drug therapy depends on the risk category of an individual and should be considered as an

adjunct to lifestyle changes, such as a low-fat, low-cholesterol diet, exercise, and not smoking.

[Slide.]

The NCEP-ATP III Guidelines were published in 2001 and updated in July of 2004. The Guidelines are endorsed by the American College of Cardiology, the American Heart Association, and the National Heart, Lung, and Blood Institute.

ATP III identifies LDL cholesterol as the primary target of therapy because multiple lines of evidence from experimental animals, laboratory investigations, epidemiology, genetic forms of hypercholesterolemia, and controlled clinical trials indicate a strong causal relationship between elevated LDL cholesterol and coronary heart disease.

Key components of the guidelines are a more aggressive treatment for higher risk patients, the establishment of goals for non-HDL cholesterol, a definition for metabolic syndrome, targeting low HDL levels as a risk factor, and an emphasis on therapeutic lifestyle changes.

In high-risk persons there is now an optional LDL goal of less than 70 mg/dl and for moderately high-risk

persons an LDL goal of less than 100 is a therapeutic option on the basis of recent trial evidence.

The nonprescription lovastatin-eligible population, based on the criteria in the LDL label paradigm corresponds with those individuals who are at intermediate risk for a cardiovascular event over 10 years.

The 2005 Advisory Committee agreed that this target population is consistent with expert recommendations for treatment based on the NCEP-ATP III Guidelines. The 2005 Advisory Committee also agreed that lovastatin 20 mg would effectively lower cholesterol levels in the proposed patient population to a degree that would represent a clinical benefit.

I will discuss later on in my presentation how well the two labels performed in capturing this target population.

[Slide.]

In the LDL and total cholesterol label, the target population is the primary prevention of coronary heart disease by consumers who are at moderately high risk of coronary heart disease consistent with the NCEP-ATP III Guidelines.

The LDL label for nonprescription lovastatin uses LDL values for selection criteria and treatment goals. In the LDL cholesterol label, consumers are considered eligible for nonprescription lovastatin if they meet the following criteria; men 45 years and older, women 55 years and older, an LDL between 130 and 170, have at least one additional risk factor, and the LDL label criteria are similar to, but not precisely the same as, the NCEP-ATP III Guidelines.

One notable difference is that for individuals who have a 10-year risk less than 10 percent with risk factors, ATP III Guidelines recommend consideration of drug therapy when LDL levels are greater than or equal to 160.

[Slide.]

The total cholesterol label uses total cholesterol values for selection criteria and treatment goals. Treatment goals based on total cholesterol do not reflect ATP III Guidelines.

In the total cholesterol label, consumers are considered eligible for nonprescription lovastatin if they meet the following criteria; men 45 years and older and women 55 years and older, total cholesterol between 200 and 240, only women must have at least one additional risk

factor, and only women must have an HDL between 1 and 59.

According to the applicant, the total cholesterol label may be more consumer friendly since consumers are generally more aware of their total cholesterol than their LDL cholesterol.

In the total cholesterol label, women must be able to select the correct age range, the correct total cholesterol range, the correct HDL range, and one of the appropriate risk factors.

While it is reasonable to accept that the concept of total cholesterol is more understandable to the consumer than LDL, it is likewise reasonable to accept that HDL is a difficult concept for the consumer to understand and utilize in determining treatment eligibility.

However, in the total cholesterol label, men only need to select the correct age group and the correct total cholesterol range. The correct HDL range and one of the appropriate risk factors is not part of the selection criteria for this paradigm for men.

For men, while this label is easier to understand than the LDL label, the male population defined by the total cholesterol label is not consistent with ATP III guidelines,

and targets male consumers without heart disease who are low

as well as intermediate and high risk of a coronary heart

disease event.

[Slide.]

To further illustrate, a 45-year-old man with no

cardiac risk factors, a total cholesterol of 200,

triglycerides of 100, HDL 50, and an LDL of 130 would have a

10-year risk for coronary heart disease of 4 percent. He

would not meet the criteria for drug therapy based on ATP

III, but would meet the criteria for Mevacor Daily based on

the total cholesterol label.

Furthermore, as he is in a lower risk category,

his LDL treatment goal is less than 160, not less than 130.

 On the other hand, a 50-year-old man who smokes, is being

treated for hypertension, and has a positive family history

of heart disease, with a total cholesterol of 240,

triglycerides of 100, HDL of 20, and an LDL of 200 would

have a 10-year risk for coronary heart disease of greater

than or equal to 30 percent.

He would meet the selection criteria for Mevacor

Daily using a total cholesterol label, but not by the LDL

label. Treatment with Mevacor Daily would lower his total

cholesterol to 239 or less, and thus, he would meet the treatment goals as per the total cholesterol label. However, he would not meet the treatment goals as per the ATP III Guidelines.

It is important to remember that it is the standard of care to use a complete fasting lipid panel, and not just total cholesterol, to determine if a patient should start on potentially life-long statin therapy.

[Slide.]

The treatment goal defined by the LDL label is an LDL less than 130. This is largely consistent with ATP III Guidelines as subjects with moderate risk and moderately high risk also have a treatment goal of an LDL less than 130. Keep in mind that according to ATP III, moderately high risk persons--and that is two or more risk factors and a 10-year risk of 10 to 20 percent--have an LDL goal of less than 100 as a therapeutic option.

Additionally, after the LDL goal has been achieved, if the triglycerides are greater than or equal to 200 mg/dl, non-F-HDL, which is total cholesterol minus HDL, and represents atherogenic lipoproteins, becomes a secondary target of therapy.

Non-HDL goals are set at 30 mg/dl higher than LDL goals for each risk category. The two treatment fine points of NCEP ATP III Guidelines are not covered by the nonprescription lovastatin label.

[Slide.]

The treatment goal defined by the total cholesterol label is a total cholesterol of less than 200. Total cholesterol is not the value used to determine treatment goals for hyperlipidemia, and it is not known if a consumer could select therapy based on total cholesterol and subsequently determine if he or she has met treatment goals based on LDL.

Furthermore, the actual-use study CUSTOM used a label based on an LDL criteria.

[Slide.]

Here is an example of an actual consumer from the SELECT study. He is a 50-year-old man with a total cholesterol of 242. He has cardiac risk factors of low HDL, he smokes and has a positive family history of heart disease.

His total cholesterol is 242. Although this is greater than the entry criteria of 240 for the total

cholesterol label, it is very close. Therapy with Mevacor
Daily would lower his total cholesterol to 239 or less.

This gentleman would meet the selection criteria
and treatment goal by the total cholesterol label. However,
his Framingham risk score is 25 percent and his LDL is 190.
Using just total cholesterol as a guide obscures the high
LDL value. His LDL goal by NCEP ATP III Guidelines is an
LDL less than 100. This is not achievable with low risk
statin 20 mg.

[Slide.]

This table displays the 10-year cardiovascular
risk estimates for participants self-assessing that over-
the-counter lovastatin was appropriate for them for both the
LDL and the total cholesterol label.

The heart-disease risk of all participants was
calculated by Merck to characterize the risk of the
population using the Framingham risk assessment tables
published in the 2001 NCEP ATP III Treatment Guidelines.

Actual measured values for total cholesterol, HDL,
and blood pressure were used for the calculation along with
the participant's self-reported values for age and smoking
status. As shown in the table, the heart disease risk

profiles of subjects who self-selected for lovastatin in the two study arms were similar.

[Slide.]

This table shows the same data as the previous slide. We see that both the LDL and the total cholesterol label had difficulty selecting the correct target population. Fewer than half of the subjects, and that is 34 percent in the LDL arm and 43 percent in the total cholesterol arm, had Framingham coronary heart disease risks of 5 to 20 percent, the range targeted by the applicant for treatment.

About 25 percent of subjects in both arms had a heart-disease risk of less than 5 percent.

Should we be concerned that these low-risk individuals are choosing to use the drug? About 15 to 20 percent of subjects in both study arms had greater than 20 percent coronary heart disease risk or had heart disease, diabetes, or stroke.

About 15 to 18 percent of consumers who made a positive self-assessment of decision were taking prescription cholesterol medication.

[Slide.]

In SELECT, more than 30 percent of the participants taking lipid-lowering medication stated that they were appropriate to use over-the-counter lovastatin.

In CUSTOM, 30 percent of participants that were using lipid-lowering medication decided to purchase over-the-counter lovastatin.

In SELECT, 55 percent of those who made a positive purchase decision, but were already on lipid-lowering medication stated that they would take Mevacor Daily in place of their lipid-lowering medication.

The three most commonly taken lipid-lowering medications used by participants who wished to purchase Mevacor Daily in the LDL cholesterol paradigm were atorvastatin, simvastatin, and rosuvastatin, significantly more potent statins than lovastatin.

Across their dose range, these three statins lower LDL an average of 30 to 63 percent. Thus, even the lowest dose of all three of these statins would, on average, have greater LDL-lowering potency than lovastatin 20 mg with a mean LDL lowering of 24 percent.

Should we be concerned that some individuals, especially those individuals at high coronary heart disease

risk, switch from more potent to less potent fixed-dose statin therapy?

[Slide.]

In SELECT, 28 percent of those who made a positive purchase decision, but were already on lipid-lowering medications, stated that they would take Mevacor Daily along with their lipid-lowering medication.

Individuals taking over-the-counter lovastatin along with their prescription lipid-lowering drug are at increased risk for myopathy and rhabdomyolysis as this risk increases with higher doses of statins and when a statin is used in combination with a fibrate drug, such as gemfibrozole.

Additionally, there are observational cohort studies, meta-analyses, and some clinical trials that have suggested an association between low cholesterol levels or high-dose statin use and at increased risk for hemorrhagic stroke.

This increased risk for hemorrhagic stroke was observed in certain subsets of patients, such as those with prior hemorrhagic stroke, those on concurrent platelet therapy, such as aspirin, and those with elevated systolic

blood pressure.

Should we be concerned that some individuals taking over-the-counter lovastatin along with their prescription lipid-lowering medication will be at increased risk for side effects?

[Slide.]

In conclusion, the LDL label criteria are similar to, but not precisely the same as, the NCEP ATP III Guidelines. The total cholesterol label criteria neither parallels the guidelines in selecting consumers at moderate to moderately high risk of coronary heart disease nor reflects the guidelines for treatment goals, which are based on LDL cholesterol goals.

[Slide.]

The majority of consumers using either label were not in the correct target population of 5 to 20 percent of coronary heart disease risk. More than a third of consumers taking lipid-lowering medication stated that over-the-counter lovastatin was appropriate to use.

More than half of those consumers who wished to purchase over-the-counter lovastatin would replace their prescription medication with over-the-counter lovastatin.

More than a quarter of those consumers who wished to purchase over-the-counter lovastatin would take over-the-counter lovastatin along with their prescription medication.

Lastly, whether a consumer self-selecting for treatment based on the total cholesterol label can appropriately assess his or her treatment goal, which is based on an LDL target, was not explored in this submission.

[Slide.]

Finally, I would like to take a moment to acknowledge my colleagues for their efforts in this review process.

Finally, I would like to introduce Captain Laura Shay from the Division of Nonprescription Clinical Evaluation, who will discuss the label comprehension studies.

History of the Label and Label Comprehension Studies

CAPT SHAY: Good morning, members of the Committee.

[Slide.]

My name is Captain Laura Shay. I am the Social Science Analyst for the Division of Nonprescription Clinical Evaluation.

[Slide.]

The objectives of my presentation is to provide an overview of the purpose of the label comprehension study, a brief history of the OTC Mevacor label development, a summary of the CUSTOM label comprehension study, the SELECT label comprehension study, the muscle warning label comprehension study, followed by an overall summary of the SELECT study.

[Slide.]

Label comprehension studies are conducted based on the regulation that an OTC label must be likely to be read and understood by the ordinary individual, including those with low comprehension, under customary conditions of purchase and use.

[Slide.]

The purpose of a label comprehension study is to evaluate whether or not consumers can comprehend important communication objectives on the label. It is important to test both literate and low literate subjects and to test a diverse population similar to that of the U.S. population.

[Slide.]

I am now going to provide a brief overview on the

history of the OTC Mevacor label. In 2000, FDA completed

the review of Merck's application for a 10 mg Mevacor

product. The product used a total cholesterol label

paradigm with total cholesterol follow-up.

[Slide.]

In 2005, FDA completed Merck's resubmission for a

20 mg Mevacor OTC product. This product used an LDL

paradigm with an LDL follow-up.

In 2007, Merck resubmitted a 20 mg product and

decided to test the two labels, one with the LDL paradigm

and follow-up, and the second with the total cholesterol

paradigm follow-up.

Merck's reason for testing both labels was because

they thought consumers could find it easier to understand

total cholesterol.

[Slide.]

The consumer behavior study conducted in 2004 was

the CUSTOM study. This label used in CUSTOM was also tested

in a label comprehension study. The label is different from

the label submitted in 2007.

In 2007, label comprehension studies were

conducted on the new labels. A self-selection study was

also conducted using the new labels. It is important to note that all of these studies are now under consideration.

[Slide.]

Now, I will review the CUSTOM label and the results of the CUSTOM label comprehension study.

[Slide.]

On the front of the CUSTOM label, the consumer begins the process for determining eligibility where it is described that the product is for people with LDL, or bad cholesterol, between 130 to 170. The purpose of Mevacor OTC is also described.

[Slide.]

On the back of the box is a Drug Facts label. As you can see, it contains a great deal of information. The selection criteria is described as a four-step process embedded between the Warnings and the Directions for Use.

[Slide.]

The results from the CUSTOM label comprehension were as follows; for the communication objectives dealing with selection criteria, the range of correct answers was 37 percent to 59 percent.

[Slide.]

For those objectives that dealt with warnings and contraindications, the range of correct answers was 55 to 79 percent.

[Slide.]

The CUSTOM label comprehension study also contained a self-selection question. Out of 209 subjects who stated they "could start Mevacor OTC today," 3 subjects, or 1 percent, were correct on all label criteria. We now recognize that being correct on all label criteria can be difficult with more complicated label paradigms.

For this reason, hierarchies were looked at when analyzing the self-selection results using the SELECT label. These results will be described further in the next FDA presentation.

[Slide.]

The label deficiencies outlined in the February 2005 Not Approvable letter, stated that Merck needed to modify and retest the label especially the pregnancy warning, unexplained muscle-pain warning, and liver-disease warning, provide justification if the label deviates from Drug Facts label format regulations, and demonstrate that consumers can make an appropriate self-selection decision

based on the information contained on the label.

[Slide.]

Now, I am going to provide an overview of the
SELECT labels and the results of the label comprehension
study.

[Slide.]

The SELECT labels are quite different from the
CUSTOM label. The front of the box or the principal display
panel begins to describe the selection criteria beginning
with the appropriate age.

[Slide.]

On the back of the box are more selection
criteria.

[Slide.]

On the inside flap there is a review of the
eligibility criteria already described, in addition to a
description of required risk factors.

[Slide.]

Across, on the inside flap, is the Drug Facts
label that is in format that meets the OTC label
regulations.

[Slide.]

On the bottom of the box is the Drug Facts label where it is continued.

[Slide.]

There are some differences between the LDL label and total cholesterol label that Dr. Craig has outlined, and I am just going to review briefly.

[Slide.]

The obvious difference is that on the LDL label, LDL is described in the parameters for selection and follow-up, in contrast to the other label which uses total cholesterol.

The major differences between these labels is in the selection criteria. The LDL label is not gender specific. Both men and women have to have more than one of the listed risk factors and a low HDL is described as one of the risk factors.

For the total cholesterol label, men do not have to have an HDL requirement, but women do. Men also do not have to have a risk factor, but women do.

[Slide.]

The following are the primary and secondary objectives for the label comprehension study.

[Slide.]

The study was a parallel two-group design.
Subjects were randomly assigned to one of the two labels.

[Slide.]

Cholesterol-concerned individuals were recruited.
The study was conducted in 20 geographically dispersed malls
on subjects who met the following inclusion/exclusion
criteria.

[Slide.]

The total sample size was 816 with an even
distribution of subjects in each group.

[Slide.]

Data collection was conducted by trained
interviewers using a scripted questionnaire. There were
open-ended questions, for example, "What is Mevacor Daily
used to treat?" and many scenarios questions which were also
used.

An example is Diane has been taking Mevacor Daily
for several weeks. She is now feeling muscle pain that she
cannot explain. Is it okay or not okay for her to use
Mevacor Daily?

What is important about the design of this study

was that everyone was asked, "Why did you say that," after they provided their okay or not okay response.

[Slide.]

Data analysis was done in two steps. Step 1 was based on the analysis of the initial response of is it okay or not okay, so results were either correct or incorrect.

The second step was an analysis of all the verbatim answers to the follow-up question "Why did you say that?"

Merck referred to these answers as gestalt answers as described in your background package in the review. This analysis provided a truly correct answer and eliminated the guessers. Because there were situations where subjects stated that a person should talk to their doctor, these responses were often considered acceptable.

Because the subject was not directed to ask if a person should talk to a doctor, and it was based on an open-ended question, the analysis of these acceptable answers was taken into consideration during our analysis.

[Slide.]

The results of the SELECT label comprehension study were as follows; for the communication objectives

dealing with selection criteria, the range of correct

answers for most of the objectives were 64 to 92 percent

with an average range of 80 percent.

The exception was a scenario question that

required a decision based on the risk factor tested. This

was having had an MI. The range of the correct answers was

29 to 44 percent. Of note, the overall scores for the total

cholesterol group were higher.

[Slide.]

For those objectives dealing with the warnings and

contraindications, the range of correct answers was 84 to 98

percent.

[Slide.]

The next few slides provide a brief review of the

differences in the results between the CUSTOM label

comprehension study and the SELECT label comprehension

study.

[Slide.]

For the selection criteria, communication

objectives of age and lipid values, the range of correct

answers for CUSTOM label was 54 to 59 percent. The range

for SELECT was 64 to 92 percent with an average range of 80

percent.

[Slide.]

For both studies, the correct range was lower for the communication objective that involved the risk factor of having had an MI. The range was 29 to 44 percent.

[Slide.]

For the objectives that dealt with the warnings and contraindications, the range of correct answers for the CUSTOM label was 55 to 79 percent. The range for the SELECT was 84 to 99 percent.

[Slide.]

Because a consumer use study was not conducted using the SELECT labels, I will compare the differences in comprehension for the communication objectives when to get follow-up lipid testing and what to do if LDL has not reached goal.

[Slide.]

On the CUSTOM label, the directions describing to retest lipids at 6 weeks is bold and underlined in red.

[Slide.]

Where on the SELECT label, the directions to retest in 6 weeks is in plain text without a red underline.

[Slide.]

The range of correct answers to the question when to retest lipids was 71 to 87 percent for the CUSTOM label and 45 to 62 percent for the SELECT label.

Adherence to the label directions for retesting was evaluated in the CUSTOM actual use study. Approximately, 70 percent of the subjects attained a follow-up cholesterol test.

[Slide.]

With the exception of the stop sign, directions describing what to do if LDL has not reached goal in the CUSTOM label is in plain text.

[Slide.]

The same is true for the SELECT Labels. In addition, these directions along with the directions when to retest are on the bottom of the box.

[Slide.]

The range of correct responses was very similar for both CUSTOM and the SELECT labels with 54 to 68 percent correct for the CUSTOM label and 59 to 69 percent for the SELECT label. In the CUSTOM label, approximately 75 percent of the subjects made a correct decision whether to continue

using Mevacor Daily based on their LDL results.

[Slide.]

Merck chose to conduct a separate label comprehension study for the muscle warning.

[Slide.]

The purpose of the study was to measure in-depth consumer comprehension of the warning about unexplained muscle pain, tenderness, or weakness.

[Slide.]

Subjects were provided with the LDL label on the SELECT label, as well as internal package materials that they could refer to at any time during the interview. The internal package materials contained the same muscle warning listed in the Drug Facts label.

[Slide.]

The internal package material also contained information describing what could happen to someone if they develop unexplained muscle pain and continues to use Mevacor Daily, and that unexplained muscle pain can occur even if someone has been taking Mevacor Daily for a long time.

These warnings are found in the following package materials that were tested.

[Slide.]

The Quick Start Guide.

[Slide.]

The package insert brochure.

[Slide.]

The refrigerator magnet.

[Slide.]

The study design. This study was a one-group design using only the LDL label, because the muscle warnings are the same for both labels. The representative sample is 316, the low literacy group was 104.

Cholesterol-interested individuals were also recruited and the study was conducted in geographically dispersed malls. The inclusion/exclusion criteria was the same as in the SELECT label comprehension study.

[Slide.]

The study was also conducted by trained interviewers using a scripted questionnaire. The questionnaire contained scenario-based questions, open-ended questions, as well as closed-ended questions, and all the questions did not focus on the muscle warning so as not to bias the subjects.

[Slide.]

Correct responses to the questions related to the side effect of muscle pain and stop using Mevacor if develop muscle pain was 97 to 98 percent correct.

Correct responses to questions related to what happens if someone who develops muscle pain continues using Mevacor Daily was 75 to 85 percent.

[Slide.]

The subjects were read a choice of answers between extremely to not too likely for the question how likely would they, the subject, contact a doctor if they developed muscle pain while taking Mevacor Daily.

Because providing a choice of answers rather than an open-ended response is leading, it is unknown how well subjects understood that someone should talk to their doctor if they develop unexplained muscle pain when taking Mevacor.

[Slide.]

However, most respondents understood that muscle pain is a side effect of lovastatin and a person who develops unexplained muscle pain should stop Mevacor Daily.

[Slide.]

In the CUSTOM study, 60 percent of the subjects

who developed unexplained muscle pain stopped using

lovastatin.

[Slide.]

So, in summary, the SELECT label comprehension

studies are all well designed studies that contain a lot of

useful qualitative data that validated correct responses,

setting the bar for label comprehension study design.

The major communication elements on the label were

tested with one exception--the part of the pregnancy warning

that describes women who may become pregnant.

The study clearly demonstrated areas of improved

comprehension from the CUSTOM label.

[Slide.]

For those communication objectives the dealt with

safety, the overall range of correct responses was greater

than 90 percent. With the exception of what could happen if

someone continues to use Mevacor if they develop unexplained

muscle pain, the range was 75 to 85 percent.

It is important to note that for those who were

incorrect on the pregnancy and the breast-feeding questions,

most were unable to find the pregnancy warning on the label.

[Slide.]

For communication objectives dealing with the selection criteria of age and lipids, the range of correct responses was 64 to 92 percent with an average range of 80 percent. For the risk factor of having had an MI, the correct range was 29 to 44 percent.

[Slide.]

For communication objectives that had to do with when to retest and what to do if have not reached goal, the range was 45 to 69 percent.

[Slide.]

So, in comparison to the CUSTOM label, the pregnancy/breast-feeding, liver, and muscle warnings were better understood.

There was improved comprehension of the selection criteria, especially total cholesterol, with the exception of one risk factor tested.

There was a decrease in comprehension that lipids should be retested in 6 weeks.

There was no improvement in comprehension for what to do if you have not reached goal.

For the SELECT studies, overall comprehension levels were similar for the low literate population compared

to the general population.

[Slide.]

So, I have just described how well subjects were able to comprehend individual label concepts on the SELECT label.

Dr. Linda Hu will now present the self-selection study which requires subjects to integrate multiple label concepts to make a self-selection decision.

Self-Selection Study

DR. HU: Hello. I am Linda Hu. I am a medical officer in the Division of Nonprescription Clinical Evaluation.

[Slide.]

I will present the SELECT study. First, I will go over the regulatory background for the Mevacor application. Then, I will go over the two labels used in SELECT and the study design. Next, the main results of SELECT, and finally, a summary.

[Slide.]

The Mevacor switch NDA was originally submitted in 1999, and FDA issued a non-approval letter in 2000. The first resubmission included the actual use study CUSTOM,

which was mentioned earlier.

There was a second non-approval letter issued in 2005 and SELECT is part of the second resubmission. I will go over the principal non-approval issues from the second non-approval letter of 2005.

[Slide.]

We saw already in CUSTOM that most of the subjects did not self-select correctly. This was an issue for non-approval in 2005. Ten percent of CUSTOM subjects selected correctly if age, LDL, risk factors, and the absence of certain conditions are considered. About half of CUSTOM users were considered appropriate by the sponsor and 416 of these subjects said that they talked to their doctor.

[Slide.]

The Agency felt that CUSTOM results demonstrated the inability of consumers, on their own, to make decisions on the appropriateness of statin therapy for their own personal use.

Remaining safety concerns for the submission we are evaluating now were use by pregnant women and women of childbearing potential, compliance with muscle pain warning, and safety when used by patients with asymptomatic liver

disease.

[Slide.]

The non-approval letter recommended to the sponsor that the resubmission should have a self-selection study or use study or studies, label comprehension studies, and information to address the risk in subjects with asymptomatic liver disease.

[Slide.]

The sponsor did a self-selection study which is SELECT and now we will go over the labels used in that study. The sponsor studied two labels in the study. Here is the first and these are the criteria in the LDL label.

[Slide.]

So, for the LDL label, consumers first checked their age, then, their LDL number, which they must already know, and then ask if they have additional cardiac risk factors.

[Slide.]

Here are the cardiac risk factors for the ATP III Guidelines for your reference.

[Slide.]

Similarly, for the other label, which is the total

cholesterol label, cholesterol should be in the range of 200 to 240, men need only to consider their total cholesterol and age. The label is different for females, who need to also know their HDL level, their age, and have one or more additional cardiac risk factors.

[Slide.]

The FDA told the sponsor that the label should be consistent with National Cholesterol Education Program ATP III Guidelines. The LDL label conforms better to the ATP III than does the total cholesterol label.

This presentation will focus on results from the LDL label arm.

[Slide.]

The ATP III Guidelines are summarized here. The rows of the table define high, moderate, and lower levels of cardiovascular risk, and the target population is highlighted in this table.

The ATP III Guidelines define LDL goals of therapy for the different risk categories.

[Slide.]

Now, for more details on the SELECT study pertaining to study design and study population.

[Slide.]

SELECT is a self-selection study to determine how many consumers decide correctly that Mevacor is okay for them to use. Self-selection is based on subjects reading and understanding the product label and then applying that understanding to his or her medical history.

The self-selection study should simulate the process that a consumer goes through when considering a product for purchase at the drugstore without extra prompting or coaching.

[Slide.]

SELECT asks two main questions, a self-assessment and a purchase question. I will be using the term self-assessment or self-selection a bit differently than how the sponsor used the term. I will be using self-selection interchangeably with the term self-assessment.

In the SELECT study, participants who responded incorrectly were also asked to explain the reasons why they gave incorrect responses, basically, to explain their reasoning. Subjects were randomly assigned to either the LDL based or total cholesterol based label arm.

Analyses were done separately in both arms, but my

presentation is going to focus on the LDL label because it is closer to ATP III.

[Slide.]

We also focused on the self-assessment rather than the purchase decision because a purchase decision is influenced by potentially confounding economic and marketing issues like cost, consumer appeal of the product or simply buying the product for someone else.

A purchase decision does not necessarily assess a consumer's understanding of whether they can use the product. We are interested in whether the consumer understands who is eligible to use it, why should one use it, and how to use it.

[Slide.]

After enrollment, participants were given directions that may have led them to pay more attention than usual to reading the label and may have led to a higher percent of correct self-selection decisions than would ordinarily occur in the consumer OTC environment.

Participants were told the product is not appropriate for everyone and that they will be asked whether the product was appropriate for them. They will also be

asked whether they wish to purchase the product and to concentrate and to take as much time as needed to read the label.

[Slide.]

After subjects were told to read the label, they were asked the following question: "Based on this label, is this product appropriate for you to use right now or not?"

Responses were characterized as Yes, No, or Other. The "Other" category was used to represent a self-assessment decision that was not a clear Yes or No, such as I don't like to take any OTC medications, I need to talk to my doctor, I am not sure, or I don't know.

[Slide.]

After the self-selection question, the participants were asked the purchase decision question, "Do you want to buy it now?"

If the answer was "Yes, I want to buy it now," they were asked another question. "Is there anything you plan to do before you start using it?"

The idea behind this question was to make subjects stop and think. Subjects knew they were being tested and wanted to give an acceptable answer, and some of them said

that they wanted to talk to a doctor.

[Slide.]

Mass media advertising aimed to attract subjects concerned about their cholesterol. Recruitment ads told subjects to know their four cholesterol numbers; their total cholesterol, LDL, HDL, and triglycerides.

Advertising may have recruited more informed subjects who were better prepared for self-selection, so the SELECT results may not generalize to a consumer population who may become interested in OTC Mevacor unless advertising has similar messages.

[Slide.]

In the SELECT study, there are 5,107 people who called the call center in response to an advertisement for cholesterol-concerned individuals. The randomized study population was 1,520 with 767 going to the LDL arm and 753 to the total cholesterol arm.

After exclusions, there are 662 in the LDL arm and 664 in the total cholesterol arm for whom self-assessment was evaluated.

[Slide.]

Recruited subjects were typically well educated

and middle-class, 90 percent were high school graduates, and 60 percent had some college, 14 percent were low literate.

[Slide.]

We will now go over the detailed results from SELECT.

This slide shows the areas targeted for improvement, bearing in mind the results of CUSTOM. So, in SELECT, the sponsor wanted to decrease the proportion of women under 55 years of age, decrease the women of childbearing potential, and decrease the proportion of users who are of low CHD risk.

[Slide.]

Now, for SELECT results.

[Slide.]

There are 15 separate eligibility criteria for consumers to apply in order to decide if the product was right for them. To be fully correct for self-assessment means a subject met all 15 eligibility criteria.

With so many criteria, it is not surprising that consumers found it difficult to get all the criteria correct. We will later go over hierarchies which are subsets of these criteria.

[Slide.]

Now for the principal results of SELECT. This is a flow chart showing the self-assessment question that was asked of 662 people, "Is Mevacor appropriate for you?"

About two-thirds of subjects said No, and one-third said Yes.

The next row of boxes show how many were right and how many were wrong for the answers. Ninety-eight percent of subjects who chose not to use were correct. So, of those who said Yes, it is appropriate for me, 16 percent, which is 34 over the 214 were entirely correct. The 34 subjects that are entirely correct make up 5 percent of the 662 individuals we started with at the top of the flow chart.

Now, if we add these 34, who are entirely correct, to the 439 subjects who correctly said No, we obtained the overall correct at the bottom, which is 71.5 percent of the 662. Note, this number is almost entirely made up of individuals who did not choose to use.

In summary, of those who would actually use the product, there were 16 percent correct. There was a high percent of correct decisions not to use, and a much lower percent of correct decisions to use.

For the rest of my presentation, I will be spending most of my time talking about those who thought the drug was appropriate to use, and for those who self-selected Yes. In other words, I will be paying more attention to the right side of this flow chart.

[Slide.]

Similar results are seen for the total cholesterol arm, which is shown in this slide. Now that we have looked at the correct responses, I would like to go back and look at those who incorrectly said the product would be okay for them to use.

So, if you look at the third tier and all the way over to the right, you will see 84 percent or 180 subjects were incorrect in their self-selection answer. These are the ones we will be looking at now.

The sponsor asked these 180 subjects why they answered as they did and assessed whether their answers were acceptable. Subjects who gave acceptable explanations for their incorrect decisions to self-select were said to be mitigated.

[Slide.]

There were three types of mitigation; if the

participant said that he or she would talk to a doctor, the participant had a justified or reasonable explanation or rationale, or did not understand the self-assessment question.

[Slide.]

For those 180 who incorrectly self-selected to use, the sponsor mitigated 85 or almost half of those subjects. The table shows how the mitigations break down according to whether subjects said they would talk to a doctor, apparently did not understand the self-assessment question, or gave other reasons for mitigation.

The largest number were mitigated because the subjects said they would talk to a doctor. In the self-selection study, we cannot verify whether subjects will, in fact, talk to their physician.

Under the Other Mitigation category, reviewers did not agree with some of the mitigations.

[Slide.]

Examples of cases where the review team did not agree with the mitigation included cases where subjects wanted to substitute Mevacor for their lipid-lowering medications without talking to their physician, or cases

where high-risk subjects chose to use without talking to a

doctor, or cases where subjects self-selected Yes, but

previously experienced side effects on statins.

[Slide.]

Based on the sponsor's analyses of the LDL label

paradigm, if we add all of those who were mitigated, the

percent correct increases from 16 percent who were

completely correct for all label criteria to approximately

50 percent correct after mitigation.

[Slide.]

Now, we will go over hierarchies.

[Slide.]

As already mentioned, there are many eligibility

criteria on the product label. Some label criteria are of

greater clinical importance. If we ask subjects to get only

some or a subset of the label criteria correct, then, we

will get a higher percent of subjects self-selecting

correctly. That is the idea behind hierarchies.

You pick the most important label criteria

according to some rationale, and then you see how many

subjects got just those criteria correct. Again, we will

focus on the self-assessment rather than the purchase

hierarchy.

[Slide.]

As we just said, if we use all the label criteria in the LDL arm, 16 percent of subjects are entirely correct for self-selection. This increases to 50 percent correct after mitigation. We are now going to go over seven different hierarchies. In each of them, there is some percent correct before mitigation and a higher percent correct after mitigation. The percent correct depends on which criteria you apply in the hierarchy.

[Slide.]

We will present results of the five hierarchies from the sponsor and two more hierarchies requested by the FDA review team. I will first present one sponsor hierarchy in detail or the safety hierarchy. It is the hierarchy with the highest percent correct. The criteria which are considered for this hierarchy are listed above.

[Slide.]

So, let's see how this works. The basic idea is to apply one criteria at a time, in a stepwise manner, and in each step remove subjects who self-selected incorrectly.

You will recall we had 214 subjects who self-

selected to use. This is the 214 we started out with at the first step in the hierarchy. We now apply the first criterion, which is pregnant or breast-feeding. Everyone got this correct, so we did not eliminate anyone and we still have 214 subjects ready to go on to the next step.

Note that if you are pregnant or breast-feeding, then, you should not use Mevacor. However, there were only two pregnant or breast-feeding subjects in the LDL arm, so only two could possibly have gotten this wrong to be kicked out.

In the next step, the criterion was "may become pregnant," and one self-selected incorrectly and was eliminated, leaving 213 left to be evaluated for the next criterion. Note again there were only a small number or 12 women who said they may become pregnant in the LDL arm, so again not many subjects could have gotten this criterion incorrect.

The next criterion is allergy, and next, interacting medication. There were 3 incorrect here who were eliminated.

[Slide.]

Similarly, for two more criteria, for the first

time we see many subjects incorrect with this criterion of already on lipid-lowering medication. Thirty-six subjects were kicked out at this stage, and 174 remained to be assessed for the next step.

After applying this stepwise procedure, at the end we are left with 174 of the 214 correct, or 81 percent correct. This is the percent correct before mitigation.

[Slide.]

This table summarizes the results for the safety hierarchy which we have just gone through. Eighty-one percent were correct before mitigation and 89 percent were correct after mitigation. The same hierarchy was applied in the total cholesterol arm, but the results before and after.

We will look at all the other hierarchies in this format. Remember that when all the eligibility criteria are applied, you had 16 percent completely correct.

[Slide.]

I just want to remind you of what all the eligibility criteria are for your reference, and this is for the LDL label.

[Slide.]

This slide and the next slide show additional

hierarchies constructed for SELECT by the sponsor. For each

hierarchy, the criteria are listed below the table in the

footnotes. First, for the safety hierarchy, which is in the

first footnote, and then the benefit hierarchy criteria are

listed in the second footnote. Then, there is the third

hierarchy, which is a combination of the two.

So, the columns of the table show the two arms and

the percent correct before and after mitigation. First, the

safety hierarchy, which we just went through. Now, the next

two sponsor hierarchies, which are in the same format.

Remember you have to get those specific criteria listed in

the footnote correct to arrive at the percent correct shown

in the table.

In these hierarchies, the percent correct before

mitigation is lower than in the safety hierarchy, because

these hierarchies include lipid values and other criteria

that more subjects got incorrect.

[Slide.]

Here are two more sponsor hierarchies, the

benefits without lipid hierarchy, which include age and risk

factors, and then the expanded benefit hierarchy. These

hierarchies give intermediate values of percent correct.

[Slide.]

The FDA review team also constructed two additional hierarchies. The team tried to choose the most clinically relevant criteria for self-selection. In the first, we required age, lipid-lowering medications, LDL value, interacting medications, and risk factors to be correct, and the percent correct is 21 percent before mitigation and 53 percent correct after mitigation.

For our second hierarchy, we also required the criteria regarding heart disease, stroke, and diabetes to be correct, lowering the percent correct to 17.8 percent with the percent correct increasing to 50.9 percent after mitigation.

[Slide.]

None of the hierarchies was defined a priori in the study protocol, and depending on which criteria are included in the hierarchies, the percent correct before mitigations ranged from 20 to 80 percent.

After mitigations, the percent correct ranged from about 90 percent in the best case and about 50 percent in the worst case.

[Slide.]

We are going to talk now about the consumers who selected Yes, that the product was appropriate for them to use.

[Slide.]

What does SELECT tell us about the population of consumers who would self-select to use? Were they the population that was targeted?

The table shows the percent of subjects who said Yes to self-assessment, and who were at various risk levels as determined by the Framingham 10-year risks and lipid values measured in the study.

Forty-one percent and 24 percent of women were within the target population, which is the 5 to 20 percent range. Many subjects at low CHD risk selected to use. Almost half, or about 46.7 percent of the women who self-selected Yes were of low risk, but only 10.5 percent of men.

In general, women in the user population were of lower risk than the men. Almost half of men were at high risk or had CHD, diabetes, or stroke or were already on prescription meds. So the 56 percent of men outside the target range, most were in the higher risk groups, whereas the 75 percent of women outside of the target range, most

were at low risk.

[Slide.]

Now, we are going to look at some of the other ineligibility criteria of interest, how many people got specific criteria wrong. First, we will look at women too young.

The issues are that they are generally of low risk and they are of childbearing potential. There were 391 women asked the self-assessment question in the LDL arm. Of these, 220, or 56 percent, were less than 55 years of age, and 29, or 13 percent, of these women self-selected Yes.

Of the 391 women in the SA population, 101 women of all ages chose to use the product. Among that group, about 29 percent were under 55 years old.

The most common reasons for their decision were age is close, I want to lower my cholesterol, or family history of heart disease.

[Slide.]

Another specific area targeted for improvement in SELECT was women who are or may become pregnant. For this slide, we are looking at both arms combined.

There were 4 pregnant women in the study. One of

these 4 responded Mevacor was okay to use. The sponsor
mitigated the subject and we agreed.

Twenty-two stated that they may become pregnant.
Two of them, or 9 percent, responded that the drug was
appropriate to use. The sponsor mitigated these 2 cases,
but the reviewers did not agree.

[Slide.]

In the LDL arm, there were 68 subjects with heart
disease. Thirty-three subjects out of the 68 with heart
disease, or almost half, said the product was appropriate to
use. Subjects at high CHD risk might be undertreated by 20
mg of lovastatin.

[Slide.]

For those who were already on lipid-lowering
medications, 140 out of 750, or about 19 percent, of the
self-select population were already on medication to lower
their blood lipids or cholesterol. Forty-four out of these
140 subjects on these medications, or 31.4 percent, said the
product was appropriate for them to use.

[Slide.]

The most frequent reasons given when asked why
they thought Mevacor Daily was appropriate to use even

though they were taking lipid-lowering medications were to

replace the prescription medication or specifically to

replace it because of lower cost.

[Slide.]

For those who decided to purchase, more than 50

percent of subjects said they would purchase Mevacor Daily

for their prescription medication. About 30 percent would

take Mevacor along with their prescription medication.

[Slide.]

The most frequent reasons for preferring OTC meds

for those who selected Yes, were that it was less expensive,

for convenience, they don't have to see a doctor, and it

feels safer, that there are fewer side effects when it is

OTC.

[Slide.]

On average, about 30 percent of subjects with

coronary heart disease, diabetes, or stroke wanted to buy.

About two-thirds of these subjects were not on any lipid-

lowering medications.

[Slide.]

The three most commonly taken lipid-lowering

medications that would be substituted for those who self-

selected to use were atorvastatin, simvastatin, and
lovastatin. The three most commonly taken lipid-lowering
medications for those who had purchased were atorvastatin,
simvastatin, and rosuvastatin.

[Slide.]

In the LDL arm, 37.5 percent did not know their
LDL value whereas, in the total cholesterol arm, 21 percent
didn't know their total cholesterol.

The proportions of subjects who selected to use
without knowing cholesterol numbers were similar in the two
arms, about 20 percent.

[Slide.]

Many of the subjects who had LDL values outside
the eligible range nevertheless self-selected Yes in the LDL
arm. Forty-three percent of subjects who had LDL too high
or above 170 self-selected to use; 17 percent of subjects
whose LDL was too low, or below 130, self-selected Yes.

[Slide.]

I will close with a summary of SELECT results.
This slide shows results from the two arms combined, and we
are rounding off some of the numbers, so they are not
exactly the same as some of the numbers you have seen

earlier.

About 20 percent who self-selected Yes were entirely correct. With mitigations, the percent increased to about 50 percent. A significant proportion of these said that they would like to talk with their physician.

Only 4 pregnant women were in the study, and of those who may become pregnant, 2 out of 22, or 9 percent, self-selected to use and were incorrect.

On average, about 30 percent of participants with coronary heart disease, diabetes, or stroke wanted to purchase the product. Two-thirds of these were not on any cholesterol medication.

[Slide.]

About 30 percent of subjects currently on lipid-lowering medications self-selected to use. Of those who would purchase and who were also on lipid-lowering medication, 50 percent stated they would take Mevacor Daily in place of their lipid-lowering meds; 30 percent would take Mevacor Daily along with their lipid-lowering medication.

The most commonly taken lipid-lowering medications were atorvastatin, simvastatin, rosuvastatin, and lovastatin.

[Slide.]

In the LDL paradigm, those who self-selected to use in the LDL arm included:

101 of 391 women who were asked the self-assessment question, 29 percent of these women were less than 55 years of age;

13.2 percent of women were less than 55 years old;

22 percent of the participants who did not know their LDL-C value;

43 percent of subjects who had LDL values too high or above 170;

17 percent of subjects whose LDL value was too low or below 130.

[Slide.]

Of those who self-selected Yes in the LDL arm, 41 percent of men were in the targeted range. Most men outside the target range were of high risk, CHD equivalent, or on lipid-lowering medication.

24 percent of women were in the targeted range. Most women outside of this range were of low risk.

Approximately 11 percent of men and over 40 percent women were of low CHD risk.

[Slide.]

Dr. Bezabeh will now present the hepatic safety study.

Hepatic Safety Study

DR. BEZABEH: Good morning, members of the Committee.

[Slide.]

My name is Shewit Bezabeh. I am a medical epidemiologist with the Office of Surveillance and Epidemiology, Division of Drug Risk Evaluation.

[Slide.]

This morning I will be discussing FDA's review of a pharmacoepidemiology study submitted by the applicant.

During the last AC meeting held in January 2005, the NDA was non-approvable due to number of deficiencies.

Among the deficiencies cited at the time of the NDA review was lack of adequate safety data of lovastatin use in patients with asymptomatic or pre-existing liver disease.

Since the AC meeting, the applicant has submitted an observational study titled, "Study of Potential Hepatotoxicity of Lovastatin in Kaiser Permanente Northern

California Liver Disease Population."

[Slide.]

The object of the presentation today is to review and critique the submitted population study. I will discuss the strengths as well as the major limitations of the study. With regard to the major limitations of the study, I will focus on three major limitations which include channeling bias, also referred as confounded by contraindication is a bias where lovastatin is channeled to patients at low risk and all were high-risk subjects are not treated.

I will also discuss the composition of the cohort where heterogeneity of baseline liver disease was included, and surveillance bias. This is a bias to monitor a liver-enzymes test in patients with liver disease and a tendency to discontinue lovastatin after a positive test.

Finally, I will discuss the study results, FDA's review and conclusions.

[Slide.]

This is a retrospective cohort observational study conducted in Kaiser Permanente Northern California. The HMO, Kaiser Permanente Northern California is a well-integrated health plan with over 3 million members and an

163

electronic information system which is conducive to conduct such pharmacoepidemiologic studies.

The health plan has been utilized to conduct similar epi studies in the past.

[Slide.]

The population, as mentioned above, consisted of HMO members with liver disease or some evidence of hepatic dysfunction. The study period was from January 1995 to June 30, 2004.

[Slide.]

The cohort of the study consisted of adult patients with evidence of liver disease at baseline or who were felt to be at high risk to develop liver disease due to either the presence of elevated liver enzymes test or the presence of liver-related diagnosis.

In addition, study subjects had at least 13 months of continuous membership in the HMO and no statin prescription one year prior to study enrollment.

[Slide.]

The study inclusion criteria included the presence of at least one of the following:

Elevated ALT or AST at least on two different

occasions 6 to 18 months apart;

Diagnosis of liver disease;

Diagnosis of viral hepatitis;

Diagnosis of metabolic disorders, such as Wilson's disease or hemochromatosis;

The presence of other chronic disease diagnosis, for example, diagnosis of chronic liver disease, alcoholic fatty liver, or biliary cirrhosis.

[Slide.]

The exclusion criteria included any past medical history of the following diagnosis; drug-induced liver disease, disorders of bilirubin excretion, or any past medical history of cancer except non-melanoma skin.

[Slide.]

The study primary endpoint was based on a laboratory outcome of Hy's Rule. Hy's Rule is a prognostic indicator of drug-induced liver injury and has three components; ALT greater than 3 times the upper limit of normal, total bilirubin greater than twice the upper limit of normal, and alkaline phosphatase less than or equal to 1.5 the upper limit of normal.

In addition, the study has three secondary

endpoints; liver injury, which is a lab-based endpoint
defined as ALT 3 times the upper limit of normal or bili 3
times the upper limit of normal, and two medical-record-
based diagnoses outcomes of cirrhosis and liver failure.

[Slide.]

For both the primary and secondary outcomes, the
study conducted a number of analyses. The major analysis
was incidence-rate ratios. Incidence-rate ratios is defined
as the incidence rates of the exposed divided by the
incidence of the unexposed.

In addition, multivariate analysis was also
conducted for both the primary and secondary outcomes.
Multivariate analysis was also to be conducted with
adjustments for potential confounders which are identified
as age, gender, general health status, and concomitant
medications.

[Slide.]

The authors also conducted a number of small sub-
studies and multiple sensitivity analyses to assess for
biases and confirm study results.

Some of the small sub-studies conducted include
analysis of liver disease etiology subgroup, dose-response

analysis where dose-response was analyzed based on

cumulative amount of prescription or cumulative number of

days.

I would like to note that there was no analysis

done on the specific dosage of 20 mg lovastatin, which is

planned for the OTC switch.

Additionally, some small studies conducted include

lovastatin discontinuation, channeling bias sub-studies and

various analysis for the earlier mentioned confounders were

conducted on secondary study outcomes.

[Slide.]

The demographic data show that the cohort

consisted of about 93,000 patients. Of these, about 13,500

or 15 percent had lovastatin exposure while 85 percent or

80,000 of the cohort did not receive the drug during the

study period.

The median age of the exposed population was about

54 years compared to that unexposed, which was about 48

years.

The percentage of men was higher in the study,

accounting for about 61 percent. The exposed population had

a longer follow-up time of about 36 months compared to that

of unexposed population, which had a follow-up period of about 28 months. The median lovastatin exposure was 9.1.

As you can see, the demographic data show that patients on lovastatin were older and were followed up for a longer period than those who did not receive the drug. This is consistent with clinical practice as patients who have a higher risk for cardiovascular disease are older and have a closer follow-up.

[Slide.]

The primary outcome of Hy's Rule, this is the lab-based outcome which is a prognostic indicator of drug-induced liver-disease injury with three components of very high ALT and total bili, and low alkaline phosphatase.

The primary outcome show that there were only 8 Hy's Rule events in the exposed population during the study period compared to 616 of Hy's Rule events observed in the unexposed population.

The calculated incident rate is based on person days of exposure was 1.69 for the exposed and 6.13 for the unexposed. The calculated incident rate ratio, which this is incident rate of exposed over the-incident rate of uneposed, was 0.28.

Based on this incident ratio, exposure to lovastatin was associated with 72 percent decrease in the risk of achieving the Hy's Rule endpoint.

I would like to point out that due to the small number of Hy's Rule events observed in the exposed group, the incident rate ratio was not adjusted for all the potential identified confounders.

[Slide.]

Similar to the results of the primary outcome, the results of the secondary endpoints showed incident rate ratio of less than 1. The incident-rate ratio for the laboratory-based outcome of liver injury was 0.5, whereas the two medical record-based outcomes of cirrhosis and liver failure reveals similar ratio of 0.25 and 0.21.

Again, I would like to point out that these results were not adjusted for all the potential confounders.

[Slide.]

The authors also analyzed the combined outcome where the first occurrence of a secondary endpoint was used since secondary outcomes were not mutually exclusive. The incident ratio was 0.48, which was similar to the previous results.

[Slide.]

Based on the results of the primary and secondary outcomes, the authors concluded that fewer adverse outcomes in Kaiser Permanente Northern California patients with baseline liver disease who were exposed to lovastatin compared to non-exposed.

In addition, the authors also postulated that lovastatin exposure appears to be protective for adverse outcomes in the liver disease population.

[Slide.]

The results of sub-studies and sensitivity analyses conducted showed that there was little evidence for channeling bias, and there was no significant evidence of lovastatin discontinuation in liver disease patients.

Furthermore, all sensitivity analyses did not alter the study results.

[Slide.]

Now, I will discuss the limitations of this study. The major limitation of the study is channeling bias. We know from actual clinical practice that lovastatin is preferentially prescribed or channeled to individuals at low risk for liver disease due to prominent labeling of risk for

hepatotoxicity.

By the same token, lovastatin also preferentially avoided in patients at high risk for liver toxicity.

[Slide.]

However, this is a retrospective observational study and given the limitations of administrative data, we were unable to appropriately evaluate or adjust for this bias. In addition, with this type of observational study, residual confounding cannot be measured accurately.

[Slide.]

Other possible evidence of channeling bias, for example, through the conduct of a lovastatin surveillance sub-study, the authors identified 6,391 patients with both hypercholesterolemia with LDL greater than 160 and liver disease. Of these 6,391 patients, only 2,746, which is 43 percent, were treated with lovastatin.

There was no explanation provided why 57 percent of these hypercholesterolemic patients did not receive the drug. The fact that 57 percent of patients were not on lovastatin is suggestive of confounding by diagnosis.

[Slide.]

The second limitation of the study, the baseline

liver disease of the cohort. The cohort of patients with liver disease consisted of multiple potentially disparate clinical entities, resulting in clinical heterogeneity and disparate outcomes.

The multiple clinical entities may also have contributed and resulted in another potential significant bias of misclassification of both the study injury criteria diagnosis and outcome diagnosis.

The fact that there were many heterogeneic clinical entities and due to the small number of primary outcome of Hy's Rule observed, further analysis by stratification of baseline liver disease and/or adjustments for confounders were not possible, therefore limiting the validity of the study results.

[Slide.]

As you can see from this table, of the 8 primary endpoints observed in the exposed patients, the majority, which is 5 out of 8, were in the group defined with a baseline diagnosis of abnormal liver function test. This is the group without any clear clinical diagnosis.

Whereas, the group with the diagnosis of fatty liver disease had the least amount of observed events in

both the exposed and non-exposed groups.

Again, due to small number of events observed, adjustments for confounding factors and stratification by diagnosis were not conducted.

[Slide.]

The third major limitation of the study, surveillance bias. This is the tendency to discontinue lovastatin after a positive test or liver disease diagnosis.

Surveillance bias sub-study conducted by the authors showed increased frequency of liver enzyme testing in subjects with liver disease.

Lovastatin-exposed subjects had 46 percent more LFT testing compared to non-exposed.

The impact of such differential surveillance on study outcome is not clear.

[Slide.]

Overall, this was a well conducted large study and most of the limitations are inherent with observational studies. However, review of the study showed that there was evidence of channeling bias, there was evidence of surveillance bias, and had a major limitation due to disparate baseline liver disease resulting in difficulty for

adjustment and stratification.

[Slide.]

As a final conclusion, the study findings are consistent with the results of other published studies and suggest that exposure to lovastatin in patients with baseline liver abnormalities did not appear to increase the risk of hepatotoxicity.

[Slide.]

However, because of the limitations and nature of the study, a clinically significant hepatotoxic effect of lovastatin cannot be ruled out.

Furthermore, it is not possible to determine if there is a protective rule for lovastatin in the setting of baseline liver disease.

Thank you very much.

[Slide.]

Next, Dr. Eric Colman will discuss lovastatin use and ALS.

Statins and a Data Mining Signal for ALS

[Slide.]

DR. COLMAN: My name is Eric Colman. I am the Deputy Director for the Division of Metabolic and Endocrine

Drugs at FDA.

[Slide.]

What I plan to do in the next 20 minutes is to discuss our experience evaluating data mining signals for ALS with statins.

In order to do that, I will first provide you with some background, then mention some key features of ALS, try to explain as briefly as I can what data mining is, then, show you the data-mining scores that we have seen in the spontaneous-reporting database at FDA, follow that up with our evaluation of these data to date, and then conclude with next steps.

[Slide.]

For some background, earlier this year a number of members from within the Center for Drug Evaluation and Research met to discuss data mining signals for ALS and statins that we observed in FDA's Adverse Event Reporting System, better known as AERS, which is a spontaneous-reporting database.

After a couple hours of discussion, presentations, the general consensus was that there really was not sufficient data to take any regulatory action. It was

agreed, though, that the information that we had, and any information that we subsequently obtained, should be made publicly available.

In fact, we are in the latter stages of putting together a manuscript and hope to get that submitted within the next few weeks.

[Slide.]

Also, by way of background, I want to point out that in June of this year, there was a paper published in the Journal of Drug Safety by Edwards and colleagues at the WHO Foundation for International Drug Monitoring in Sweden.

Their paper was titled Statins, Neuromuscular Degenerative Disease and an ALS-Like Syndrome, Individual Case Safety Reports from Vigibase.

Vigibase is like FDA's AERS. It is a spontaneous-reporting database, and has a host of limitations which I will mention throughout this talk. They did find a signal and they published the signal in some of the cases.

[Slide.]

I don't want to get into the paper, but I do want to show you the conclusions that they reached, and they are quoted as saying, "... we hope that the signal [for an ALS-

like syndrome with statins] will be accepted not as anything more than a hypothesis that needs to be followed up to ensure the safer use of an important group of medicines."

It sounds very reasonable and given that it came from a spontaneous-reporting database, I think it was cautious and prudent to phrase it that way.

[Slide.]

Of course, it did catch the eye of the mainstream media, and a couple weeks later, in the Wall Street Journal, there was an article entitled, "A Risk in Cholesterol Drugs Is Detected, but Is It Real?"

Again, I am not going to get into the details of this paper, but I do want to mention this because it points out that the issue of whether statins cause ALS or are involved in ALS in any way is out in the public and it is being debated most notably on a number of different web sites, so it is an issue that we have taken seriously and we continue to take it seriously.

[Slide.]

If I could switch gears for a second and just run down a few key features of ALS.

This is a disease that is characterized by

progressive destruction of motor neurons with resultant retraction of the axons from the neuromuscular junction, so people often present with muscle weakness.

But this is not a disease primarily of muscle, it is a disease of motor neurons, and the motor neurons are actually destroyed. That leads to the muscle weakness.

The annual incidence is about 1.5 to 2 cases per 100,000 people, but that does increase notably with age. Men tend to be affected slightly more than females, and the etiology of this condition is unknown.

[Slide.]

Now, the basis for this presentation obviously is drug-safety data mining, so I want to spend some time trying to explain what this process is, and hopefully, I can do that in a way that is clear.

Strictly speaking, data mining is the use of computer algorithms to analyze adverse-event data in a large, complex database. Again, in our situation, we are talking about FDA's Adverse Event Reporting System or AERS. This is a spontaneous-reporting database.

Healthcare professionals, consumers, when they think that there is a drug that caused an adverse event,

they send it in to the system and it gets logged in. Drug

companies also submit data. This is where Med Watch reports

end up.

The goal of data mining is to identify reporting

relationships that could possibly signal adverse drug

reactions. The best way to think about data mining is a way

to generate hypotheses regarding adverse drug reactions.

In no way should data mining be used to prove or

refute causal associations between drugs and adverse

reactions. That is stepping way beyond what this system is

capable of doing.

[Slide.]

This is kind of the essence for data mining. This

is what we actually do when we perform proportional

reporting ratios. Assume that these are data that were in

the AERS database, and we have a particular drug that we are

interested in, Drug X, and a particular Adverse Event Y.

So, you have a number of adverse events of Y for

Drug X. Then, you have the remainder of the adverse events

that don't include Event Y for Drug X.

You then look at all the other drugs in the system

and how many are there that have Adverse Event Y, and then

you compare that to the total number of adverse events for all of the drugs that don't have Y.

What you are really looking for is the observed reporting ratio over the expected, and mathematically, that would be shown as: a/(a+b)/c/(c+d).

In the next slide, I hope to give you a example that makes this clear.

[Slide.]

Let's just say for the sake of discussion we have a new drug called Lipovent. It has been on the market for a year or so, and the safety evaluator at FDA was constantly getting reports, seems to think that there is more pancreatitis than there should be.

So, they initiate a formal proportional reporting ratio, and again we have 10 pancreatitis cases for Lipovent, we have 200 adverse events for Lipovent that don't contain pancreatitis. That is the observed ratio of pancreatitis, so that would be 10/10 + 200 or 0.048.

For the expected ratio, you look at all the other drugs in the system and how often these adverse events are reported relative to the total. So, we have 3 cases of pancreatitis for all the other drugs in AERS, but we have

180

2,000 total adverse events that don't include pancreatitis.

So, the expected ratio would be 3/3 + 2000 or 0.001. So the proportional reporting ratio would be equal to 0.048/0.001 or 48.

[Slide.]

Now, the 48 would not stand alone. That is an unadjusted value, and these are always adjusted, and the term you will see it becomes an EBGM, which is an Empirical Bayes Geometric Mean. That simply is a statistical measure that takes into account small cell counts.

So, when this was applied to that unadjusted 48, it might turn out to be more like 2 or 3.

Two other terms that you frequently will see when you are looking at data mining, are an EB05 and an EB95. The EB05 is like any other confidence interval. It is the lower bound for the geometric mean, and the EB95 is the upper bound for that mean.

[Slide.]

Before I show you the actual data that people are waiting to see, I want to quickly remind you of what a data mining signal is, how do you determine what is a signal. Firstoff, it is not written in stone. It depends on what

situation you are dealing with, what drug, what you are
looking for.

So, for example, if you had an old drug that has
been around for a long time, you might want to be strict and
say I want to use an EB05 of greater than 2, and this would,
in theory, limit the false positive signals.

On the other hand, if you had a relatively new
drug or you are looking for very serious and rare adverse
reactions, you might use an EBGM of greater than 2 as your
score for greater sensitivity.

So, people use various different criteria to
define a data mining signal.

[Slide.]

With that in mind, let me show you the data that
maybe some people have been wanting to see. This shows you
the FDA data mining signal scores for the statins and ALS.

I have highlighted the mean, the EBGM, and if we
use an EBGM of greater than 2 to define a signal, you will
see that all but fluvastatin would be considered as showing
a signal. So, I think it is safe to say that, as a class,
there is clearly a signal for ALS and statins.

The question then becomes what does that mean, and

I want to stress a couple of points about what it doesn't

mean. The EBGM is not an odds ratio, it is not a measure of

relative or absolute risk.

You can't look at these numbers and say the risk

for ALS is 2.7, and it's for pravastatin. That is absolutely

not what these numbers mean. They tell you nothing about

causality.

They are simply proportional reporting ratios.

So, people need to keep that in mind. And I would hate for

people to look at this and think that these represent

relative risk for ALS for these drugs, because that is not

what it means.

[Slide.]

So, we saw these data. The next question is what

do we do about it. The first thing we did is we downloaded

all the reports in AERS and looked at those. We contacted

the statin companies and said, you know, we are interested

in knowing how many people were diagnosed with ALS in your

statin trials, please provide us with that information.

We also looked to see if there is any evidence

over the last 15 or 20 years, has the incidence of ALS

increased, because we know the use of statins has increased

quite dramatically.

[Slide.]

So, one by one, again we downloaded all the AERS cases. They are all individually reviewed by a safety evaluator and two neurologists. Ended up with 57 domestic reports that did legitimately look like they were ALS. Of those reports, the mean age was 67. A little over half were male.

Of the reports that included this information, clinical course after the statin was discontinued, 84 percent reported no improvement in their clinical symptomatology.

Most reports were received by FDA during or after the year 2000. In terms of who sent in the reports, a little over half came from non-healthcare consumers and 33 percent from physicians. That is a little unusual. We normally see it the other way around where we see more healthcare versus consumer. I am not sure what to make of that.

[Slide.]

Again, I mentioned that we contacted the statin companies and specifically, we said please let us know how

many cases of ALS were diagnosed in any of your placebo-controlled trials that were at least six months in duration.

We ended up with 42 placebo-controlled trials of all of the marketed statins including cerivastatin, which was taken off the market in 2001. These ranged in duration from 6 months to 5 years.

Obviously, these were primary and secondary CAD trials. There was no attempt during the study to collect data on neurodegenerative diseases. There was quite a bit of data.

In total, we had about 200,000 person years of statin exposure and 200,000 person years of placebo exposure, so quite a large set of data. There were 9 cases of ALS diagnosed in the statin group and 9 cases of ALS in the placebo group. Can't get much closer than that.

So, they were almost identical in terms of the incidence.

[Slide.]

This figure shows you the prescriptions in millions on the Y axis and calendar year on the X axis starting around 1990. You know that lovastatin was approved in 1987. But if you focus on this line, which is all

statins together, you can see that there has been a fairly

dramatic and constant increase in the use of statins over

the last 15 to 20 years.

That leads one to ask an obvious question has

there likewise been an incidence of ALS during this time

period. The first thing I would say is there is very little

data to address this question.

There was a paper published by Eric Sorenson at

the Mayo Clinic, and he reported that prior to 1990, the

incidence of ALS was 1.5 cases per 100,000 people per year,

and then he looked from 1990 to 1998, and it was roughly the

same, 1.9 cases per 100,000 people per year.

He does have some unpublished data. He has looked

at more recent time frames and didn't see anything much

different than this. But this obviously was just conducted

in a small segment of the population, I believe in

Minnesota.

[Slide.]

So, what should we make of the data mining

signals? Clearly, the signals are there. The issue is what

do you make of them.

I mentioned that there was no imbalance in ALS

from the placebo-controlled trials, but I do need to point

out some of the shortcomings of the trials. Clearly, the

studies were not designed to detect, to track down and to

calculate the incidence of ALS in these trials.

Some patients were on statins prior to entering

these trials. Theoretically, you could have enriched the

study by enrolling statin-tolerant people.

The fact that there was only 18 cases of ALS in

total, even though the incidence was almost identical, given

that number, you still cannot rule out a small to a small to

modest excess risk in ALS, and if all those trials were

treated as one huge study, we might have an upper bound of a

relative risk. The upper bound, somewhere around 2.7, so we

are not talking about huge relative risk.

These data certainly don't allow you to rule out a

small excess risk.

In similar fashion, there is very little data out

there to see if the incidence of ALS has changed

dramatically over the years when statin use increased

dramatically. I haven't seen it ever broken down by age

group.

I mean theoretically, is it possible that the

incidence has gone up in patients who are in their fifties,

sixties, seventies, the patients who are on statins, but

then you have seen a concomitant reduction in incidence in

younger individuals to balance it out, so there is no

change? I mean that would be unusual, but something to

think about.

Could statins unmask or exacerbate muscle symptoms

of ALS? This has come up because there are case reports of

individuals who had latent muscle disease that was unmasked

by a statin, and again the case reports, difficult to make

anything about causality.

If this were true, you might expect to see that

individuals on statin would have their ALS diagnosed sooner

than those on placebo, and we looked at the trial data and

we didn't see any evidence of that, but again it's only 18

cases.

[Slide.]

Finally, could the data mining signals be due to

one or more reporting biases? This is always a concern when

you are dealing with spontaneous-reporting databases. We

have no control over who or why someone submits a suspected

drug adverse event pair to the systems. They can be

influenced by all kinds of outside forces.

Both the statins and ALS are associated with muscle symptoms, so it is not crazy to think that perhaps some people, particularly if they have started a statin within the recent past, and then did develop ALS with the muscle symptoms, to link that with the use of the statin, that is a possibility.

The fact that we detected in AERS a data mining signal for ALS with fenofibrate, which is another lipid-altering drug associated with myopathy, and we found signals for dermatomyositis and polymyositis with statins, again two conditions with prominent muscle symptomatology does lend some support to the possibility that reporting bias has influenced the statin ALS signals.

There certainly are limitations, the data are far from perfect, but what I have shown you does not suggest that statins increase the risk for ALS, certainly not to any large extent.

[Slide.]

However, I think it is fair to say there still is some level of uncertainty here, and given the uncertainty, we do believe that this issue needs to be studied further,

and the logical next step would be to do a case control study.

In fact, there is an ongoing case control study that is being led by Lorene Nelson at Stanford University. She is working with a colleague at Kaiser, and they are using a Kaiser database, which Merck can correct me if I am wrong, but I believe it still does contain a lot of lovastatin.

These are the three aims or the issues that this study will address. It is broader than just statin. It is cholesterol, drugs in general. I won't read those. You can look at those on your own.

Luckily, the study results should be coming in next year, so it is not too far off.

I would also mention that we at FDA are currently exploring whether or not we have the resources to do our own epidemiologic study to look at this issue. This is an ongoing process, it is not going to go away any time soon.

Let me conclude by acknowledging the colleagues that have worked on this statin ALS project, and I will call it quits there.

Questions/Clarifications

DR. TINETTI: Thank you all from the FDA. We have a few moments now before we break for lunch again for the panel, any clarifying questions, questions you didn't quite understand or issues you want to clarify with any of the FDA presentations before we break for lunch.

DR. PICKERING: Thank you. I would like to ask Dr. Hu or somebody from Merck, what was the actual proportion of subjects in the SELECT study who said they were taking statins overall?

DR. TINETTI: While you are getting that information, Dr. Colman, I have a clarifying question for you.

If you could define for us more specifically reporting bias. My understanding is reporting bias is there really is no increase in the disease, it is just because these people are being observed or whatever, were reporting a condition that had nothing to do with the drug.

Examples that you used, sort of unmasking, or even the polymyositis, isn't the possibility that they have the potential for an underlying disease or the early state of a muscle disease, but that the cholesterol-lowering drugs might precipitate that or bring it on quicker?

So, if you could clarify what you meant by "reporting bias" and differentiate those two explanations.

DR. COLMAN: I will try to do that. The first occasion would be if someone was started on a statin, say, within a few weeks or a month, and then they did start to develop muscle weakness from ALS. Perhaps it wasn't known yet that that was ALS, it was just progressing.

Because I think a lot of people, physicians certainly know that statins can cause muscle pain and weakness, they might attribute the muscle symptomatology of ALS to the statin, and that would represent a form of reporting bias.

I think the issue of unmasking or exacerbating the symptoms would probably be more of an ascertainment bias than a reporting bias.

DR. TINETTI: Thank you. So, in this situation, we really can't differentiate those two. Thank you.

Dr. Hu, do you have the information?

DR. HEMWALL: We actually have a number for the overall people that were taking lipid-lowering medications and if you add up all the people, of the 58 people that were taking a lipid-lowering medication that said Yes, about I

would say 60 percent of them were taking statins.

I can do the actual calculation to give you that
exact number, but that is the approximate number. I think
we have a greater story to tell about this particular issue,
so if you want to talk about that later, we are happy to do
so.

DR. HU: Overall, if you look at the whole self-
selection population, there were 140 out of 750, or about
18.7 percent who were on lipid-lowering meds, and out of
those, the percent who chose to use it or self-selected Yes
was about 31 percent.

DR. SHRANK: A quick clarification. Of those who
were taking some lipid-lowering medication, who self-
selected Yes, one of the two reasons Dr. Hu cited, that they
self-selected Yes was that they wanted to replace it because
of lower cost.

Was there any discussion about cost, if patients
asked about cost, was there an answer? How was that dealt
with?

DR. HEMWALL: Remember the study was designed for
people thinking that they were going to get a lipid-lowering
therapy when they came into the study, and they would have

had to pay $20 for a 45-day supply.

What is important to recognize is that although we told people they had to know their lipid numbers, we didn't say what the range was or anything, or give any other information to these folks, so what they heard in the study recruitment ads was an opportunity to participate in a cholesterol-lowering study.

So, what it does is it overenriches a population from people that already know that they could qualify for such a study.

DR. TINETTI: I think we are just clarifying the cost question right now.

DR. HEMWALL: But this is actually a cost answer.

DR. TINETTI: Can you get right to that question, please answer the question. Thanks.

DR. HEMWALL: Because what you see is the type of behavior where people think that if they participate in a study, they can get their medication for a much cheaper price for the term of the study.

DR. TINETTI: Any other clarifying questions?

I had one question, I think for I guess Captain Shay. The discussion of the low literacy rate, I wonder,

does the FDA have a specific definition of low literacy?

I was a little surprised that it is at an 8th grade reading comprehension. Is that the acceptable standard for low literacy?

CAPT SHAY: Currently, that is the cutoff, but that is always something that is under continued debate, because we recognize that 8th grade is fairly high, however, we also recognize that it is very difficult to get a label's reading level down low, not that it is impossible, but at this point we do use that as a cutoff.

DR. TINETTI: One other question as long as I have you. Some of the discussion talks about muscle pain or weakness, which may be related, but are quite different, but all the questions related to pain.

I was sort of curious in terms of the safety issue is how much you are pushing their ability to understand weakness as well as pain, because weakness got dropped and I just wondered if that was acceptable to the FDA, if that was FDA discussions with Merck that it was acceptable to focus on pain rather than weakness.

CAPT SHAY: No. Actually, that is a point well taken.

DR. TAYLOR: I just wondered whether there was any difference that FDA makes between literacy and health literacy, which is a whole new term that has sort of come into the discourse in the last few years. So, there is literacy and there is health literacy out there.

CAPT SHAY: The actual criteria to test for literacy for these studies is the rapid estimate of adult literacy in medicine. It is called the REALM. I don't know if I am allowed to have Dr. Parker weigh in on it. She knows a lot about testing for health literacy, but there is a high correlation with standard literacy tests to health literacy, but a health literacy tool is what is used to screen people for their literacy level.

DR. TAYLOR: I am curious. How is literacy measured? Is testing done in the SELECT and the CUSTOM studies?

CAPT SHAY: Yes, sir, it was using the REALM, the rapid estimate of adult literacy in medicine test. All subjects in both the SELECT and in the label comprehension studies had that test. It takes, what, about 5 minutes to administer. It is a quick screening tool.

DR. PROSCHAN: I didn't quite get the correct

pronunciation, Dr. Bezabeh. Sorry. Slide No. 20, it says

of 6391 patients with both hypercholesterolemia and liver

disease, only 43 percent were treated with lovastatin.

I am wondering, you know, given that we have heard

that there is underprescribing going on, what percentage

would you expect that to have been if they just had

hypercholesterolemia, and not liver disease.

DR. BEZABEH: This is from the study report where

the authors were doing a sub-study to look at channeling

bias, and they identified this cohort of people, and just by

accident there were only, as mentioned, about 43 percent on

cholesterol.

There was no further investigation to see if

channeling bias was playing a role, or were there any other

factors where there is, for example, did they have very

severe liver disease or other comorbidities that prevented

it.

I just put this as an assertion that there could

be channeling bias.

DR. HEMWALL: We actually did that study for

channeling bias, and perhaps it would be helpful to the

committee if Dr. Adamsons explains how that was carried out.

DR. ADAMSONS: The answer to the question is that it is a very similar percentage of people who are hypercholesterolemic who did not have liver disease, who received lovastatin in this Kaiser Permanente population.

The study that was mentioned by the FDA reviewer was separate from our channeling bias study, which he recognized showed that the risk of channeling bias was small.

Could I see 336.

[Slide.]

Slide on, please. This is a slide with several columns, so let me try to orient you. The different rows are the different levels of diagnosis of disease. The top level is you had a diagnosis like cirrhosis and you had at least two liver function tests abnormalities.

The second row is you only had cirrhosis, no evidence of LFT abnormalities. The third and fourth rows are two or more or one or more liver function abnormalities.

The bottom row, please note, are hypercholesterolemic people who did not have any diagnosis of liver disease or liver abnormality, and there were nearly 300,000 of them, so a very robust control group.

The third column from your left gives you the percent of people who were taking lovastatin before the index date, and the index date is when they were diagnosed with the disease.

That, I believe is where the reviewer got the 43 percent from, because you will see the top row, 43 percent of the people who had the most definitive diagnosis of liver disease were taking lovastatin.

I will direct your attention all the way to the bottom of that column, and you will see that the hypercholesterolemic people who didn't have any evidence of liver disease, only 39 percent of them were taking lovastatin.

So, as the panel member pointed out, there is a significant treatment gap, and these data here would seen to reinforce that.

DR. TINETTI: I applaud your ability to get that plunked in to answer that question.

DR. NEILL: A question for Dr. Shay. In your discussion of the SELECT label comprehension trial, you noted on Slide 25, that is page 13 in your handout, that the inclusion and exclusion criteria included the ability to

speak and read English.

The sponsor, in discussing the SELECT self-selection process, noted that in the recruitment process there were minority ads, and there wasn't any further discussion although I did hear that they were either targeted towards or in Spanish.

I am wondering if you could address the issue of whether, in the label comprehension and the self-selection study, that ability to read and speak English was, in fact, an inclusion criteria and how you feel that relates to the recruitment methods that were used for minority groups.

CAPT SHAY: Well, currently, yes. As far as the self-selection study, I believe it was English is who they tested in order to understand the testing, but as far as the label comprehension study, I do know it was English speaking and able to read English.

This issue does come up quite frequently because we have a lot of minorities that English is not their primary language, however, at this point, you know, based a lot on the regulations, the label is required to always be written in English, and is not required to be a bilingual language.

Therefore, testing would be very difficult just as if we were testing in another country. I mean it is a point also, you know, well taken, but it is very difficult to test minorities based on the range of minorities. It couldn't just be Spanish, it would have to be certainly other minorities also.

DR. HEMWALL: If I may add to that, GSK has a very strong record of reaching out to Spanish-speaking minorities in their programs.

The ones that George Quesnelle outlined earlier all have Spanish, hispanic components to them, and that is really where the opportunity is to reach these sometimes underserved populations, but Captain Shay is correct. For practicalities of conducting the studies, we do use English labels and they do ultimately become English labels when we go to market.

There are examples, and we have done this ourselves in our other OTC products from Merck, where we do produce identical Spanish labels to go with the English labels, and are sold in neighborhoods where there is a high Spanish population.

DR. TINETTI: Thank you.